Day 1
Wednesday 28.08.2019

Workshop Special Talk

**MOLECULAR SYSTEMS NEUROSCIENCE OF MEMORY LEARNING**

Alcino Silva (UCLA, USA)

Molecular genetic studies in mice showed that CCR5 is a memory suppressor: genetic, viral and pharmacological manipulations of this receptor result in enhancements in a) molecular mechanisms of memory, b) LTP and, c) hippocampal dependent memory. Additionally, these same CCR5 manipulations result in enhancements in recovery after stroke and traumatic brain injury in mice. Human studies showed that a relatively common null allele of CCR5 in the human population is also associated with higher recovery rates of cognitive and motor function after stroke. However, circuit studies showed that CCR5 plays a key role in closing the temporal window for contextual memory linking. Our studies of memory linking and associated hippocampal ensemble mechanisms demonstrated that following contextual learning increases in CCR5 and its ligand CCL5 close the window for memory linking, an important function that regulates how time regulates the linking of information. Importantly, aging increases the levels of Ccl5 and Ccr5, and thus impairs memory linking, while manipulations that decrease this receptor rescue memory linking in aged mice. These results demonstrate the perils and complexities of manipulations designed to enhance cognitive function: Our results show that while certain cognitive functions are enhanced, others are likely to be compromised. These results argue that for the foreseeable future, efforts directed at cognitive enhancement should be focused on conditions that compromise cognitive function.

Opening Lecture

**PROMISES AND PITFALLS OF TRANSLATIONAL RESEARCH IN ADDICTION**

Harriet de Wit (Department of Psychiatry and Behavioral Neuroscience, University of Chicago, USA)

Addiction remains an urgent public health problem with both cultural and biological determinants. There have been enormous advances in our understanding of the biological determinants of drug use and mechanisms of drug action from studies of drug-seeking behavior using animal models. Yet, there are challenges in applying the findings from behavioral and neurobiological studies with laboratory animals to human drug use. One way to address this important translational issue is to ensure that there is good cross-species concordance in the basic behavioral processes, by using parallel designs and operational definitions in both laboratory animals and humans. Concordance between animal and human behavioral studies will provide much-needed validation for animal studies investigating underlying mechanisms. In my lecture, I will review human laboratory studies that illustrate the challenges and successes in conducting human translational research. Among the challenges are the difficulties in selecting appropriate outcome measures, issues related to the existence of language in humans, relatively greater heterogeneity of human subjects (e.g., histories of drug use and other experiences, education, psychological traits), and the possibility that some drug effects are species-specific. I will also describe successes, which provide validation that basic behavioral processes follow similar patterns in humans and nonhuman subjects.
Day 2
Thursday 29.08.2019

Symposium 1
Nature, nurture and redemption: how human cross-sectional imaging studies of cocaine users are informed by longitudinal clinical and preclinical research

ENIGMA-ADDICTION: IDENTIFYING RELIABLE BRAIN MARKERS OF ADDICTION THROUGH DATA POOLING
Hugh Garavan (University of Vermont, USA)

Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) was established to investigate brain structure, function, and disease by combining genomic and neuroimaging datasets from multiple sites. Its goal is to maximize statistical power and the yield from existing datasets through very large data pooling efforts. This goal has added importance today in light of concerns over the rigor and reproducibility of many neuroimaging and genomic findings. The ENIGMA-Addiction group has pooled data from over 18,000 participants including recreational, dependent, and former users of alcohol, nicotine, and numerous illicit drugs. I will present findings on brain structural differences (cortical thickness and subcortical volumes) between cocaine users and controls and describe how these effects compare to brain differences associated with dependence on other drugs. I will also describe some smaller cross-sectional studies that suggest increased grey matter volume as a function of abstinence duration. Notably, brain regions that show these “recovery” effects are distinct from regions showing differences between current users and controls suggesting that the neurobiology of recovery may be distinct from the neurobiology of disease.

ENHANCING BRAIN RECOVERY IN HUMAN COCAINE ADDICTION WITH COGNITIVE-BEHAVIORAL, PHARMACOLOGICAL AND DIRECT STIMULATION APPROACHES
Rita Goldstein (Icahn School of Medicine at Mount Sinai, USA)

Persistent deficits in self-control and reward valuation/salience attribution characterize drug addiction, marked by abnormalities in functional and structural integrity of the prefrontal cortex (PFC). We previously showed that a 6-month abstinence in treatment-seeking cocaine addicted individuals was associated with PFC grey matter increases, functional recovery of the anterior cingulate cortex (implicated in inhibitory control) and midbrain (implicated in motivated goal-driven behavior) responses during a salient task, and with scalp-based Event-Related Potential responses to non-drug pleasant pictures. Here we will summarize results of novel studies aimed at enhancing recovery of these brain and behavioral functions, providing drug addicted individuals with tools that ultimately could be deployed in a timely and individually tailored fashion to increase self-control and balance salience processing with the goal of reducing craving and risk of relapse. Specifically, this talk will describe a multi-pronged approach and ongoing studies to target the enhancement of PFC function in cocaine addicted individuals. Several approaches, spanning cognitive-behavioral, pharmacological and direct stimulation principles, were used whereby (1) cognitive reappraisal reduced salience of drug (vs. other) related cues as measured with the Late Positive Potentials and eye gaze duration and modulated by severity of addiction; (2) oral methylphenidate normalized dorsolateral PFC function during cognitive reappraisal as associated with trial-by-trial regulation of craving; and (3) tDCS over the dorsolateral PFC was applied for 15 sessions (over 3 weeks) to reduce drug-related attention bias and craving in 15 abstinent treatment-seeking cocaine addicted individuals. Results will be integrated within a dynamic context emphasizing the importance of considering the differential and non-linear effects of abstinence duration on cognitive-behavioral and emotional functions (including incubation of craving) in cocaine addiction as potentially generalizable to other drugs of abuse.
FUNCTIONAL NEUROIMAGING OF ANIMAL MODELS OF DRUG USE DISORDERS: ATTEMPTS TO UNCOVER BRAIN-BEHAVIOR LINKS
Marcelo Febo (University of Florida College of Medicine, USA)

A limitation in many functional neuroimaging studies of cocaine use disorders is an inherent lack of pre-drug baseline measurements. While functional connectivity and network analysis approaches comprise a powerful strategy to quantify brain-region-specific alterations in neural activity, within-subjects' measurements are needed to determine patterns of neural activity in the brain that may be involved in facilitating or protecting against chronic drug use disorders. Also, the course of neuroadaptations might be strongly influenced by pre-drug exposure conditions. Indeed, functional brain network analyses at specific stages of acquisition, abstinence, and relapse of cocaine use may provide novel links between neural activity changes and behavior. Our recent approach in an animal model of extended access cocaine self-administration supports the importance of pre-drug measurements of functional connectivity. Rats were subjected to 14 days of daily 6-hour cocaine self-administration, and then a 14-day abstinence period. Functional magnetic resonance imaging was carried out at pre-cocaine baseline, at 1- and 14-days post cocaine self-administration. The results of this body of work indicate that network-based clustering coefficient and modularity are increased at 1d post-cocaine administration, while the strength of functional connectivity between brain areas was not significantly altered. We posit that changes in connectivity observed at 1d or 14d Abs reflect differential involvement of cognitive and emotional networks across stages of abstinence from chronic cocaine use. The results also suggest that including a pre-drug baseline can have a significant impact on the interpretation of the results.

Symposium 2
Neuropharmacology and Neurogenetics of Aggression as Reward

ALCOHOL SELECTIVELY ENHANCES MOTIVATIONAL PLASTICITY TOWARDS FIGHTING THROUGH CRFR1 ACTIONS IN BRAIN
Herbert Covington III (Tufts University, USA)

Alcohol-escalated violence inflicts significant harm and suffering on a global scale. At least half of all violent crimes are associated with alcohol in the perpetrator, victim or both. From a translational view, aggression that serves as a reward after the completion of a fixed interval (FI) schedule is pathologically intense. Alcohol drinking has the potential to escalate violent behaviors, despite the loss of coordinated behavior. The present series of experiments were designed to determine how alcohol, when self-administered in C57 mice, augments (1) the motivation to fight, or (2) the execution of fighting performance. Here, we allowed a chain-schedule for access to multiple reinforcers, including alcohol deliveries and social rewards. We sought to examine if daily access to alcohol self-administration would alter the motivation to fight, with, or without, shifts in the performance of fighting behavior. Alcohol reinforcements when delivered under the control of a simple schedule of reinforcement was chained to a short (five-minute) FI5 schedule for an aggression reward. Daily access to this chain schedule was allowed for 21 consecutive days. Only a small percentage of these mice demonstrated repeated binge-like behavior by consuming greater than 1.5 g/kg on at least seven of the 21 days of access. These mice also produced more accelerated rates of responding for the opportunity to fight, even though their fighting performance remained disrupted by alcohol. A precise role for CRFR1 receptors in the VTA appears to be particularly important for the motivation to fight, which interestingly, can also be dissociated from fighting performance. CRF in the VTA appears to modulate dopamine release in the ventral striatum during the anticipation of a fight. This
ethological approach links the selective neural actions of CRF in the VTA to the triggering of an urge to facilitate maladaptive aggression.

**TITLE**
Jozsef Haller (Budapest, Hungary)

**Abstract**

**AGGRESSION REWARD AND RELAPSE: BEHAVIORAL, CELLULAR AND SYSTEMS APPROACHES**
Sam Golden (UWashington, USA)

Aggression is an ethologically complex behavior with equally complex underlying mechanisms. Here, I present data on one form of aggression, appetitive or rewarding aggression, and the behavioral, cellular and system-level mechanisms guiding this behavior. I will briefly present one way in which appetative aggression is modeled in mice, and extend aggression motivation to compulsive aggression seeking and relapse. I will then briefly highlight recent advances in computer vision and machine learning for automated scoring of aggressive behavior, the role of specific cell-types in controlling aggression reward, and close with preliminary data on the whole brain aggression reward functional connectome using light sheet fluorescent microscopy (LSFM).

**NEURAL MECHANISMS OF AGGRESSION**
Dayu Lin (New York University School of Medicine, USA)

Aggression is an innate social behavior essential for competing for resources, securing mates, defending territory and protecting the safety of oneself and family. In the last decade, significant progress has been made towards an understanding of the neural circuit underlying aggression using a set of modern neuroscience tools. Here, I will talk about our recent progress in the study of aggression.

**Symposium 3**

Orexin as a critical mediator of cortical and subcortical regulation of motivated behaviors

**BEHAVIORAL GENETIC EVIDENCE SUGGESTS THAT HYPOCRETIN RECEPTORS 1 CRITICALLY REGULATE COCAINE SENSITIZATION, MAYBE NOT COCAINE REWARD, THROUGH NORADRENALINE SIGNALING**
Ben Boutrel (University of Lausanne, Switzerland)

Integration and processing of basic needs are regulated by a complex network of intermingled hypothalamic nuclei. The precise mechanisms by which these intricate networks are organized to coordinate vital functions remain largely unknown. The hypocretin/orexin system participates to the control of alertness through multiple interactions with brain structures involved in the regulation of emotion, reward, stress and sleep/energy homeostasis. While substantial evidence points to a role for hypocretin-1 (orexin-A) peptides in driving reward seeking through activation of brain stress pathways, concordant observations rather suggest hypocretin (HCRT) peptides drive reward seeking through activation of the mesolimbic dopaminergic system. We report here evidence suggesting that mice with conditional inactivation of Hcrt receptor-1 (Hcrt1) gene specifically in adrenaline and noradrenaline neurons exhibit reduced cocaine sensitization and decreased cue-induced reinstatement of a previously extinguished saccharin seeking behavior but express a strong cocaine-induced conditioned place preference compared to appropriate controls. These observations suggest a partial contribution for Hcrt1 signaling through
adrenergic/noradrenergic neurons in cocaine responses. The multiple sources of compensatory mechanisms, most likely occurring during in utero development in absence of HCRTR1, call for cautious interpretation. Nevertheless, our data suggest, in line with a previous report, that by fine-tuning arousal, HCRT-to-NA signaling may down the attention for contextual cues previously paired with saccharin reward, whose reinforcing properties are not as high as those of cocaine.

OREXINERGIC TRANSMISSION IN THE PARAVENTRICULAR NUCLEUS OF THE THALAMUS AFFECTS THE ATTRIBUTION OF INCENTIVE MOTIVATIONAL VALUE TO REWARD-ASSOCIATED CUES
Paolo Campus (University of Michigan, USA)

Reward-associated cues elicit complex emotional and motivational states as a function of their ascribed value. Individuals vary in the extent to which they attribute value to such cues, and this variation may contribute to vulnerability to cue-motivated psychopathologies, like addiction. We can elucidate the neural processes underlying this individual variation using the goal-tracker / sign-tracker animal model. Goal-trackers primarily attribute predictive value to reward cues, and sign-trackers attribute both predictive and incentive value. It has recently been discovered that the paraventricular nucleus of the thalamus (PVT) is a critical component of the neural circuitry underlying the attribution of incentive value. The PVT contains a high density of orexin receptors and several studies have found that orexin transmission plays an important role in cue–motivated behaviors. Furthermore, local delivery of orexin into the PVT increases dopamine release in the nucleus accumbens, and Pavlovian incentive learning is dependent on accumbens dopamine. Based on these data, we hypothesize that orexinergic activity in the PVT is critical for the attribution of incentive value to reward cues, and thereby sign-tracking behavior. To test this hypothesis, we trained rats on a Pavlovian Conditioned Approach task and then evaluated the effects of the intra-PVT infusions of either the orexin 1 receptor (OX-1) antagonist, SB334867, or orexin 2 (OX-2) receptor antagonist, TCSOX229, on the expression of sign-tracking behavior and on the conditioned reinforcing properties of a reward-cue. We found that either OX-1 or OX-2 antagonism attenuated sign-tracking behavior, and the OX-2 antagonism also attenuated the incentive motivational value of the reward-cue as measured with a conditioned reinforcement test. These results highlight a role for the orexin system, and specifically, that in the PVT, in mediating individual variation in the propensity to attribute incentive motivational value to cues associated with rewards.

COCOAINE-SEEKING BEHAVIOR: EVIDENCE OF A ROLE FOR OREXIN TRANSMISSION IN THE PARAVENTRICULAR NUCLEUS OF THE THALAMUS
Alessandra Matzeu (The Scripps Research Institute, USA)

Hypothalamic (HYP) orexin (Orx) neurons that project to the paraventricular nucleus of the thalamus (PVT) have received growing interest because of their role in drug-seeking behavior. OrxA administration in the posterior PVT (pPVT) reinstated extinguished cocaine-seeking behavior in cocaine dependent rats after an intermediate period of abstinence (I-Abst). Considering the long-lasting nature of drug-seeking behavior, we examined whether the priming effect of OrxA is preserved after protracted abstinence (P-Abst). The central nucleus of the amygdala (CeA) and bed nucleus of the stria terminalis (BNST) are strongly engaged during drug-seeking behavior, and the pPVT projects to both the CeA and BNST. Thus, we examined the activation patterns of the CeA and BNST following intra-pPVT OrxA injections. After cocaine self-administration training, the animals were either subjected to 14-21 days of extinction training (I-Abst) or placed for 14 days in the vivarium followed by extinction training for 14-21 days (P-Abst). Once the animals’ behavior was extinguished, they received intra-pPVT microinjections of OrxA and tested for OrxA-induced cocaine-seeking. OrxA reinstated cocaine-seeking behavior at I-Abst but not at P-Abst and the reinstatement of cocaine-seeking behavior was associated with activation of both the CeA and BNST. To test whether CeA and BNST activation is necessary for OrxA-induced cocaine-seeking behavior at I-Abst, a separate group of rats was tested with simultaneous injections of OrxA in the pPVT and a combination of muscimol+baclofen in the CeA or BNST. Transient inactivation of the CeA prevented OrxA-induced cocaine-seeking behavior, whereas inactivation of the BNST did not affect the ability of OrxA to reinstate cocaine seeking. Altogether these findings indicate that the HYP(Orx)>pPVT>CeA circuit is strongly recruited shortly after abstinence in animals with a history of cocaine dependence. The differential behavioral outcomes observed at I-Abst vs. P-Abst suggest that cocaine abuse perturbs Orx
OREXIN/HYPOCRETIN SYSTEM PLASTICITY IN MOTIVATIONAL DISORDERS
Morgan James (Rutgers University, USA)

Significant evidence indicates that orexin (hypocretin) signaling is important for coordinating behavior under situations of high motivational relevance. Thus, pharmacological strategies that interfere with orexin signaling are highly effective at reducing a variety of drug and food seeking behaviors. Recently, we showed that exposure to a cocaine self-administration procedure that promotes a multifaceted addiction phenotype is associated with significant plasticity in orexin system function, such that the number of orexin cells is persistently increased and an orexin receptor antagonist is more effective at attenuating drug-seeking behaviors. Here, we present evidence that this plasticity in orexin system function is also observed in a model of binge-like eating in obese rats. We also show data supporting a role for orexin input onto ventral tegmental area in compulsive food seeking behavior following binge-like eating. We discuss the implications of these changes with respect to the development and optimization of orexin-based therapies designed to treat addiction and other motivational disorders.

Symposium 4

Modelling comorbidity of chronic pain and affective disorders: towards improved mechanistic understanding and treatment

RECI PROCAL INTERACTIONS BETWEEN PAIN AND NEGATIVE AFFECT: SITES AND MECHANISMS OF ACTION
David Finn (National University of Galway, Ireland)

Pain and affective state interact reciprocally, whereby the latter can both influence, and be influenced by, the pain experience. We have used animal models to elucidate supraspinal neurochemical and receptor mechanisms involved in (1) hyperalgesia associated with negative affect (anxiety/depression) and (2) fear-induced analgesia. Wistar-Kyoto rats exhibit an anxiety- and depressive-like phenotype and also display hyperresponsivity to noxious stimuli. These effects are associated with alterations in levels of endogenous cannabinoids (endocannabinoids) and related N-acylethanolamines and altered expression of their receptor targets or metabolizing enzymes in key brain regions regulating pain and affect. Pharmacological blockade of the CB1 receptor exacerbates hyperalgesia to persistent inflammatory pain in Wistar-Kyoto rats, while pharmacological blockade of endocannabinoid degradation attenuates hyperalgesia. Additional data suggest an important role for the endocannabinoid system in the periaqueductal grey and rostral ventromedial medulla in regulating hyperalgesia in the Wistar-Kyoto model of hyperalgesia associated with negative affective state. Our results also suggest an important role for TRPV1, PPARγ and µ-opioid receptors in the periaqueductal grey in the Wistar-Kyoto model. Further evidence that deficits in the functionality of the descending inhibitory pain pathway likely underlie the hyperalgesic phenotype of Wistar-Kyoto rats comes from our recent data suggesting that these rats exhibit impaired expression of fear-induced analgesia. Interestingly, we have also shown that induction of neuropathic pain in the Wistar-Kyoto rat (L5 spinal nerve ligation) is associated with significantly increased anxiety- and depressive-like behaviour compared with Sprague-Dawley counterparts, results which may be due, at least in part, to deficits in endocannabinoid signalling. This result maps onto clinical data that we and others have generated indicating increased anxiety and depression in neuropathic pain patients. Finally, using the place escape avoidance paradigm we have generated evidence for an affective component associated with our recently developed novel rat model of post-operative pain associated with inguinal hernia repair and we are elucidating the role of the endocannabinoid system in the affective dimension of post-operative pain in both rodents and humans. Increased understanding of the neural connectivity with the pPVT as abstinence progresses.
mechanisms regulating pain-affect interactions may facilitate identification of novel therapeutic targets for the treatment of pain, affective disorders, and their co-morbidity.

NORADRENALINE AND PAIN: A DOUBLE EDGED SWORD
Esther Berrocoso (Universidad de Cadiz, Spain)

The activation of the descending noradrenergic pathway has been implicated in the analgesic effects of antidepressants. However, many patients fail to achieve adequate analgesia with these medications or they do not tolerate them. Thus, it is possible that pain produces specific neuroplastic changes that modify the influence of noradrenaline. Furthermore, little is known about the role of the ascending noradrenergic projections on the activity of the limbic structures where the emotional aspects of pain are processed. During this symposium, novel data will be presented about the noradrenergic system and the basolateral amygdala (BLA) circuits mediating the effects of chronic pain, and pain-induced anxiety. The speaker will show that endogenous activation of the noradrenergic locus coeruleus (LC) can produce both pro- and anti-nociceptive effects, suggesting that it contains and interacts with different neuronal subgroups. In addition, the noradrenergic circuit that mediates stress-induced anxiety and aversion will be described, and we will show that the noradrenergic system is a critical hub for the development of the anxiodepressive consequences of long-term pain. These data stimulate interest in novel therapeutic options that modulate the noradrenergic and amygdalar circuits. (Supported by “Consejería de Salud de la Junta de Andalucía” and FEFER “Iniciativa Territorial Integrada (ITI) 2014-2020 para la provincia de Cádiz” PI-0080-2017, RTI2018-099778-B-I00, PI18/01691, CIBERSAM CB/07/09/0033).

CHRONIC PAIN AND SOCIAL BEHAVIOR IN RATS: A TWO-WAY ROAD
Hugo Leite-Almeida (University of Minho, Portugal)

Chronic pain impact on behavior is complex and multidimensional fashion. Our group and others have been showing in experimental models the manifestation of maladaptive behaviors including anxiety, depression and cognitive deficits. Curiously, social behavior, despite being an important feature of rodents' behavioral repertoire, has been sparsely explored in the context of chronic pain. In a series of studies recently carried on our laboratory, we demonstrate in a rat model of chronic neuropathic pain (spared nerve injury) diminished social activity. The phenotype is stable and manifests equally in encounters between familiar and unfamiliar pairs. Analgesic pharmacotherapy recovered the phenotype as well as housing in a socially enriched environment altogether suggesting that social behavior can be a good proxy of pain in rodents. Data regarding our behavioral paradigms will be present as well as anatomical and/or molecular data attempting to uncover the neural basis of the phenomena.

REACHING CIRCUITY LEVEL OF UNDERSTANDING OF THE COMORBIDITY OF CHRONIC PAIN AND MOOD DISORDERS
Ypek Yalcin (Université de Strasbourg, France)

Uncontrolled and persistent pain strongly associates with anxiety and depressive disorders, and is among the most common cause of disability impairing the quality of life. Over the last 10 years, our group has established and validated paradigms designed to model this comorbidity in the mouse. We then exploited this model to uncover individual brain structures and molecular mechanisms affected by chronic pain. Among candidates, the anterior cingulate cortex (ACC), a structure common to the default mode, salience and reward networks, appears critical in pain and emotional processing. Our rodent studies further supported the implication of the ACC in mood control. Indeed, in naïve mice, a short-term optogenetic activation of glutamatergic pyramidal neurons was sufficient to trigger anxiodepressive-like behaviours. Secondly, in a neuropathic pain model, our in vivo electrophysiological single unit recordings highlighted changes in ACC neuronal activity, with a long-lasting increase in spontaneous firing and bursting activity during pain-induced depressive-like behaviours. To go further, we now aim at reaching a network-level of understanding of these issues. Our resting state functional magnetic resonance imaging results clearly showed modifications in the circuitry of the Basolateral amygdala (BLA)-ACC in our rodent model of comorbid chronic pain and
depression. By using optogenetic approach, we further showed that the optogenetic activation of the BLA-ACC pathway induced depressive-like behaviours in naïve mice. Importantly, inhibiting this pathway was sufficient to block neuropathic pain-induced depressivelike behaviours. Altogether these data reveal the importance of BLA-ACC pathway in emotional dysregulation and highlight the need of dissecting circuits rather than single structure to deepen our understanding of the mechanisms underlying mood disorders.

Symposium 5
Novel insights into the molecular mechanisms and cell ensembles regulating the neural circuits underlying negative emotion

FEAR AND FRAGILE X SYNDROME: “ALTERNATIVE FACTS” FROM THE AMYGDALA
Shona Chattarji (NCBS, Bangalore, India)
Fragile X Syndrome (FXS) is the most commonly inherited form of mental impairment and autism. Current understanding of the molecular and cellular mechanisms underlying FXS symptoms is derived mainly from studies on the hippocampus and cortex. However, FXS is also associated with debilitating emotional symptoms, which are likely to involve changes in the amygdala. However, the synaptic basis of amygdalar dysfunction in FXS remains largely unexplored. Of particular importance in this context is the “mGluR theory”, proposed by Mark Bear and colleagues, according to which various aspects of FXS area consequence of exaggerated metabotropic glutamate receptor (mGluR) function. One of the major findings leading to the mGluR theory is that in the hippocampus the group1 mGluR receptor, mGluR5, is involved in long-term depression (LTD) of synaptic strength, a form of synaptic plasticity that is enhanced in the Fmr1-KO mouse. Notably, while hippocampal mGluR5-LTD is enhanced, we find that amygdalar mGluR5-LTP is impaired. Does this contrast imply that the “mGluR theory”, which was based on findings in the hippocampus, needs to be revised for the amygdala? Moreover, the mGlur theory, as envisioned in the hippocampus, also proposed that blocking mGlur-activity should reverse defects observed in rodent models of FXS. Since the features of defective mGlur-dependent synaptic plasticity caused by FXS in the amygdala are opposite to those reported in the hippocampus, this raises an intriguing possibility — activation, not blocking, of mGlurs should help reverse the defects in the amygdala. Indeed, we find that, activation of mGlurs in the amygdala is capable of correcting FXS-induced deficits in the amygdala. Thus, I will describe our recent findings that provide the first comprehensive framework, across biological scales from behaviour to synapses, for analysing and treating emotional dysfunction caused by FXS.

CREATE AND MAINTAIN FEAR MEMORIES IN THE NEURONAL NETWORK
Gisella Vetere (ESPCI Paris, France)
Understanding how memories are created and maintained over time is a fundamental problem in neuroscience. Our data show that a memory can be artificially created through the precise co-activation of brain regions that process olfactory inputs with regions that process affective valence, in the complete absence of any sensory experience. This study emphasizes both the critical role of sensory input in establishing highly specific memories, as well as the need for coordinated activity of neural networks in memory. The neural networks of co-active brain regions that support memory recall are here investigated. Within such networks, highly connected hub regions are assumed to disproportionately influence behavioural output. We tested this hypothesis by chemogenetically silencing hub or non-hub regions, and assess the effects on long-term memory recall. Our data show that inhibition of hub regions impaired memory performances, in contrast with non-hub regions. The graph theory analysis of memory networks opens new doors in the discovery of brain regions and pathways involved in memory performance. Moreover, the network-based approach is a powerful tool that can provide testable predictions about the regions that may be impaired in cognitive disease. Subsequent manipulations of
these pathways can provide causal evidences of their involvement in the disease.

A NEURAL CONSTRAINT ON SOCIALLY-LEARNED FEAR
Andrew Holmes (NIH, Bethesda, USA)

To identify neural circuits underlying socially-learned traumatic memory, we assessed observational fear learning (OFL) in mice. We found OFL produced ex vivo plasticity in projections from ventral hippocampus (vHPC) to dorsomedial prefrontal cortex (dmPFC). In vivo calcium imaging and photosilencing showed that engagement of vHPC-dmPFC neurons associated with reduced OFL. Thus, the vHPC-dmPFC circuit may serve to constrain socially-learned fear. Research supported by the National Institute on Alcohol Abuse and Alcoholism Intramural Research Program.

THE EFFECTS OF CHRONIC STRESS ON TRANSCRIPTOMICS, MITOCHONDRIAL FUNCTION AND DEPRESSIVE-LIKE BEHAVIORS
Meltem Weger (Brain Mind Institute, Switzerland)

Chronic stress is a major risk factor for the development of depression. Importantly, individuals differ in their vulnerability to stress, which suggests important a priori individual differences in the mechanisms underlying susceptibility to develop depression. In particular, mitochondrial dysfunction was highlighted as a crucial vulnerability factor. Systematic profiling of mitochondria associated gene responses to chronic stress can help to understand how mitochondrial dysfunction can act as a vulnerability factor for the manifestation of depression. Here, we investigated the transcriptional profiles of mitochondria associated genes in the Prefrontal cortex (PFC) and Nucleus accumbens (NAc) of mice followed by chronic stress (CS). Mice submitted to CS exhibited changes in physiology and behavior resembling a depressive-like phenotype and showed decreased mitochondrial respiration and energy metabolites in the PFC. Transcriptional profiling pointed to CS-induced alterations in mitochondrial pathways in the PFC and to a certain extent also in the NAc. A focused analysis on mitochondria-associated genes revealed a CS-related imbalanced expression of mitochondria associated genes in the brain, including genes encoding for oxidative phosphorylation (OXPHOS) complex subunits. By reanalyzing a previously published transcriptome data set, we found that CS-induced changes in mitochondrial genes in mice were similarly detected in post-mortem brain tissue of major depressive disorder (MDD) subjects. We further compared our data with transcriptomic changes elicited by transgenic deactivation of the glucocorticoid receptor (GR) gene in dopaminergic D1-receptor containing neurons, and found that GR down-regulation mimics some of the CS-induced transcriptional changes in mitochondria associated genes in the PFC. Lastly, we showed that mitochondrial gene expression relates to the mice behavioral profile in terms of emotionality. Collectively, our work emphasizes a higher vulnerability to CS-induced transcriptional changes in the PFC than in the NAc and identifies alterations in mitochondria-related genes in both brain regions. Furthermore, our data points at the GR in the dopaminergic system as a regulator of mitochondrial gene expression. Altogether, our data supports the view that brain mitochondrial modulation is a key contributor to chronic stress-induced neurobehavioral adaptations.

Symposium 6
Recent insights into mesocorticolimbic circuit mechanisms of appetitive behaviours

DIETARY PROTEIN RESTRICTION INDUCES A PREFERENCE FOR PROTEIN THAT MAY INVOLVE BOTH RAPID SENSORY INPUT AND POST-INGESTIVE EFFECTS
James McCutcheon (University of Leicester, UK)

Intake of dietary protein is tightly controlled in many species. However, whether this involves development of a specific appetite for protein when protein-restricted is still a matter of debate.
In addition, the neural structures that allow protein intake to be regulated with respect to need state are not well defined. We have shown that rats maintained on a low protein diet (5%) develop a preference for a solution containing the dairy protein casein (4%), relative to an isocaloric solution of the carbohydrate maltodextrin. This preference is not seen in non-restricted control rats (Murphy et al., 2018). Our recent data show that this preference in protein-restricted rats is expressed rapidly and can be observed within the first few minutes after rats first experience the nutrient-containing solutions. Moreover, we have shown that the post-ingestive properties of protein in the gut and after absorption may be important in development of this preference. As such, rats will learn to prefer a novel flavor paired with protein that is infused directly into the stomach, relative to a carbohydrate-paired flavor.

Finally, to understand the neural circuits that are important for this preference we have used fiber photometry to monitor calcium fluctuations, via GCaMP, and neurotransmitter release, via dLight. Our results so far implicate the mesolimbic dopamine system as being involved in this preference as in protein-restricted rats, consumption of protein evokes greater neural activity than consumption of maltodextrin.

In summary, dietary protein restriction leads to a preference for foods containing protein that may result from both changes in chemosensory pathways as well as the post-ingestive effects of protein.

ACCUMBENS ACETYLCHOLINE-DOPAMINE INTERACTIONS REGULATE CUE-MOTIVATED BEHAVIOR
Kate Wassum (Brain Research Institute, UCLA, USA)

Dopamine transmission is vital for motivated behavior and disruptions in such signaling are thought to contribute to a variety of mental illnesses and diseases of behavioral control, as well as to neurological conditions such as Parkinson’s disease. Much focus has been given to the activity of midbrain dopamine neurons and the resultant release of dopamine into the striatum during motivated behavior. Emerging evidence suggests that modulatory mechanisms within striatal terminals can regulate the ‘decoding’ of dopamine cell activity into chemical messages and, thus, regulate adaptive and maladaptive motivation. I will discuss how accumbens acetylcholine regulates dopamine release to gate the ability of reward-predictive cues to motivate behavior. We assess cue-motivated behavior using the translationally-analogous Pavlovian-to-instrumental transfer task designed to assess the motivating influence of a reward-predictive cue over an independently-trained instrumental action. We couple this with neural monitoring and pharmacological, chemogenetic, and optogenetic manipulations of NAc dopaminergic and cholinergic signaling. Our data are indicating that NAc acetylcholine signaling gates the expression of cue-motivated behavior via terminal modulation of cue-evoked phasic dopamine signaling. Maladaptive behavior can result from both excessive or blunted cue motivation, thus, these data have implications for the understanding and treatment of compulsive overeating, addiction, depression, and other diseases marked by maladaptive motivation.

CORTICOLIMBIC REGULATION OF EXTINCTION LEARNING
Mihaela Iordanova (Concordia University, Canada)

Our environment is dynamic often providing conditions in which behaviour is seemingly under the control of conflicting information. Extinction learning is one such example when two conflicting memories compete for behavioural control. In extinction, a previously established predictor for a rewarding (or aversive) event is presented in the absence of that event. Such non-reinforced exposures lead to a reduction in the behavioural response (conditioned approach). Yet, the capacity of the cue to predict upcoming reward is not entirely erased and under certain conditions it is readily expressed in the form of behavioural restoration. How the brain is able to resolve the conflict between acquisition and extinction remains unknown. Here we show that the infralimbic cortex specifically regulates learning about extinction of reward-predicting cues, but not in other theoretically similar and conflict-inducing situations (i.e., overexpectation). Electrophysiological and chemogenetic (daun02 inactivation) approaches revealed that extinction of reward predicting cues is likely sent to the central nucleus of the amygdala where specific neuronal ensembles are critical for supporting this learning. Our data
provide important parallel between the neural circuit involved in extinction of fear and extinction of reward predicting cues.

**TITLE**
Leslie Whitaker (NIDA IRP/NIH, USA)
Abstract

**Plenary Lecture**

**HABENULAR REGULATION OF OBESITY-RELATED ABNORMALITIES IN FOOD PREFERENCE AND MOTIVATION**
Paul Kenny (Icahn School of Medicine at Mount Sinai, USA)

Increased preference for, and consumption of, energy-dense palatable food contributes to obesity, but underlying mechanisms are poorly understood. We found that obese rats or mice with access to a cafeteria-style diet show profound shifts in food preference, reflected by volitional starvation when palatable food was withheld and only standard chow available. Paradoxically, obese animals are less willing to work for standard or palatable food than lean animals. The lateral habenula (LHb) is known to regulate preference and motivation and receives food-relevant information from the lateral hypothalamus (LH). Using fiber photometry, we found that access to standard chow decreased LHb activity in hungry lean rats, which readily consumed the food, and this effect was absent in obese rats, which rejected the food. Conversely, access to palatable energy-dense food decreased LHb activity in lean rats, and this effect was enhanced in obese animals, which both consumed the food. Lesion of the LH-LHb pathway enhanced preference for palatable food and precipitated obesity-like deficits in food motivation in lean rats, whereas chemogenetic simulation of this pathway had opposite effects. Glutamate- and GABA-producing neurons in LH project to LHb. We found that LHGLU-LHb neurons but not LHGABA-LHb neurons are hypoactive in obese animals, and single cell RNA sequencing revealed profound obesity-related transcriptional plasticity in LHGLU-LHb neurons. Using an intersectional genetics approach, we found that very selective lesion of LHGLU-LHb neurons precipitated obesity-like deficits in food motivation and preference. Together, these findings show that LHGLU-LHb neurons regulate abnormalities in food motivation and preference in obesity.

**Lecture**

**ALTERNATIVE NONDRUG REWARDS TO TREAT DRUG ADDICTION: SYSTEM, CIRCUIT AND CELLULAR MECHANISMS**
Marco Venniro (NIH/National Institute on Drug Abuse, USA)

Addiction treatment has not been appreciably improved by neuroscientific research. The reasons for the limited translational success of studies using rodent addiction models are complex and multifactorial. But this state-of-affairs have led us to develop animal models that mimic successful behavioral treatments in humans—contingency management and community reinforcement approach—to improve mechanistic understanding of abstinence and relapse. In the lecture, I will first summarize results from our studies using a rat model of relapse after cessation of contingency management. In these studies, abstinence is achieved using a discrete choice between palatable food and the self-administered drug (methamphetamine or heroin). Next, I will introduce our more recent “community reinforcement approach” rat model whose goal is to improve the translational utility of the animal model by using rewarding social interaction as the alternative nondrug reward. I will first show the profound protective effect of operant social reward on methamphetamine self-administration in three established addiction models, and on incubation of drug craving. Next, I will describe our initial circuit studies in which we identified a potential cell-type specific mechanism (PKCdelta-expressing neurons in central amygdala) for the inhibitory effect of rewarding social interaction on incubation of methamphetamine craving. I will also introduce a fully automatic social reward self-administration model that eliminates the intense workload and extensive rat–human interaction of the original semiautomatic model.
I will conclude the lecture with a discussion of the implications of my studies to preclinical research on drug addiction and addiction treatment.

**Selected Oral Presentations**

**PO 27 - DBS-LIKE OPTOGENETIC STIMULATION OF ACCUMBENS DOPAMINE D2 RECEPTOR-CONTAINING NEURONS ATTENUATES COCAINE REINSTatement**
Sarah Swinford-Jackson (University of Pennsylvania, USA)

**PO 32 - DIET INDUCED OBESITY ALTERS EXCITABILITY OF THE ORBITOFRONTAL CORTEX AND IMPAIRS OUTCOME DEVALUATION**
Lauren Seabrook (University of Calgary, Canada)

**PO 33 - DISCOVERY OF A NOVEL BRAINSTEM CIRCUIT INVOLVED IN ENERGY BALANCE REGULATION**
Marie Le May (University of Gothenburg, Sweden)

**PO 35 - DORSOMEDIAL STRIATUM ACTIVITY DURING ONLINE MONITORING OF LEVER PRESS SEQUENCES**
Youna Vandaele (Johns Hopkins University, USA)

**PO 37 - DRD1 AND DRD2 IN NAC CORE ARE CRITICAL TO THE INCUBATION OF METHAMPHETAMINE CRAVING AFTER VOLUNTARY ABSTINENCE**
Ludovica Rossi (Università di Roma Sapienza, Italy)

**PO 46 - ELEVATED ANANDAMIDE VIA FAAH INHIBITION PROMOTES FEAR EXTINCTION AND PROTECTS AGAINST STRESS IN HEALTHY HUMANS**
Leah Mayo (University, Linköping, Sweden)

**PO 64 - LATERAL HYPOTHALAMIC OREXIN PROJECTIONS TO VENTRAL TEGMENTAL AREA MODULATE DOPAMINE NEUROTRANSMISSION AND REWARD-RELATED PROCESSES**
Catherine Thomas (University of Calgary, Canada)

**PO 70 - MORPHINE AS AN INTEROCEPTIVE PAVLOVIAN DISCRIMINATIVE STIMULUS IN MALE AND FEMALE SPRAGUE-DAWLEY RATS**
Allyson Andrade (University of Guelph, Canada)

**PO 78 - OPTOGENETIC INHIBITION OF CUE-ELICITED DOPAMINE ACTIVITY ATTENUATES SIGN-TRACKING BEHAVIOR TO A PAVLOVIAN FOOD CUE**
Amanda Iglesias (University of Michigan, Ann Arbor, USA)

**PO 101 - THE ROSTROMEDIAL TEGMENTAL NUCLEUS: AT THE CROSSROADS OF REWARD AND AVERSIO**
Peter Vento (Medical University of South Carolina, USA)
Human neuroimaging research has consistently shown that cocaine addiction is associated with structural and functional changes within the orbitofrontal cortex (OFC). In view of the important role of the OFC in value-based decision-making, these changes have been hypothesised to bias choice towards cocaine despite and at the expense of other competing pursuits, thereby explaining cocaine addiction. Here I will present direct evidence for this hypothesis in a choice-based model of cocaine addiction where rats could choose between two actions, one rewarded by cocaine, the other by a nondrug alternative. OFC neuronal activity was recorded while rats performed each of these two actions separately or while they chose between them. First, we found that these actions are encoded by two non-overlapping neuronal populations and that the relative size of the cocaine population represented individual preferences. A larger relative size was only observed in cocaine-preferring individuals. Second, OFC neurons encoding a given individual's preferred action progressively fired more than other action-coding neurons few seconds before the preferred action was actually chosen, suggesting a pre-choice neuronal competition for action selection. In cocaine-preferring rats, this manifested by a pre-choice ramping-up activity in favour of the cocaine population. Finally, pharmacological manipulation of pre-choice activity in favour of the cocaine population caused nondrug-preferring rats to shift their choice to cocaine. Overall, this study suggests that an individual preference for cocaine is represented in the OFC by a population size bias that systematically advantages cocaine use-coding neurons during pre-choice competition for action selection.

LINKING MEMORIES
Denise Cai (Icahn School of Medicine at Mount Sinai, USA)

Memories are encoded in neural ensembles that are dynamically updated across time and experience. Enhancing the valence of a memory leads to retrospective linking (linking new experience with a previous memory) through an overlapping neural ensemble shared by the two memories. This may be a circuit mechanism underlying causal inference, linking a predictive cue with the outcome.

NEUROBIOLOGICAL SUBSTRATES OF DISCRIMINATIVE STIMULUS-CONTROLLED INCUBATION OF COCAINE CRAVING
Rajtarun Madangopal (NIDA IRP/NIH, USA)

In abstinent drug addicts, cues formerly associated with drug-taking experiences gain relapse-inducing potency (“incubate”) over time. Animal models of incubation may help develop treatments to prevent relapse, but these models have ubiquitously focused on the role of conditioned stimuli (CSs) signaling drug delivery. Discriminative stimuli (DSs) are unique in that they exert stimulus-control over both drug taking and drug seeking behavior and are difficult to extinguish. For this reason, incubation of the excitatory effects of DSs that signal drug availability, not yet examined in preclinical studies, could be relevant to relapse prevention. We trained rats to self-administer cocaine (or palatable food) under DS control, then investigated DS-controlled incubation of craving, in the absence of drug-paired CSs. DS-controlled cocaine (but not palatable food) seeking incubated over 60 days of abstinence and persisted up to 300 days. We then used microinjections of a GABA receptor agonist cocktail (0.3 nmol/side baclofen + 0.03 nmol/side muscimol) to suppress activity in sub-regions of the prefrontal cortex and found that injections into the infralimbic cortex reduced DS-controlled drug
seeking during the day 21 relapse test session but not DS-controlled drug-taking during training. In contrast, microinjections of the selective D1 receptor antagonist SCH39166 (1μg/side) into either the prelimbic or infralimbic cortex had no effect during either DS-controlled cocaine-taking or cocaine seeking. This suggests that incubation of DS-controlled drug seeking is mediated in part by infralimbic cortex in a D1-independent manner. We are currently using in vivo calcium imaging in awake behaving rats to record neuronal activity in infralimbic cortex during multiple days of discriminated cocaine self-administration in our trial-based procedure. Using these longitudinal recordings, we can identify distinct neuronal ensembles activated during presentation of discriminative stimuli that predict cocaine reward availability/omission within the same animal and understand how these maladaptive learned associations lead to persistent cocaine seeking in these animals several months after their last cocaine exposure. This work was supported by NIDA/NIH.

**ALCOHOL-CUE REACTIVITY IN MICE IS MAINTAINED BY A PERSISTENT CORTICAL ENGRAM**
Michel Vanden Oever (VU Amsterdam, The Netherlands)

In patients with alcohol use disorder, alcohol-associated environmental cues can evoke strong urges to consume alcohol, even after prolonged periods of abstinence. Therefore, it is crucial to understand how such learned associations are stored and retrieved by the brain. Human and preclinical animal models point to an important role of the medial prefrontal cortex (mPFC) in cue-induced relapse to alcohol seeking, but whether and how the mPFC is involved in the long-term storage of alcohol-cue associations is yet unknown. Recent studies indicate that conditioned behavior is encoded and expressed through the activity of sparsely distributed neurons, referred to as engram cells, in relevant brain regions. Here, we investigated in mice whether mPFC neurons that are activated during cue-paired alcohol consumption are subsequently required for cue-induced relapse after prolonged (>3 weeks) abstinence. For this, we used a viral-TRAP approach to express hM4Di (an inhibitory DREADD) in mPFC neurons that were activated during a final operant alcohol self-administration (SA) session. We found that viral-TRAP tagged a small percentage (~6-7%) of mPFC neurons that were activated during alcohol SA and selective chemogenetic suppression of these neurons one month later attenuated cue-induced relapse to alcohol seeking. Notably, chemogenetic suppression of mPFC neurons activated by exposure to a novel context or a sucrose self-administration session did not affect cue-induced reinstatement. We conclude that the mPFC neurons activated during cue-paired alcohol consumption function as a persistent engram that maintains cue-reactivity long after cessation of alcohol intake.

**Symposium 8**
**Novel pharmacological approaches toward remediating negative symptoms in schizophrenia**

**PRECLINICAL STUDIES SUPPORT EFFICACY OF ATYPICAL ANTIPSYCHOTIC DRUGS AND IDENTIFY PHARMACOLOGIC TARGETS FOR TREATING NEGATIVE SYMPTOMS IN SCHIZOPHRENIA**
Herbert Meltzer (Northwestern University, USA)

Negative symptoms, positive symptoms, and cognitive impairment (CI) are the three core domains of psychopathology in patients with schizophrenia. Each consist of specific symptoms which vary in severity and response to treatment, based upon differences in underlying brain processes, genetic and epigenetic patient differences, and environmental interactions. It is commonly stated that there are no effective treatments of negative symptoms. This is not true, the result of failure to appreciate that many patients with schizophrenia do show treatment related improvement in cognition or negative symptoms during treatment with atypical antipsychotic drugs (APDs). Poor clinical trial design and execution, e.g. the CATIE study, has led to negative results. Unwillingness to focus on subgroups who respond well, in some but not all types of CI and negative symptoms, has been a major problem. To test whether the atypical APDs are effective to treat negative symptoms, we have utilized animal models, accepting that they may relate only to a portion of the patients with schizophrenia and, even within them, not all types of negative symptoms of cognitive domain.
Treatment of rodents with phencyclidine, an NMDAR antagonist, for 7 days followed by withdrawal leads to indefinite deficits in social interaction (SI), as well as deficits in novel object recognition (NOR), a type of episodic memory, and other types of CI, e.g. working memory and executive function. A variety of mechanisms have been shown by us, and others, to be effective in restoring SI and NOR in scPCP-treated mice, suggesting a common mechanism for SI and CI. Effective treatments include many AAPDe.g. aripiprazole, blonanserin, clozapine, lurasidone, olanzapine, risperidone and RP5063. These are all serotonin (5-HT)\(\text{2A}\) inverse agonists. This effect, along with weak dopamine (DA) \(\text{D}_2\) receptor blockade, and direct and indirect effects on other neurotransmitters, contributes to their ability to stimulate dopamine (DA), 5-HT, and, in some cases, acetylcholine and glutamate release in cortical regions and hippocampus. Their effect on 5-HT\(\text{1A}\), 5-HT\(\text{7}\) and 5-HT\(\text{2C}\) receptors can be shown to contribute to their efficacy, as well as effects on GABA receptors. The selective 5-HT\(\text{2A}\) inverse agonist, pimavanserin, is ineffective to restore SI, but potentiated subeffective doses of aripiprazole in scPCP mice. Clinical trials of pimavanserin for negative symptoms are in progress. Enhancing GABAergic activity with the GABA\(\text{A}\) agonist, TPA023, and other GABAergic drugs with diverse and complicated mechanisms of actions, were also effective to improve SI and NOR. Several novel 5-HT\(\text{2C}\) agonists improved both SI and NOR in scPCP mice, although data with rats overexpressing striatal \(\text{D}_2\) receptors led others to the conclusion that 5-HT\(\text{2C}\) antagonism was the appropriate target for negative symptoms. We will present some preliminary data with CaMKII heterozygote knock out mice, another model of schizophrenia, which will illustrate the heterogeneity mechanism. In general, drug effects on negative symptoms and CI are congruent. Taken together, these results are promising that multiple treatments for negative symptoms are possible, particularly ones which augment AAPDs.

Clinical trials of these mechanisms must consider heterogeneity in schizophrenia and interactions with other psychotropic drugs.

**AFFECTIVE BIASES AND REWARD AND THEIR POTENTIAL RELEVANCE TO NEGATIVE AFFECT AND PSYCHIATRIC SYMPTOMS IN HUMANS**

Emma Robinson (University of Bristol, UK)

Loss of interest in previously rewarding activities is a common symptom seen in psychiatry particularly in patients with major depressive disorder or schizophrenia. Conventional approaches to modelling these reward deficits in rodents have mainly focused on consummatory and motivational aspects of food rewards e.g. sucrose preference test and progressive ratio tasks. However, there is limited evidence to support the validity of these approaches across disease models. In putative models of depression only those generated through exposure to chronic stress produce reliable deficits and few studies have found impairments in models of schizophrenia. Our research has focused on more cognitive aspects of reward processing and specifically how affective biases might modulate reward-related behaviour. Affective biases (the process, whereby cognitive processes are modified by emotional state) have been shown to influence many cognitive domains and recently have been observed in several non-human species. This talk will focus on our affective bias test which measures biases in reward learning and memory. We have shown that acute pharmacological or psychosocial manipulations induce either positive or negative biases consistent with their predicted impact on an animal’s affective state. I will also discuss recent work using a modified affective bias test. In this task animals undergo independent associative learning sessions with different values of reward. When subsequently tested in a preference test, normal animals exhibit a reward-induced positive biases, making more choices for the cue associated with the higher value reward. However, when the same task is run in either models of depression or schizophrenia the reward induced bias is lost. Importantly, these effects were distinct from any effects on reward sensitivity or motivation. We suggest that cognitive aspects of reward processing, as measured in this task, may be particularly relevant to psychiatric disorders including anhedonia in MDD and negative symptoms in schizophrenia.

**STIMULATION OF ALPHA 7 NICOTINIC ACETYLCHOLINE RECEPTORS AMELIORATES SOCIAL WITHDRAWAL IN RAT MODELS OF SCHIZOPHRENIA**

Agnieszka Nikiforuk (Institute of Pharmacology Polish Academy of Sciences, Poland)
Perturbations to social functioning, such as social withdrawal or asociality, represent a key item of the cluster of negative symptoms of schizophrenia. Social deficits may also be modelled in preclinical paradigms. Specifically, rodents exhibit structured and stable social behaviour patterns connected to well-defined biological functions that can be assessed in laboratory rats using the social interaction test. The social behaviour of pairs of rats in the open field arena may represent an ethologically valid approach for the preclinical assessment of social functions. Negative symptoms are an important target for therapeutic intervention in schizophrenia because the efficacy of currently used antipsychotics remains equivocal. One of the promising strategies is based on the activation of alpha 7 nicotinic acetylcholine receptors (α7-nAChRs). The activity of α7-nAChRs can be modulated through either orthosteric agonists or positive allosteric modulators (PAMs). α7-nAChR PAMs might offer several advantages over the direct agonist approach, as the PAM-induced activation of α7-nAChR occurs exclusively in the presence of an endogenous agonist, thereby preserving the temporal integrity of neurotransmission. Therefore, we examined the ability α7-nAChR PAMs to reverse social deficits in a pharmacological model based on the administration of the NMDA receptor antagonist ketamine and in a neurodevelopmental model based on the prenatal injection of methylazoxymethanolaceta (MAM) to rats. The results of the present study demonstrated the preclinical efficacy of α7-nAChR PAMs against the social withdrawal aspects relevant to schizophrenia. This study was supported by the Polish National Science Centre (NCN) Grant No 2016/23/B/NZ7/01131.

INCREASING ORBITOFRONTAL CORTICAL GLUTAMATE ACTIVITY IN RATS IMPAIRS PROBABILISTIC REVERSAL LEARNING BY DISRUPTING INFORMATIVE OUTCOME EVALUATION
Mark Geyer (University of California San Diego, USA)

Value-based decision-making is a multidimensional construct that is impaired in several psychiatric disorders. Understanding relevant mechanisms may identify novel strategies to treat these impairments. The ability to appropriately integrate feedback to update value representations in an unpredictable environment is essential for value-based decision-making and can be evaluated in the Probabilistic Reversal Learning (PRL) task. The PRL task requires the discrimination of target and non-target stimuli that reverse upon identification. Because responses sometimes generate misleading negative or positive feedback, the ability to appropriately use informative feedback while ignoring misleading is required for optimal performance. The orbitofrontal cortex (OFC) mediates processes necessary for PRL performance and is impacted in several psychiatric disorders. We assessed how alterations in OFC glutamate transmission influenced PRL performance to identify mechanisms that may be disrupted in disorders associated with PRL impairments.

First, we optogenetically activated OFC glutamate neurons in adult male Wistar rats performing a PRL task. Stimulation was delivered during either informative or misleading feedback. Second, glutamate neuron activity was measured with fiber photometry to study normative OFC responses during PRL performance. Stimulating OFC glutamate transmission during informative feedback evaluation impaired PRL performance. Rats completed fewer reversals, required more trials to reach criterion, and displayed a selective deficit in Win-Stay responding. Fiber photometry revealed that OFC activity was greater for target responses vs. non-target responses; this effect was evident despite contingency reversals. This change in OFC activity was correlated with Win-Stay responding. These findings demonstrate that abnormal elevations in OFC glutamate transmission during feedback evaluation disrupt value-based decision-making, due to decreased reward sensitivity and increased exploration of alternative options. Since disruptions in cortical activity are seen in many psychiatric disorders, these findings support the hypothesis that pharmacological strategies to normalize task-relevant modulation of OFC glutamate activity may ameliorate impairments in value-based decision-making in mental illness.

Symposium 9
Reward, stress and effort in food related decision-making

GHRELIN SIGNALLING IN THE GUT-BRAIN-AXIS AT THE INTERFACE OF
HOMEOSTATIC APPETITE AND FOOD REWARD
Harriët Schellekens (University College Cork, Ireland)

The ghrelinergic system, comprising of the neuroendocrine peptide, ghrelin, and its receptor, the growth hormone secretagogue receptor (GHSR-1a), have been steadily investigated as therapeutic targets in the treatment of metabolic disorders and the central modulation of food intake, motivation, reward and mood. It is becoming increasingly clear that ghrelinergic signalling has both unexpected and unexploited complexities in its pharmacology, including high constitutive activity, signalling bias and functional selectivity, which have likely been hindering the development of successful GHSR-1a targeting molecules to market. Here, we characterize the in vitro downstream signalling of 2 novel synthetic GHSR-1a ligands, Anamorelin and HM01, and demonstrate their potent effects on food intake. We demonstrate a novel divergent activation of central reward circuitry and behavioural effects in food intake and reward paradigms. Furthermore, we also demonstrate for the first time, the ability of gut microbiota-derived short-chain fatty acids (SCFAs) and bacteria-derived metabolites to modulate GHSR-1a signalling, highlighting a novel concept of microbiota-metabolite driven modulation of appetite and hedonic and motivational drive for food reward.

SENSORY DETECTION OF A FAMILIAR PALATABLE FOOD INDUCES FOOD-SEEKING BEHAVIOUR, GHRELIN RELEASE, OVER-EATING OF CHOW AND NEURONAL ACTIVATION IN THE ARCUATE NUCLEUS IN RATS
Marie Le May (University of Gothenburg, Sweden)

Environmental cues indicating food availability are ubiquitous and motivate eating beyond metabolic need. We sought to explore the impact of chronic exposure to a palatable food odour cue on behaviours important for over-consumption, with a view to exploring the neural mechanisms involved, including the possible engagement of the orexigenic ghrelin system. We evaluated whether such odour cues influence (a) over-eating of regular chow, (b) ghrelin release, (c) motivation for food and (d) neuronal activity in the arcuate nucleus (Arc) of the hypothalamus. We found that the sensory detection of a palatable food (peanut butter, PBu) did not affect chow intake in rats that were naïve to its taste. However, when PBu-familiar, sated rats were exposed to PBu odour, chow intake was enhanced both acutely and in the long-term (up to 12 h). Likewise, PBu-familiar mice also over-ate chow acutely whilst being exposed to the PBu odour cue. Plasma ghrelin levels (known to be high in fasted animals) could be further increased by the familiar PBu odour. Notably, PBu-familiar but not PBu-naïve rats, showed increased incentive salience when tested in a PBu-odour baited open field. We identified the Arc as an area of striking neuronal activation upon sensory detection of PBu in familiar sated rats. These data underline a key role of the ghrelin system in mediating cue-inducing over-eating. We conclude that, under a positive nutritional state, the sensory detection of a (familiar) palatable food-linked cue activates endocrine and neuronal responses in brain areas linked to the control of food intake. Research supported by Vetenskapsrådet (2016-02195) and Hjärnfonden (FO2017-0180; FO2018-0262; FO2019-0086).

LEPTIN TARGETS VTA AND LH GABA NEURONS TO REDUCE DOPAMINERGIC DRIVE TOWARD FOOD REWARD
Roger Adan (University Medical Center Utrecht, The Netherlands)

Leptin reduces the motivation to obtain food by modulating the activity of the mesolimbic dopamine (DA) system. Given the presence of leptin receptors (LepR) on ventral tegmental area (VTA) DA neurons, it is generally assumed that these effects are direct, but we find that leptin depolarizes LepR-expressing gamma-aminobutyric acid (GABA) neurons in the VTA and hyperpolarizes LepR-expressing neurons in the lateral hypothalamus (LH) that synapse onto VTA GABA neurons. Activation of VTA LepR neurons reduces the motivation to lever press for a sucrose reward in food-restricted mice, whereas activation of LH LepR neurons conversely increases this motivational response, likely by decreasing VTA GABAergic input onto VTA dopamine neurons. Thus, we identify neurocircuitry through which leptin targets multiple inputs to the dopamine system to reduce food reward seeking. Targeting these cell types provides a strategy to suppress the temptation to give in to cues that drive overconsumption.
The mesolimbic dopamine (DA) system plays a critical role in aspects of motivation such as behavioural activation and effort-based decision-making. DA depletion has been shown to induce anergia in effort-based decision tasks. DA has been implicated in food motivation, especially in food seeking behavior. It has been demonstrated that DA impairments only affect food consumption if effort and vigor are determinants of the decision to choose between different behavioral options leading to food. Caffeine, the most consumed psychostimulant in the world, has been reported to affect appetite. Caffeine acts as a non-selective adenosine receptor antagonist (A1/A2Areceptors). There is a functional interaction between and co-localization of adenosine and DA receptors in striatum. In the present series of experiments, we evaluate the effects of DA depletion and antagonism on food consumption under conditions that require effort-based decision making. In addition, we study how caffeine, other adenosine antagonists, or adenosine receptor deletion can improve the behavioral activation that is required to obtain food with no changes in food consumption when no effort is required. CD1 male adult mice received DA antagonists or DA depleting agents to induce anergia and they were evaluated in two different tasks; one that lead to reduction of food consumption (T-maze barrier task), and another one that lead to increases in food consumption (T-maze-RW task). Caffeine and selective A2A adenosine antagonists did not change appetite, but were able to reverse the anergia induced by DA antagonism and depletion, with no effect on free food intake. These behavioral effects were parallel to changes in DARPP32 synthesis and phosphorylation, suggesting a functional adenosine-DA interaction at the receptor level in nucleus accumbens that modulates motivational processes.

Symposium 10
Putting the effort in: translational models of the allocation and application of effort and its role in psychiatric illness

NEURAL SYSTEMS UNDERLYING THE EVALUATION VERSUS EMPLOYMENT OF COGNITIVE EFFORT IN RATS
Catharine Winstanley (University of British Columbia, Canada)

The degree to which we are willing to select options that require more cognitive effort but which have the potential to lead to greater rewards has far-reaching consequences for our economic and personal success. However, relatively little is known regarding the neurobiology governing the adjudication and application of cognitive effort in the decision-making process. We therefore developed a decision-making paradigm for rats which requires animals to choose between two options that differ in the degree of cognitive effort required to attain success. In this rat cognitive effort task (rCET), animals decide at the start of each trial whether to perform an easy or difficult attentional challenge. In the easy condition, rats must correctly localize a visuospatial target which is illuminated for 1.0s, whereas on hard trials, the target is only presented for 0.2s. Hard trials are therefore more attentionally demanding, but accurate performance is rewarded with double the number of sugar pellets. We have observed that rats differ dramatically in their preference for the hard option, independent of their attentional ability, leading to their classification as either “workers” or “slackers”. Through a series of pharmacological inactivation experiments, we have begun to characterize a network of regions within the affective corticostriatal loop that are involved in determining choice. Collectively, these studies indicate that the evaluation versus employment of cognitive effort are regulated by somewhat unique and dissociable neurobiological mechanisms.

TRANSLATIONAL STUDIES ON EFFORTFUL MOTIVATION IN SCHIZOPHRENIA AND BIPOLAR DISORDER
Jared Young (University of California San Diego, USA)
People with psychiatric conditions exhibit abnormal effortful motivational (EM). The quantification of such deficits have been problematic, but recent efforts have identified potential tests, e.g., the progressive ratio breakpoint test (PRBT).

We demonstrated that deficits in EM in patients with schizophrenia account for 24% of variance of their global cognition scores (Bismark et al 2017). We recently discovered that patients with bipolar disorder (BD) without symptoms of depression exhibit elevated EM as measured by the PRBT, relative to healthy participants (HC; F(1,77)=3.7, p<0.05). Reducing expression of Specificity protein 4 (Sp4) reduced the EM of mice (Young et al 2015), while reducing dopamine transporter (DAT) expression elevated EM in mice (Young et al 2019).

Hence, psychiatric populations exhibit altered levels of EM, the direction of which can be modeled in mice identifying potential underlying mechanisms. The link between these models remain unidirectional however. Developing biomarkers of performance remain vital. We recently developed EEG-markers of performance of both the PRBT and an effortful decision-making task, the Cognitive Effort Task (CET). We discovered that both humans and mice exhibit elevated posterior alpha power as they begin to give up in the PRBT. Interesting for the CET, we observed heightened delta power in those likely to choose easy vs. hard choices, AKA 'slackers' vs. 'workers'.

This work affirms that differential levels of EM can be quantified in psychiatric populations, with patients with schizophrenia and BD exhibiting opposite profiles. Reducing Sp4 and DAT recreate EM profiles of the patient populations respectively. Determining whether these differences are reflected in altered EEG biomarkers, and confirming consistency of biomarkers differences in the models, will greatly support their translational relevance. Thus, the development of future therapies from these models will have increased chance for translatability into patient populations.

**DOPAMINERGIC MODULATION OF THE COSTS OF COGNITION**
Roshan Cools (Donders Institute, The Netherlands)

Recent advances in the human neuroscience of cost/benefit decision making about cognitive control will be reviewed. Evidence will be summarized from pharmacological PET and fMRI studies showing that catecholaminergic ‘smart’ drugs, like methylphenidate, have paradoxical effects on human cognitive control, depending on task demands and individual differences in the baseline dopamine levels. For example, she will show that both methylphenidate enhances or undermines the willingness to exert cognitive control, depending on baseline dopamine synthesis capacity, trait impulsivity and the nature of the cognitive cost.

**DOPAMINE, DEPRESSION, AND DRUG DEVELOPMENT: NOVEL ATYPICAL DOPAMINE TRANSPORT INHIBITORS IN ANIMAL MODELS OF MOTIVATIONAL DYSFUNCTION**
Renee Rotolo (University of Connecticut, USA)

Individuals diagnosed with depression and other psychiatric disorders often suffer from fatigue, anergia, and motivational dysfunctions, which are among the most difficult symptoms to treat. Animal studies have been developed to measure effort-related decision making, offering animals a choice between high effort instrumental actions leading to highly valued reinforcers, or low effort/low reward options. A low effort bias can be induced in animals by administration of the vesicular monoamine transport (VMAT-2) inhibitor tetrabenazine, which induces depressive symptoms in people, or by injections of pro-inflammatory cytokines such as IL-1β to provide an inflammatory challenge. Previous studies have shown that dopamine (DA) transport inhibitors, including GBR12909, lisexamfetamine, methylphenidate, and PRX-14040, can reverse the effort-related effects of tetrabenazine. Because many drugs that block DA transport (DAT) act as major stimulants and produce a number of undesirable side effects including psychotic symptoms and abuse liability, there is a need to develop and characterize novel atypical DAT inhibitors with unique binding profiles. The present studies focused on the recently synthesized atypical DAT inhibitors, CT-5404 and (S)-CE-123. These compounds bind to DAT with high selectivity relative to the serotonin and norepinephrine transporters, and can elevate extracellular levels of DA as measured by microdialysis without stimulating DA release. In the present studies, these drugs were assessed for their ability to reverse the effort-related motivational effects of tetrabenazine when co-administered during a fixed ratio 5/chow feeding choice test. Tetrabenazine (1.0 mg/kg) shifted choice behavior, decreasing lever pressing and
increasing chow intake. Co-administration with either CT-5404 (15.0-30.0 mg/kg PO) or (S)-CE-123 (24.0 mg/kg IP) reversed TBZ-induced impairments. In addition, CT-5404 (15.0-30.0 mg/kg PO) demonstrated the ability to reverse the effort-related effects of the pro-inflammatory cytokine IL-1β (4.0 µg/kg IP), which significantly reduced lever pressing when administered alone. Studies from our lab have also shown that (S)-CE-123 (24.0 mg/kg IP) significantly increases high-effort lever pressing on a progressive ratio (PROG)/chow feeding choice test. In summary, enhancement of DA transmission by CT-5404 and (S)-CE-123 is able to reverse the effort-related effects of tetrabenazine or the pro-inflammatory cytokine IL-1β and/or increase high-effort responding. Though their neurochemical profile is still not entirely understood, it is possible that atypical DAT blockers offer potential as a new avenue for drug treatment of effort-related motivational dysfunction in humans.

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Symposium 11
Opioids and opioid use disorder: What we know and what we (still) don’t know
HEROIN: FROM INJECTION TO BEHAVIOR
Fernando Boix Escolan (Oslo University Hospital, Norway)

Heroin, with a very low efficacy at the µ-opioid receptor and fast metabolism, can actually be considered a pro-drug. It was believed that morphine was the main active metabolite conveying heroin effects, this last acting as an effective carrier of morphine to the brain. However, preclinical experimental data shows that, with a very short half time of less than half a minute, most of injected heroin is metabolized to 6-acetylmorphine (6-AM) in the blood. After heroin administration, 6-AM is the predominant opioid in blood and brain the first 30 minutes, and only a minor fraction of heroin is directly transferred into the brain. 6-AM is also active at the µ-opioid receptor with an even higher potency and efficacy than morphine. Preclinical data implies that: 1. 6-AM is the active metabolite mediating the early acute effects of heroin; 2. most of the active metabolites, 6-AM and morphine, reaching the brain likely arise from 6-AM in the blood relocating to the brain. However, brain levels of 6-AM are significantly higher after heroin administration than after equimolar doses of this active metabolite. The use of a specific monoclonal antibody raised against 6-AM reveal that the different fractions of heroin following diverse distribution or metabolic pathways can significantly contribute to different behavioral outcomes. Thus, heroin pharmacokinetics is an important factor determining its behavioral effects and addiction potential.

WHAT WE KNOW AND WHAT WE (STILL) DON’T KNOW ABOUT OPIOIDS IN HUMANS
Siri Leknes (University of Oslo, Norway)
The endogenous opioid system is thought to modulate pain, stress and reward across species, including humans. Here, we review the current state of knowledge on opioid modulation of reward in humans, discussing both acute and chronic effects. Drugs acting on the endogenous µ-opioid receptor are associated with euphoria, yet laboratory evidence for such drug-induced pleasure is mixed. Similarly, whilst many studies report that blocking endogenous opioid signaling can reduce responses to rewarding stimuli, people’s affective state typically remains unaltered even with blockade of 90-100% of µ-opioid receptors. These results contrast with reports from recreational and dependent opioid drug users, where opioid-induced euphoria is often reported. Opioid dependence is also associated with anhedonia for non-drug rewards, and it has been debated whether opioid maintenance therapy could normalize sensitivity to non-drug rewards. We will present evidence for intact responsiveness to non-drug rewards in a sample of mothers on opioid maintenance therapy, as well as new data indicating the presence of anhedonia symptoms in chronic pain patients misusing their opioid analgesics.
Efforts at developing pharmacological treatment for drug addiction in the past four decades have substantially rested on unitary models of drug reward and drug addiction, which focus on the ability of all addictive drugs to activate similar mechanisms in the reward centres of the brain. These models have turned a blind eye to the crucial behavioural and neurobiological differences among the various drugs of abuse, and in particular between opioid and psychostimulant drugs. The failure to anticipate, and then to deal with the recent ‘epidemics’ of opioid abuse in certain countries might at least in part be result of this theory-induced blindness. We will briefly highlight recent data indicating that heroin and cocaine have distinct subjective and neurobiological effects. We will then review evidence that the certain environmental settings facilitate the experienced utility (‘liking’) and decision utility (‘wanting’) of heroin but dampen those of cocaine. The opposite in observed in other settings. None of the extant models, and in particular computational models, of drug reward is fully compatible with the results of our studies, as they lack a component mediating substance-specific influences of environmental context on rewarding effects. In closing we will examine what features a model must possess to account for the rewarding effects of drugs in real world contexts.

Symposium 12
Emerging strategies for the treatment of stress-related psychiatric disorders

FK506 BINDING PROTEIN 51 (FKBP51): AN EMERGING THERAPEUTIC TARGET FOR STRESS-RELATED PSYCHIATRIC DISORDERS
Olivia O’Leary (University College Cork, Ireland)

FK506 binding protein 51 (FKBP51) is a co-chaperone protein of the glucorticoid receptor (GR) that regulates GR’s translocation from the cytoplasm to the nucleus. GR-mediated negative feedback of the Hypothalamic-Pituitary-Adrenal axis is frequently disrupted in the stress-related psychiatric disorder, depression, and has been implicated in treatment-resistant depression. Thus, regulators of GR activity are attractive targets for antidepressant drug development. Emerging evidence from clinical and preclinical studies suggest that dis-inhibition of FKBP51 is associated with susceptibility to phenotypes associated with stress-related psychiatric disorders, while inhibition of FKBP51 may increase stress resilience and may have antidepressant-like effects. Here, we present unpublished data on the effects of FKBP51 inhibition on depression-, anxiety- and antidepressant-like behaviour in a mouse model of chronic psychosocial stress, as well as the effects of FKBP51 inhibition on hippocampal neurogenesis and neurite outgrowth, mechanisms previously implicated in antidepressant action.

OPIOID MECHANISMS ASSOCIATED WITH RAPIDLY ACTING ANTIDEPRESSANT DRUGS
Irwin Lucki (Uniformed Services University of the Health Sciences, Maryland, USA)

There is a critical medical need for the development of novel drugs that can rapidly treat symptoms of depression and suicidal ideation. Opioid mechanisms are exciting new targets that regulate brain circuits associated with the behavioral effects of depression, including reward processing and the stress response. Because kappa opioid receptors (KORs) cause dysphoria, reduced signaling at KORs could mediate the antidepressant effects of a number of opioid medications. Buprenorphine, a mu opioid partial agonist and kappa antagonist, has been
shown at low doses to produce rapid antidepressant effects in several clinical studies. Several other opioid medications with effects at mu and kappa opioid receptors (ALKS 5461 and JNJ-67953964) are under investigation in clinical trials for treatment resistant depression. Ketamine is the prototypic rapid acting antidepressant drug, demonstrating rapid antidepressant effects in patients with treatment resistant depression and suicide ideation. Glutamatergic mechanisms are thought to evoke the neural and behavioral changes that can persist for days following ketamine administration. However, a recent clinical study (Williams et al. 2018) has suggested that pretreatment with the opioid receptor antagonist naltrexone prevented the rapid antidepressant effects of ketamine. Moreover, recent preclinical studies modeling the behavioral effects of buprenorphine and ketamine in rodents have provided evidence that opioid receptor mechanisms may be associated with their rapid antidepressant effects in humans.

CANNABIDIOL AS NOVEL ANTIDEPRESSANT DRUG: STATE OF THE ART AND CHALLENGES
Sâmia Joca (Aarhus University, Denmark)

Significant limitations with the currently available antidepressants have inspired research on finding new and more efficient medication to treat depression. Cannabidiol (CBD) is a non-psychotomimetic component isolated from Cannabis sativa which has emerged as a promising novel antidepressant. CBD induces antidepressant-like effect in different animal models and, more recently, we and others have observed both rapid and a sustained antidepressant-like effect in stressed animals treated with CBD. Such effects seem to involve increased Brain Derived Neurotrophic Factor (BDNF) signaling and subsequent increased neuroplastic effects in brain regions important for stress adaptation and depression neurobiology, such as the medial prefrontal cortex and the hippocampus.

CBD has a complex pharmacology, with the ability to interact with multiple neurotransmitter systems involved in depression, including the serotoninergic, glutamatergic, and endocannabinoid systems. It is not yet clear how these mechanisms are integrated to promote the molecular and behavioral effects induced by CBD.

The aim of the talk is to present a comprehensive and critical overview of the current evidence concerning to the antidepressant effects of CBD, including new unpublished results from our group. Finally, challenges and perspectives for future research will be discussed.

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THE ROLE OF CENTRAL PITUITARY ADENYLATE CYCLASE ACTIVATING POLYPEPTIDE (PACAP) SIGNALING IN STRESS AND EMOTION
Sayamwong Hammack (University of Vermont, USA)

Exposure to stressful stimuli has been argued to play an important role in the etiology of anxiety disorders. Consistent with this role, increases in anxiety-like behavior are often observed in rodents repeatedly exposed to environmental stressors. Several brain nuclei have been implicated in coordinating the autonomic, endocrine and behavioral response to stressor exposure, including subregions in the bed nucleus of the stria terminalis (BNST) and hippocampus. BNST activity has been argued to mediate anxiety-like behavioral responding to long-duration anxiogenic stimuli, coordinate autonomic and endocrine stress responses, and also play a critical role in stress-related drug relapse. We will present evidence demonstrating that BNST PACAP and PAC1 receptor activation are critical for the behavioral consequences of stressor exposure, and also describe some of the PAC1-related signaling events mediating this response. Moreover, the hippocampal dentate gyrus (DG) has been implicated in contextual memory processes that may be dysfunctional in stress-related psychopathologies. PAC1 receptor transcript expression is dense in the DG neurons and PACAP fibers project to the inner molecular layer of the DG. Hence, we will present studies characterizing the excitatory response of DG granule cells to exogenous PACAP application, and demonstrate that DG PACAP infusion enhances the expression of conditioned fear. These data corroborate gene association studies showing PACAP dysregulation in several stress-related disorders, including post-traumatic stress disorder, and suggest that the BNST and DG may be critical brain regions mediating these effects. Hence, central PACAP signaling may represent an important target for the prevention and/or treatment of stress-related psychopathology.
**Plenary Lecture**

**HOW NEURONAL CIRCUITS CAN SHAPE “IMMUNE BEHAVIOR”**  
Asya Rolls (Israel Institute of Technology, Israel)

The brain and the immune system share many similarities. They both respond to the external environment and act to restore homeostasis. The brain receives multiple layers of information from the body (e.g., tissue damage, metabolism, temperature), which it can integrate with other sensory and cognitive inputs (e.g., potential threats in the environment, past experiences) to trigger an orchestrated, corrective response. This talk will be focused on the entire organism perspective demonstrating mechanisms whereby these two systems can work in coordination. Specifically, I will demonstrate how brain activity, via targeted sympathetic innervations to immune organs, can orchestrate immune activity and response to cancer and gut inflammation.

**Symposium 13**

**A role for the Insular cortex in Alcohol and Substance Use Addictions?**

**BRAIN MECHANISMS INVOLVING INSULA ASSOCIATED WITH HEAVY ALCOHOL DRINKING AND SEVERITY OF DEPENDENCE IN ALCOHOL USE DISORDERS (AUD)**  
Theodora Duka (School of Psychology, University of Sussex, UK)

In AUD brain function deteriorates, resulting in altered motivation, disturbed emotional processing as well as impaired executive functions. The present report will evaluate the role of Insula in emotional processing in AUD and will examine neurochemical indices in Insula and their association with heavy drinking.

Twenty-nine AUD participants were compared with 31 matched controls in structural and functional magnetic resonance imaging under emotional challenge involving fear recognition in morphs of fearful facial emotional expressions. Lower gray matter volume compared with controls were found in frontal brain areas, including Insula. Under emotional challenge, the strength of neuronal connectivity between Insula and Anterior Cingulate Cortex was lower, whereas between Insula and the Colliculus neuronal cluster was higher in AUD compared to controls.

In a study with twenty-three individuals the implication of compromised insula integrity in AUD was examined. Magnetic resonance spectroscopy (MRS) with voxel and surface-based morphometry (VBM, SBM) were performed to test the hypothesis that the neurochemical and structural properties of the Insula relate to alcohol use. Right mid-Insula glutamate/glutamine (Glx) and total N-acetylaspartate/N-acetyl-aspartylglutamate (TNAA) concentrations were measured. Reduced Insular Glx concentration was associated with increased alcohol compulsions and with greater alcohol use severity. A negative relationship between alcohol use severity and levels of insular gyrification was also observed.

These data taken together indicate that compromised insula integrity is associated with increased alcohol abuse; furthermore as the severity of AUD intensifies insula is being damaged and its functional connectivity under emotional challenges becomes aberrant, with a decrease in integration of neural networks in cortical regions responsible for a top-down emotional regulation, whilst integration of neural networks in sub-cortical regions, underlying a bottom up emotional input, is increased.

Implications for prevention and treatment strategies will be discussed.

**FUNCTIONAL CONNECTIVITY OF THE ANTERIOR INSULA IN ALCOHOLIC PATIENTS AND ALCOHOL-DEPENDENT RATS**  
Giulia Forcellini (CiMec, University of Trento, Italy)

Abnormal resting state functional connectivity, as measured by functional MRI, has been reported in alcohol use disorders (AUD). However, the specific neuronal substrates involved and the functional implications of aberrant connectivity in these patients remain unknown. Here, we investigated functional connectivity in 35 recently detoxified alcohol dependent patients vs 37 healthy controls using a graph theoretical approach. We found region-specific differences in the organization of basal brain networks and of insular-supramarginal cortices in patients
compared to healthy controls, with a strong increase in the centrality of the anterior insula. Abnormal insular connectivity was partially normalized after two weeks of abstinence. We also performed a functional MRI study in Post Dependent rats, an animal model of alcohol dependence. Similarly we found converging evidence of alcohol-induced alterations in functional connectivity of the insular cortex that recovered upon pharmacological treatment with a dopamine D3 receptor antagonist. Taken together, these convergent results suggest that the anterior insula may play a role in alcohol dependence, perhaps in the excessive integration of interoceptive states with decision-making and emotional states. Importantly, our findings suggest that functional connectivity of the insula is a dynamical condition that may be amenable to treatment.

CHEMOCENETIC INTERROGATION OF THE ROLE OF INSULA IN ALCOHOL CONSUMPTION
Petri Hyytia (University of Helsinki, Finland)

The anterior insular cortex plays a key role in the representation of interoceptive effects of drug and natural rewards and their integration with attention, executive function, and emotions, making it a potential target region for intervention to control appetitive behaviours. Here we aimed at elucidating the role of the insula and its efferent projections in alcohol consumption using chemogenetic tools. We expressed excitatory or inhibitory designer receptors (DREADDs) in the anterior insula of alcohol-prefering rats by means of adenovirus mediated gene transfer. Anterior insula stimulation by the excitatory Gq-DREADDs significantly attenuated both alcohol and sucrose consumption, whereas the inhibitory Gi-DREADDs had no effects. To characterize the brain network recruited by chemogenetic insula stimulation we measured brain-wide activation patterns using pharmacological magnetic resonance imaging (phMRI) and c-Fos immunohistochemistry. These methods revealed downstream activation of the posterior insula and medial prefrontal cortex, as well as of the mediodorsal thalamus and amygdala. Next, we targeted the efferent insula projections by expressing FLEX-DREADDs in the insula following injections of retrograde AAV-Cre in the insula projections areas. We showed that stimulation of the insula-nucleus accumbens projection and insula-central amygdala projection increased alcohol intake, whereas inhibition of these projections had no effect. These data suggest that the insula is an important cortical hub in mediating alcohol reward and could be a target for circuit-based therapy.

INCUBATION OF OPIOID CRAVING AFTER ELECTRIC BARRIER-INDUCED VOLUNTARY ABSTINENCE: BEHAVIOR AND CIRCUITS
Yavin Shaham (NIDA/NIH, Baltimore, USA)

In humans, abstinence is often self-imposed, and relapse typically involves a conflict situation in which addicts choose between the desire to experience the drug’s rewarding effects and the adverse consequences of drug seeking. To mimic this human condition, we recently developed a rat model of incubation of oxycodone craving after electric barrier-induced voluntary abstinence. In our studies, we train male and female rats to self-administer oxycodone (0.1 mg/kg/infusion, 6-h/d) for 14 days. We then expose them to either homecage forced abstinence or introduce an electric barrier of increasing intensity (0.1 to 0.4 mA) near the drug-paired lever that causes cessation of oxycodone self-administration (voluntary abstinence). We test the rats for relapse to oxycodone seeking in extinction tests in the absence of shock and drug on abstinence days 1, 15, or 30. In behavioral studies, we found that the time-dependent increase in oxycodone seeking after cessation of drug self-administration (incubation of craving) was stronger after electric barrier-induced voluntary abstinence than after homecage forced abstinence. In the lecture, I will describe results from our initial studies on incubation of drug craving after electric barrier-induced voluntary abstinence in which we used the activity marker Fos, reversible inactivation of discrete brain regions, and a rat fMRI method (a collaboration with Yihong Yang lab, NIDA-IRP) to characterize the circuit mechanisms of incubation of craving after electric barrier-induced voluntary abstinence. Relevant to the topic of the symposium, I will show data on anterior insular cortex neuronal activity during the incubation of craving tests.

Symposium 14
Punishment and aversive decision-making: Basic mechanisms and clinical applications

DISSECTING THE ROLE OF THE VENTRAL HIPPOCAMPUS IN LEARNED APPROACH-AVOIDANCE DECISION MAKING
Rutsuko Ito (University of Toronto Scarborough, Canada)

Approach-avoidance conflict arises in situations in which one encounters stimuli with competing outcomes. Its resolution (approach or avoid) is a form of decision making that is essential for survival and health, and relies on the ability to successfully evaluate the meaning of stimuli/events and consequences of one’s actions. Dysregulated approach-avoidance (AA) decision making is a feature of a range of mental disorders, including addiction and obesity, in which the propensity to approach dominates, and anxiety and depression, in which avoidance tendencies are heightened, highlighting the importance of furthering our understanding of its underlying neural circuit basis.

In this talk, I will present a set of studies that provides evidence for the ventral hippocampus playing a key role in the regulation of AA decision making in rats. I will demonstrate that subfield-specific pharmacological or optogenetic inactivation of the ventral hippocampus leads to differential control over approach-avoidance behaviors when animals are exposed to motivationally bivalent (conflicting) cues. More specifically, inactivation of the CA3 led to an increase in approach tendency, while inactivation of the CA1 led to increased avoidance behavior in the face of a motivational conflict, indicating that the ventral hippocampus exerts bidirectional control over learned approach-avoidance behavior. I will also present some recent fibre photometry work examining neural activity in the ventral CA1 at the point of AA decision making, and the role of the vHPC-nucleus accumbens circuit in AA decision making. These findings have implications for the neural substrates underlying addictive behaviors in which approach tendencies predominate, and implicate the ventral hippocampus as a potential target of therapeutic intervention.

ALCOHOL RELAPSE AFTER PUNISHMENT-IMPOSED ABSTINENCE: BEHAVIOURAL AND NEURONAL MECHANISMS
Nathan Marchant (Amsterdam UMC, Netherlands)

Alcoholics typically abstain because of negative consequences associated with excessive drinking, and exposure to contexts previously associated with alcohol use often triggers relapse. To study the neurobiology of relapse after abstinence imposed by negative consequences, we developed a rat model that uses punishment-induced suppression of alcohol self-administration in a context that differs from the original training context. We used reversible inactivation with muscimol+baclofen to demonstrate that ventral subiculum (vSub) and lateral hypothalamus (LH) are both critical for context-induced relapse to alcohol seeking. We then assessed neuronal activity associated with context-induced relapse by measuring Fos, a marker of neuronal activity. We combined Fos with the retrograde tracer cholera toxin subunit B, to assess activation in neurons various circuits. In rats with CTb injection into LH, we found that context-induced relapse was associated with more Fos+CTb neurons in nucleus accumbens shell (NAc shell) neurons that project to LH. In rats with CTb injection into NAc shell, we found more Fos+CTb neurons in vSub neurons that project to NAc shell. Using chemogenetics we found that selective inhibition of vSub>NAc shell neurons decreased context-induced relapse. Finally, we will discuss the inherent variability in the response to punishment that was observed over these series of experiments. We re-examined the training and punishment data from a large cohort of rats (n = 499) collected throughout these experiments. We found evidence for a bimodal distribution in the response to punishment in alcohol preferring P rats. The implications of this observation will be discussed in reference to prior observations using punishment of other addictive drugs (cocaine and methamphetamine), the potential causes of this phenomenon, and with broader implications for the cause of alcohol and drug addiction in humans.

COMPULSIVE ALCOHOL SEEKING IS ASSOCIATED WITH AN INABILITY TO DISENGAGE DORSOLATERAL-DOPAMINE DEPENDENT CONTROL OVER BEHAVIOR
Chiara Giuliano (University of Cambridge, UK)

For most individuals seeking and taking drugs may be intermittent, but some lose control over their drug use and are unable to stop despite deleterious consequences. Within the theoretical framework that with prolonged drug exposure the shift from voluntary to habitual drug seeking reflects a shift in neural control over foraging to become dependent on the dorsal lateral striatum (DLS), we investigated the contribution of DLS dopamine-dependent mechanisms to the development of compulsive alcohol seeking. Alcohol-preferring P rats, whose phenotype was confirmed through an intermittent 2-bottle choice procedure, were implanted bilaterally with cannulae in the anterior DLS. They were subsequently trained instrumentally on a seeking-taking chained schedule of alcohol reinforcement in which instrumental seeking responses resulted either in the opportunity to respond on a second lever (taking response) resulting in the opportunity to drink alcohol, or in unpredictable mild foot-shock punishment (i.e. probabilistic punishment of seeking). In a subgroup of animals trained under this task, alcohol seeking persisted despite the unpredictable, intermittent delivery of 0.45 mA foot shock punishment, thereby revealing a shock-resistant compulsive alcohol seeking behaviour. The inter-individual differences in the recruitment of DLS-dopamine-dependent control over seeking behaviour were investigated by probing with intra-DLS infusions of the dopamine receptor antagonist, alpha-flupenthixol (5-10-15 μg/side) soon after acquisition of instrumental responses for alcohol, after well-established alcohol seeking behaviour and after the development of punishment-resistant alcohol-seeking. Well-established alcohol-seeking became reliant on DLS-dopamine-dependent mechanisms and predicted which rats developed compulsive alcohol-seeking. Only in compulsive rats did responding remain dependent on aDLS dopamine transmission, whereas non-compulsive rats were able to relinquish this control. The engagement and maintenance of DLS dopaminergic mechanisms may therefore underlie the rigidity of maladaptive alcohol seeking and the vulnerability to compulsive behaviour.

PHASIC ACTIVITY OF BLA NEURONS DURING PAVLOVIAN AND INSTRUMENTAL AVERSIVE LEARNING
Phil Jean-Richard-Dit-Bressel (University of New South Wales, Australia)

Aversive reinforcement, such as delivery of footshock, can have two distinct consequences for learning and behavior. First, it supports learning about its environmental antecedents to imbue such stimuli with the ability to elicit conditioned responses (Pavlovian fear conditioning). Second, it supports learning about its behavioural antecedents and alters the probability that these behaviors will be emitted again in the future (punishment). Basolateral amygdala (BLA) principal neurons are essential to both fear and punishment but whether and how these are differentially encoded in BLA is unknown. We report a novel within-subjects task permitting concurrent assessment of these two different forms of learning in the same animals during the same sessions. We show that animals concurrently learn both Pavlovian and instrumental aversive associations and that these exert contrasting control over behaviour. Then, we use a genetically-encoded calcium indicator expressed in BLA CaMKII neurons to describe the different profiles of BLA neuronal activity associated with these different forms of aversive learning.

Symposium 15
Peripheral mediated changes to motivational salience

LATERAL HABENULA PROJECTING HYPOTHALAMIC NEURONS GOVERN FOOD PREFERENCE IN A LEPTIN DEPENDENT MANNER
Richard O’Connor (Icahn School of Medicine at Mount Sinai, USA)

Obesity rates are on the rise worldwide, resulting in a growing threat to public health. Pharmacotherapies that safely reduce body weight in obesity remain elusive, partially due to our incomplete knowledge of the complex neuronal mechanisms that control food choice (palatable high-calorie versus less palatable low-calorie food). The lateral hypothalamus (LH) is considered a critical node in the maintenance of energy homeostasis and prominently expresses the receptor for leptin, an adipocyte derived anorectic hormone. The development
of obesity in rats is associated with deficits in LH sensitivity to rewarding stimuli, a switch in preference towards palatable calorically dense food items yet a seemingly paradoxical deficit in food-related motivation measured by the willingness of obese rats to deploy instrumental responding to receive food rewards. A major output of the LH terminates in the lateral habenula (LHb) which has been described as a “preference center”. We tested the hypothesis that leptin signaling on LHb innervating LH neurons plays an important role in food-related motivation. We found diphtheria toxin induced ablation of this pathway decreased levels of instrumental responding, and shifted preference towards palatable calorically dense food, phenotypes conspicuously similar to that seen in rats with diet-induced obesity. Interestingly, inhibition of leptin activity in LHb projecting LH neurons of obese rodents led to similar increases in preference for palatable food and rejection of standard chow. Furthermore, electrophysiological recordings revealed obesity induced disruptions to leptin mediated glutamatergic and GABAergic LH innervation of the LHb suggesting the involvement of leptin in communication between the LH and LHb. Based on these findings, we hypothesize that deficits in leptin mediated communication between the LH and LHb may emerge during weight gain contributing to obesity-associated behavioral abnormalities.

TARGETING THE GUT-BRAIN AXIS TO MODIFY Dopamine-DEPENDENT CIRCUITS AND FUNCTIONS IN HUMANS
Dana Small (Yale School of Medicine, USA)

It is becoming increasingly evident that neural signals originating in the periphery convey key information about the nutritive properties of foods to the brain to guide behavior. Recent work in rodents has elucidated a vagal afferent pathway that projects to the midbrain and striatum to regulate dopamine release and reinforcement (Han et al., 2018). A critical physiological role of the pathway is to translate nutritional signals into reinforcing signals to guide ingestive behavior, through flavor nutrient learning and regulating preferences to fat (Tellez et al., 2013). This pathway is also severely blunted in animals maintained on a high fat diet (HFD); an effect that can be reversed by administration of oleoylethanolamide (OEA)(Tellez et al., 2013). Likewise, in humans, HFD can decrease striatal response to fat ingestion and shift fat preference (De Feliceantonio et al., in prep). Work will be presented from a 14-month randomized control trial showing that supplementation with the precursor for OEA compared to placebo, coupled with a behavioral weight loss program, can rescue fat preference, striatal response to fat and produce an 8% decrease in body weight in overweight/obese humans who do, compared to do not, endorse consuming a high fat diet upon study enrolment. These findings suggest that the vagal afferent pathway identified in the rodent model translates to humans and may be a promising target for weight loss in individuals who habitually consume a HFD.

IMPACT OF PERIPHERAL REGULATORS OF ENERGY BALANCE ON THE REWARD SYSTEM
Suzanne Dickson (University of Gothenburg, Sweden)

The brain’s reward system is engaged in food intake, no matter whether this is driven by energy deficit or by the anticipated pleasure of a palatable meal. Human functional resonance imaging studies have revealed that brain pathways involved in (visual) food reward processing are regulated by dietary, hormonal and potentially other energy metabolic signals. The neural substrates engaged include the ventral striatum and rodent studies have shown that the ventral tegmental area is an important target for adiposity signals (such as leptin and insulin) and gut-derived hormones (such as ghrelin, PYY(3-36) and GLP-1). We have shown that the orexigenic hormone ghrelin engages the mesoaccumbal dopamine pathway [1] involved in incentive salience and that this is important for its effects on food motivated behavior [2, 3]. Ghrelin also alters food choice [4], food anticipatory [5] and other behaviours in ways that would lead us to question whether it is only a hunger hormone (for which its release and effects might be expected to be limited to a state of negative energy balance) or whether we should instead be considered an “appetite-stimulating” hormone.

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VISCERAL AND CHEMOSENSORY CONTROLS OF BRAIN REWARD SYSTEMS
Ivan De Araujo (Icahn School of Medicine at Mount Sinai, USA)

The presentation will discuss recent evidence supporting a role for the gut-brain axis in controlling brain circuits involved in reward, emotion and motivation. It will be argued in particular that gut-innervating vagal sensory neurons function as reward neurons. Via asymmetric ascending pathways of vagal origin, gut signals reach brain reward regions via dedicated visceral nuclei in pons. This gut-brain reward axis functions in parallel to an analogous oral cavity-brain reward axis, resulting in a gastrointestinal vs. orosensory topographic organization for food reward within the striatum. The extent to which these findings are mirrored by recent human neuroimaging studies will be also discussed, as well as potential clinical applications including novel targets for stimulation therapies in eating and affective disorders.

Day 4
Saturday 31.08.2019

Plenary Lecture

HOW WE GOT ALCOHOL ADDICTION WRONG: ONE LEVER AT A TIME
Markus Heiling (Linköping University, Sweden)

Alcohol use causes an ongoing public health crisis, and effective treatments are largely lacking. Neurobiological research on alcohol addiction has grown exponentially, and has become increasingly sophisticated in its ability to identify neural circuits behind alcohol seeking and taking in animal models. To date, however, these advances have not translated into novel clinical treatments; while promising candidate therapeutics brought forward by basic science have failed in clinical development.

This talk will discuss emerging limitations of target identification and validation strategies commonly used by our own and other laboratories. These efforts have typically relied on models where drug taking is studied in single reinforcer self-administration models, where responding for alcohol has no other consequences than delivery of the reinforcer, and where behavior is studied at the group level. This is in stark contrast to key features of clinical alcohol addiction: individual variation in vulnerability, choice of alcohol over natural rewards, and continued use of alcohol despite adverse consequences.

These conceptual challenges will be discussed in the context of our recent discoveries implicating impaired GABA transmission in central amygdala (CeA) as a key mechanism behind alcohol choice
and aversion-resistant alcohol seeking. First, in a sub-population of vulnerable rats, excessive GABAergic inhibition is present in CeA due to reduced expression of the GABA-transporter GAT-3, and drives alcohol choice. Second, an overlapping but larger subpopulation is susceptible to aversion-resistant alcohol self-administration; in these rats, activity of a cell population in centrolateral CeA is strongly associated with the behavior, while GABA-ergic manipulations that inhibit the activity of these cells also inhibit aversion-resistant self-administration. Third, an epigenetic enzyme is induced in the amygdala of rats susceptible to aversion-resistant self-administration; in preliminary experiments, blockade of this enzyme selectively rescues the behavior.

**Symposium 16**

**Role of neuroinflammation and glial mechanisms in anxiety and depression: novel therapeutic approaches**

**INVESTIGATING STRESS-INDUCED SUSCEPTIBILITY TO DEPRESSION: ROLE OF NEUROINFLAMMATION IN THE EFFECT OF ANTIDEPRESSANT-TREATMENT**

Raffaella Molteni (University of Milan, Italy)

It is well-known that stressful events during life may expose a subject to the development of stress-related diseases such as major depressive disorder (MDD), a severe psychiatric disease estimated to become the second leading cause of disability in the world by 2020. At molecular level, MDD is characterized by dysfunctions in multiple systems including neurotransmitters, hormones, neurotrophic factors and neuroplastic mediators. Moreover, increasing clinical and preclinical studies indicate that it is also associated with alterations of the immune/inflammatory system.

On this basis, it is important to clarify if the activation of immune/inflammatory system plays a pathogenic role or it represents a merely epiphenomena. To this end, the evaluation of the immune/inflammatory system in experimental MDD models might help to fill this gap. Accordingly, we used the chronic mild stress (CMS) paradigm in the rat to evaluate to what extent the development of a stress-induced anhedonic phenotype is associated with brain inflammation, through molecular analyses in key brain structures for depression. We found that stress exposure increased the levels of pro-inflammatory markers only in the stressed animals that developed anhedonia, but not in those showing resilience, an effect related to the critical role of microglia in vulnerability or resilience to stress response. These alteration were ameliorated by chronic pharmacological treatment with different antidepressants, supporting the idea that immune/inflammatory system may contribute to the subject’s vulnerability for depression and also represent a therapeutic target for more effective antidepressant drugs.

**EVIDENCE FOR AN ALTERED NEUROINFLAMMATORY SYSTEM IN HIGH ANXIETY MICE: UTILITY AS TREATMENT TARGET**

Nicolas Singewald (University of Innsbruck, Austria)

Whilst inflammation has been identified as a contributing factor to stress-induced anxiety, much less is known about potential dysregulation in the inflammatory system in individuals with a genetic predisposition to hyperanxiety. In a mouse model of trait anxiety (HAB), we combined behavioral methods, immunohistochemistry and multiplex immunoassays to reveal potential inflammatory imbalances in brain and plasma respectively, and comparing such parameters to genetically related normal anxiety/depression (NAB) controls.

We identified neuroinflammatory imbalances in anxiety-related brain regions between both groups, which were particularly evident in the dentate gyrus (DG): HAB exhibited significantly increased iba1+, and phagocytically active (CD68+iba1+) microglia densities compared to NAB. Also, average microglia cell size was significantly enhanced in the DG of HAB. In addition, HABs showed alterations in a range of cytokine/chemokine levels in plasma. Chronic oral treatment with the microglia inhibitor minocycline successfully reduced HAB hyperanxiety, which was associated with a significant decrease in the enhanced iba1+ and CD68+ iba1+ cell densities, and average microglia cell size, in the DG; also accompanied by modulation of cytokine levels in HAB plasma. Similar effects on behavior and microglial markers were found by exposing HABs to an environmental enrichment as a positive behavioral intervention.
Taken together, disturbances in the inflammatory system can be observed in an animal model of innate anxiety, even without exposure to stress. We identify the DG as a specific anxiety-relevant brain region where microglia alterations in particular seem to be the most evident. Minocycline reduced hyperanxiety, at least in part via affecting microglial mechanisms in the DG, since local intra-DG minocycline administration also had an anxiolytic-like effect. Thus, inhibiting microglial ‘activation’ could serve as a useful treatment strategy in hyperanxious individuals with an altered neuroinflammatory system. Supported by the Austrian Science Fund (FWF) I 3875-B26, SPIN:W1206-B18, SFB F4410 to NS, DFG WO-1418/6-1 (SAW).

GLIAL PLASTICITY AS A KEY MECHANISM UNDERLYING THE PATHOPHYSIOLOGY OF DEPRESSION
Luisa Pinto (University of Minho, Portugal)

Post-natal neuro and glio-plasticity is largely driven by the transduction of environmental stimuli into essential neuroadaptations. Neuro-glio-plastic maladaptations often result in the manifestation of pathological traits, from which depressive behavior is a paradigmatic example. We are investigating the pathological basis of both physiological and behavioral impairments and their potential epigenetic molecular determinants. It is also our aim to study how depression and antidepressant drugs can modulate epigenetic patterns in key limbic areas and how this impacts in the transduction of their effects. In this talk I will focus on the mechanistic link between neuro- and glio-plasticity and depression, taking into account the dynamic spatio-temporal events that define plasticity and the dichotomy between dorsal and ventral hippocampus. We intend to dissect the molecular cascade leading to neuron-glia/behavioral dysfunction to gain insights into the underpinnings of susceptibility and resilience to depression.

STRESS IMPACT ON MICROGLIA (AND NEURONS): GENDER DIFFERENCES AND BEHAVIORAL IMPLICATIONS
Ana João Rodrigues (University of Minho, Portugal)

Prenatal exposure to stress or glucocorticoids (GC) can induce long-term changes in the brain, and has been associated with increased vulnerability for neuropsychiatric disorders later in life. Microglial cells, considered the immune players of the brain, are responsive to GC and are altered in stress-related disorders. We have been studying a model of in utero exposure to GCs, that presents prominent anxiety and depressive-like behavior. In parallel with these behavioral alterations, we observe long-lasting neuronal molecular, morphological and functional alterations in different brain regions, including the nucleus accumbens, PFC and hippocampus. Importantly, microglia are differentially affected in males and females, and morphological changes are also region-specific. These results show that stress/GC not only affects neurons but also glial cells, raising the need to perform additional studies in order to understand which changes are related to the observed maladaptive behavior.

Symposium 17

The need for weed: Emerging roles of cannabis and cannabinoids in reward-related behaviours

CB1 RECEPTOR-MEDIATED LIMBIC PLASTICITY DURING MEMORY RECONSOLIDATION SHAPES COCAINE MEMORY STRENGTH
Rita Fuchs (Washington State University, USA)

Contextual cocaine memories are maintained over time through a protein synthesis-dependent memory reconsolidation process in the basolateral amygdala (BLA). Here, we investigated the role of cannabinoid receptors type 1 (CB1R) as well as anandamide (AEA) and 2-arachidonoylglycerol (2-AG) signaling in this phenomenon using a context-induced rodent model of drug relapse in combination with pharmacological manipulations, western immunoblotting, whole cell electrophysiological recordings, and radioimmunoassays. We show that systemic
CB1R antagonism during cocaine-memory reconsolidation inhibited context-cocaine memory strength as indicated by a time- and memory retrieval-dependent decrease in subsequent cocaine-seeking behavior in the cocaine-paired context. This effect was associated with CB1R-dependent changes in immediate-early gene expression and glutamate subunit phosphorylation indicative of synaptic maturation and an increase in excitatory input or new synapse formation in the BLA. Remarkably, unlike systemic CB1R antagonism, CB1R antagonism in the BLA during memory reconsolidation enhanced memory strength likely by blocking the effects of 2-AG, but not AEA, signaling on concomitant context-induced HPA axis activation. Importantly, bi-directional manipulations of 2-AG signaling in the BLA had opposite effects on memory strength during memory reconsolidation. Together, these findings suggest that CB1R populations are functionally heterogeneous: CB1Rs in some extra-BLA brain regions facilitate cocaine memory reconsolidation, whereas CB1Rs in the BLA gate changes in the affective salience of cocaine memories so as to effect faithful memory maintenance.

CHEMOGENETIC VENTRAL TEGMENTAL AREA DOPAMINE STIMULATION REVEALS PERSISTENT PREFRONTAL CORTEX ENDOCANNABINOID DISRUPTION AFTER ADOLESCENT CANNABINOID MICRODOSING
Stephen Mahler (University of California Irvine, USA)

Adolescence is a sensitive period for the maturation for brain reward circuits, which are modulated by endocannabinoids (ECBs). We have seen that developmental exposure to exogenous cannabinoid drugs persistently alters motivated behaviors in rats, and alters ECB signaling in reward structures. Yet most adolescent exposure studies to date (including ours) have used moderate to high doses of cannabinoid drugs, which can produce anxiogenic states, or other nonselective effects when administered to adolescent animals. Persistent effects of low doses of cannabinoid drugs, which are reinforcing in adolescents and therefore potentially more relevant to human use, have rarely been tested.

Here we examine persistent changes in endocannabinoid regulation of dopamine circuits, and resulting behavioral changes, caused by reinforcing adolescent cannabinoid drug exposure. In tyrosine hydroxylase:Cre (TH:Cre) rats, we test how repeated adolescent exposure to a rewarding “microdose” of the CB1/2 agonist WIN55,212-2 causes long-lasting changes in mesolimbic ECBs, resulting in altered dopamine-stimulated behavior and neural activity within mesolimbic circuits. Our findings confirm that adolescence is a critical window for development of prefrontal cortex reward circuits, when even small doses of cannabinoid drugs can persistently alter mesolimbic dopamine circuits. These results hold relevance to the mechanisms by which adolescent cannabinoid drug use could facilitate later-life emergence of psychiatric disorders like addiction or schizophrenia.

CB1 SIGNALING MODULATES PAVLOVIAN APPETITIVE PROCESSES IN SIGN-AND GOAL-TRACKING RATS
Donna Calu (University of Maryland, USA)

Endocannabinoids are critical gatekeepers of dopaminergic signaling, and disrupting cannabinoid receptor-1 (CB1) signaling in the Ventral Tegmental Area (VTA) alters dopamine (DA) dynamics to attenuate cue-motivated behaviors. Prior studies suggest that DA release plays a critical role in driving sign-, but not goal-tracking. We first test the prediction that CB1 signaling mediates the attracting properties of a reward predictive lever cue. Here, we trained rats in Pavlovian lever autoshaping prior to systemic rimonabant injections (0, 1, 3 mg/kg) during early and late Pavlovian lever autoshaping test sessions. We show that systemic injections of rimonabant, a CB1 receptor inverse agonist, during Pavlovian lever autoshaping impairs the expression of both sign- and goal-tracking after limited training. With extended training, many previously goal-tracking and intermediate rats shifted to lever approach, which remained dose-dependently sensitive to rimonabant. We find that intra-VTA rimonabant selectively decreases sign, but not goal-tracking early in training, suggesting that endocannabinoids in the VTA specifically mediate sign-tracking. Ongoing studies evaluate the extent to which VTA CB1 signaling is necessary after extended training and after changes to reinforcer value. We also examined whether rimonabant blocks the reinforcing properties of the Pavlovian lever cue in a conditioned reinforcement test. Here, we trained rats in Pavlovian lever autoshaping prior to systemic rimonabant injections (0, 1 mg/kg) during a conditioned
reinforcement test. We find that the inserted lever cue served as a robust conditioned reinforcer after Pavlovian lever autoshaping, and 1 mg/kg rimonabant blocked conditioned reinforcement. Together, our results suggest that CB1 signaling mediates two critical properties of incentive stimuli; their ability to attract and their ability to reinforce behavior.

NEUROADAPTATIONS AND BEHAVIOR IN A RAT MODEL OF DELTA-9- TETRAHYDROCANNABINOL + CANNABIDIOL USE
Sade Spencer (University of Minnesota, USA)

Internationally there is a push toward legislation to legalize cannabis, the most widely used “illicit” drug in the world. Thus, as drug availability increases it is vital to understand the long-term effects of cannabinoids on the brain. A preponderance of the evidence suggests that chronic cannabinoid use can produce lasting impacts on brain structure and function. The current study was designed to determine whether self-administration of the primary psychoactive component of cannabis, delta-9-tetrahydrocannabinol (THC) produces neuroadaptations akin to other classically abused drugs that converge upon the glutamatergic system in the adult brain. Adult male rats were trained to self-administer THC in combination with cannabidiol (CBD) in a 10:1 THC:CBD ratio on a short access FR1 schedule for (10-20 days) followed by extinction (7-21 days). Self-administration and extinction of THC produced enduring adaptations in the nucleus accumbens core associated with altered glutamatergic transmission including decreased dendritic spine density of accumbens medium spiny neurons and loss of NMDAR-LTD. Following extinction rats reinstated to THC-conditioned cues, and this reinstatement could be blocked by administration of n-acetylcysteine (NAC), an anti-oxidant glutathione precursor, or a matrix metalloproteinase (MMP) inhibitor. NAC is an anti-inflammatory compound that has been shown to work, at least in part, through augmenting the expression of the glial glutamate transporter GLT-1. GLT-1 expression and function is down-regulated by many drugs of abuse. NAC also inhibits MMP-2 and MMP-9 from the gelatinase family. We probed for changes in GLT-1 expression/function as well as MMP activity in nucleus accumbens following THC self-administration. Surprisingly, the expected changes were not observed. These results suggest that THC may be at least partially mechanistically different from other drugs we have investigated. This work was funded by NIH grants DA003906, DA012513, DA015369, DA037722, DA016511, GM072643, DoD grant W81XWH-13-2-0075 and a Burroughs Wellcome Fund postdoctoral enrichment grant.

Symposium 18
Brain circuits of prosocial behavior

EVALUATING THE PROSOCIAL POTENTIAL OF OPIOID AND OXYTOCIN DRUGS IN HUMANS
Siri Leknes (University of Oslo, Norway)

Pharmacological manipulation of the oxytocin and opioid systems in non-human animals can have powerful effects on affiliative behaviours. For instance, mice genetically engineered to lack mu-opioid receptors fail to develop a preference for their mother as pups. Similarly, oxytocin blockade can prevent bond formation between mothers and their offspring across several species. Here, I will critically review the state of the evidence for oxytocin and opioid modulation of affiliation in humans. Current knowledge largely stems from psychopharmacological studies in healthy adults. We lack of an oxytocin antagonist suitable for human use; results from intranasal oxytocin studies show modest or no effects on measures related to affiliation. The opioid literature on human bonding is still limited. I will argue that different and more naturalistic paradigms may be more suited to tease out the contributions of opioids and oxytocin for human affiliation.

THE ROLE OF THE ACC IN EMOTIONAL CONTAGION AND HARM AVERSION (PART OF SYMPOSIUM 'BRAIN CIRCUITS OF PROSOCIAL BEHAVIOR
Christian Keysers (Netherlands Institute for Neuroscience, University of Amsterdam, Netherlands)

Human fMRI studies have long evidenced that the ACC is activated both during the experience and observation of pain. This has led to speculations, that the ACC contains mirror neurons for
pain, and is causally involved in emotional contagion and prosocial motivation. I will present recent work we have conducted in rats to show (i) that the ACC indeed contains pain mirror neurons, (ii) that deactivating the ACC reduces emotional contagion and (iii) reduces the motivation to move away from behaviors that harm others.

SOCIAL DECISION MAKING IN RATS
Marijn van Wingerden (Heinrich Heine University Duesseldorf, Germany)

Rats are highly social animals living in large groups characterized by hierarchies, with a rich and complex social behavior repertoire. In the lab, rats have been shown to act pro-socially and perform helping behavior. These results seem to suggest that rats place a value on the well-being of, or outcomes delivered to their peers. If so, this process of social valuation should be observable in tasks sensitive to value estimation and manipulation. We aimed to quantify these social preferences with a range of behavioral paradigms. Adapting the 3-chambered social maze, we examined and quantified rats' social preferences when choosing to spend time investigating a conspecific or a non-social outcome, equating one in terms of the other. Using reinforcement learning paradigms, we examined whether social value can unblock learning about cues that predict reward delivery to others. We have found that, indeed, rats act as if trading off social reward and non-social reward based on their relative appetitive strength. Furthermore, we have found that social outcomes can unblock reinforcement learning, suggesting that rats process social value as valuable to themselves. Rats in these paradigms emit ultrasonic vocalisations (USVs), a prime candidate signal for transmitting social value. Playback of USVs results in Dopamine (DA) release, making the dopamine-producing cells in the VTA, that are involved in socially motivated (reward) seeking behavior in turn a candidate for representing such value signal. Using single-cell electrophysiology, we recorded activity from VTA-DA producing cells during playback of USV and indeed found a subset of cells responding differentially to the valence of the USV playback. For the automated detection of USVs, we have employed machine-learning approaches that can differentiate between USVs and noise with high accuracy.

FUNCTION OF SEX DIFFERENCES IN THE BRAIN FOR SOCIAL BEHAVIOR: INSIGHTS FROM VASOPRESSIN AND OXYTOCIN
Alexa Veenema (Michigan State University, USA)

Sex differences in the brain are highly prevalent, yet, we know little about their impact on behavior. For example, the sex difference in vasopressin (AVP) fiber projections from the medial amygdala (MeA) and bed nucleus of the stria terminalis (BNST) to the lateral septum (LS) is one of the best-characterized sex differences in the vertebrate brain. Yet, little is known about its functional consequences. We recently demonstrated that this sex difference is already present at juvenile age in rats, suggesting a sex-specific role of the MeA/BNST-to-LS AVP pathway across the lifespan. In support, we showed that the LS-AVP system regulates juvenile social play behavior in sex-specific ways. In detail, pharmacological blockade of AVP 1a receptors (V1aR) enhances social play in males but reduces it in females. We further demonstrated that dopamine neurotransmission is involved in the sex-specific regulation of social play by the LS-AVP system. In contrast to AVP, we found no sex differences in oxytocin (OXT) fiber projections in forebrain regions encompassing the social behavior network. However, robust sex differences were found in OXT receptor (OTR) binding density in the MeA and BNST of rats across the lifespan, with denser OTR binding in males. This sex difference was associated with a sex difference in extracellular BNST-OXT release during exposure of adult rats to a social encounter. Finally, OXT administered into the BNST prolonged social recognition in male rats but not in female rats. Overall, these findings demonstrate that sex differences in both the AVP and OXT systems have functional implications for the sex-specific regulation of social behaviors across the lifespan. These findings may be informative for the evaluation of AVP and OXT as potential therapeutic targets in the treatment of social dysfunction in sex-biased and early onset neuropsychiatric disorders. Supported by NIH R01MH102456 and NSF IOS1253386.
**Symposium 19**

**Novel opioid agonist-based medications for pain and opioid addiction**

**EFFECTIVENESS OF G-PROTEIN BIASED MU-OPIOID RECEPTOR AGONISTS TO ATTENUATE OPIOID-VS-FOOD CHOICE IN OPIOID-DEPENDENT ANIMALS**

Drew Townsend (VCU, USA)

**Background:** The only U.S. Food and Drug Administration-approved medication for the treatment of Opioid Use Disorder for highly opioid dependent patients is the mu opioid receptor (MOR) agonist methadone. However, methadone can produce undesirable effects such as respiratory depression. Emerging evidence suggest that G-protein biased MOR agonists may retain the desirable effects of MOR agonists while lessening undesirable effects. The aim of this ongoing study is to determine the potency and effectiveness of the G-protein biased MOR agonist oliceridine to produce antinociception, respiratory depression, and prevention of withdrawal-associated increases in opioid choice (WIOC).

**Methods:** The potency of oliceridine to produce thermal antinociception and decreases in blood oxygen saturation was initially determined in three male rhesus monkeys. Three other adult male rhesus monkeys were trained to respond under an intravenous heroin vs. food choice procedure (2h/day). Opioid dependence will be induced by providing supplemental heroin access during 21h/day self-administration sessions. Spontaneous opioid withdrawal will be achieved by omitting supplemental heroin access. Oliceridine, methadone, and saline will be administered during this abstinence period.

**Results:** Oliceridine produced dose- and time-dependent thermal antinociception, with 3.2 mg/kg producing near-maximal antinociception for 300 min at the 50°C stimulus. This dose of oliceridine also produced a 25% reduction in blood-oxygen saturation. Under baseline, non-dependent conditions, heroin-maintained a dose-dependent increase in heroin vs. food choice. The evaluation of the effects of oliceridine to block WIOC is ongoing.

**Conclusions:** Antinociception and oxygen-saturation data suggest that oliceridine produces effects typical of high efficacy MOR agonists within these procedures (i.e., antinociception at 54°C and depression of blood-oxygen saturation). The relative potency and effectiveness of oliceridine to produce each behavioral effect will provide empirical evidence regarding the potential clinical utility of G-protein biased MOR agonists as candidate Opioid Use Disorder medications in highly opioid dependent patients.

**MIXED MU OPIOID/NOCICEPTIN RECEPTOR PARTIAL AGONISTS FOR CHRONIC PAIN MANAGEMENT**

Stephen Husbands (Bath U, UK)

The misuse and abuse of prescription opioids poses huge medical and economic burdens to communities around the world. One potential solution that has been proposed is to develop improved analgesics that have partial agonist action at both mu opioid peptide (MOP) and nociceptin/orphanin FQ peptide (NOP) receptors. NOP agonists have been reported to interact with MOP agonists in a synergistic manner in non-human primates (NHP) to produce antinociceptive effects without respiratory depression. Using an understanding of the key pharmacophores required for activity at the two receptors, we have developed compounds (e.g. BU08028 and BU10038) from two chemical series but sharing the desired MOP/NOP partial agonist activity. In both cases this led to robust analgesia in NHPs with greatly improved side-effect profile as compared to standard of care opioids. The lead compound (BU10038) has now been independently evaluated, including in NHPs, and the profile has been confirmed and extended. Thus BU10038 displays significant, long-lasting analgesia in primates at doses >100x lower than morphine and has significant analgesia in models of postoperative and inflammatory pain. BU10038 shows limited tolerance effect on chronic dosing, a significantly improved profile in primate self-administration models andependency studies compared to standard of care opioid analgesics, no constipation or pruritus in preclinical models and no observed respiratory depression and has a promising ADME/safety profile.

That this favourable behavioural profile is exhibited by compounds sharing similar receptor pharmacology, but from different chemical series, and that one of the compounds has been
evaluated in vivo by independent groups, provides strong evidence for the validity of this approach to new analgesics.

**BIFUNCTIONAL AGONISTS TARGETING THE NOCICEPTIN OPIOID RECEPTOR AND MU OPIOID RECEPTOR AS A NEW APPROACH FOR NEXT GENERATION ANALGESICS AND TREATMENTS FOR OPIOID USE DISORDERS**

Nurulain Zaveri (Astraea Therapeutics, USA)

The nociceptin opioid receptor (NOP, previously known as the opioid receptor-like receptor, ORL1) is well known as the 'fourth' opioid receptor, whose endogenous ligand is a heptadecapeptide, nociceptin/orphaninFQ (N/OFQ). N/OFQ and small-molecule NOP agonists have been known to modulate the pharmacology of mu opioid (MOP) agonists in antinociception, reward and tolerance development. In rat neuropathic pain models and in nonhuman primate inflammatory pain assays, intrathecally delivered N/OFQ and NOP agonists are antihyperalgesic, but importantly, also synergistically enhance the antihyperalgesic effects of intrathecal morphine. This synergism is evident without the exacerbation of morphine's adverse effects such as tolerance development, itch or reinforcing effects. On the other hand, N/OFQ and NOP agonists decrease opioid-induced dopamine release in the nucleus accumbens and attenuate morphine conditioned place preference in rodents and self-administration of mu opioids such as alfentanil and morphine in rats and nonhuman primates. Given these functional interactions, we hypothesized and later showed that small-molecule ligands possessing bifunctional agonist efficacy at the NOP and mu opioid receptor demonstrate enhanced antinociception compared to morphine, without opioid adverse effects such as respiratory depression, tolerance and dependence. With an appropriate balance of NOP and MOP agonist efficacy, such bifunctional NOP/MOP agonists also do not show any reinforcing effects, but in fact, decrease the reinforcing effects of opioids. Overall, compounds with bifunctional NOP agonist activity and mu agonist activity have a promising non-addicting analgesic profile, and may provide an innovative solution as next-generation analgesics in the era of the opioid crisis, especially for patients experiencing pain and addiction to prescription opioids.

**IN A RAT MODEL OF OPIOID MAINTENANCE, THE G-PROTEIN MOR BIASED AGONIST TRV130 DECREASES RELAPSE TO OXYCODONE SEEKING AND PREVENTS OXYCODONE-INDUCED BRAIN HYPOXIA**

Jennifer Bossert (NIH/NIDA, USA)

Background: Maintenance treatment with opioid agonists (buprenorphine, methadone) is effective for opioid use disorder (OUD), though it does not entirely eliminate opioid use in all patients. We modeled maintenance treatment in rats that had learned to self-administer oxycodone. The maintenance medication was either buprenorphine or the novel mu opioid receptor (MOR) G-protein biased agonist TRV130. We then tested prevention of relapse to oxycodone seeking using a modified ABA context-induced-reinstatement procedure.

Methods: We trained rats to self-administer oxycodone (6-h/d, 14-d) in context A; infusions were paired with a discrete tone-light cue. We then implanted Alzet osmotic pumps containing buprenorphine or TRV130 (0, 3, 6, or 9 mg/kg/d) and performed three relapse-related tests: (1) lever pressing reinforced by oxycodone-associated discrete cues in non-drug context B, (2) reinstatement of oxycodone seeking induced by reexposure to context A, and (3) reacquisition of oxycodone self-administration in context A. We also tested whether TRV130 maintenance would protect against acute oxycodone-induced decreases in oxygen levels in nucleus accumbens.

Results: Buprenorphine decreased cue-reinforced oxycodone seeking in context B and reacquisition of oxycodone self-administration in context A. TRV130 decreased oxycodone seeking in all three relapse-related measures in male rats, whereas in female rats, TRV130 only decreased cue-reinforced oxycodone seeking in context B. TRV130 also prevented acute oxycodone-induced brain hypoxia.

Conclusions: Chronic TRV130 delivery decreased oxycodone seeking in a partly sex-specific manner and prevented acute opioid-induced brain hypoxia. We propose that G-protein-biased MOR agonists, currently in development as analgesics, should also be considered as a maintenance treatment for OUD.
THE KEY ROLE OF TAU PROTEIN IN STRESS AND ALZHEIMER'S DISEASE SYNAPTIC PATHOLOGIES
Ioannis Sotiropoulos (University of Minho, Portugal)

Despite emerging studies implicating Tau in synaptic and cognitive impairment associated with Alzheimer’s disease (AD), the physiopathology of the disorder is complex and poorly understood. Chronic stress and the major stress hormones, glucocorticoids (GC), are suggested precipitating factors for AD, and have been shown to trigger Tau hyperphosphorylation and neuronal malfunction. However, the mechanisms that regulate Tau clearance and degradation remain unclear. In the current studies, we use in vitro and in vivo studies to uncover the role of two essential degradation mechanisms, the endolysosomal pathway and autophagy, in Tau proteostasis under control and pathological conditions. We demonstrate for the first time that Tau undergoes degradation via endolysosomal sorting in a pathway requiring the small GTPase Rab35 and the endosomal sorting complex required for transport (ESCRT) machinery. Interestingly, we detect a phospho-dependent selectivity of Tau sorting into the Rab35/ESCRT pathway. Furthermore, we find that chronic stress and high GC levels impair Tau degradation by suppressing Rab35 expression, while Rab35 gain-of-function rescues GC-induced Tau accumulation and related neurostructural deficits (J. Vaz-Silva et al., EMBO 2018 doi: 10.15252/embj.201899084). In addition, stress/GC trigger an mTOR-dependent inhibition of autophagy, leading to accumulation of Tau aggregates and cell death in AD Tg mouse and cell models. We also found that environmental stress and GC disturb cellular homeostasis and trigger insoluble accumulation of different RNA-Binding Proteins forming Stress granules(SGs). Interestingly, an mTOR-driven pharmacological stimulation of autophagy attenuates the GC-driven accumulation of Tau and SG-related proteins as well as related cell death, suggesting a critical interface between autophagy and the SG-related proteins response in the neurodegenerative role of chronic stress (J. Silva et al., Cell Death & Diff 2018 doi: 10.1038/s41418-018-0217-1). Conclusively, these studies indicate that the Rab35/ESCRT pathway and autophagy are essential for Tau clearance and part of the mechanism through which chronic stress precipitates AD.

STRIATAL CHOLINERGIC INTERNEURONS DYSFUNCTION IN PARKINSON’S DISEASE
Marianne Amalric (CNRS, Marseille, France)

Striatal cholinergic interneurons (ChIs) involvement in movement disorders has recently received renewed interest. In the context of Parkinson’s disease (PD), the loss of nigral dopaminergic (DA) neurons innervating the striatum creates an imbalance between dopaminergic inputs and ChIs within the striatum. The efficacy of anticholinergic drugs, one of the earliest therapy for PD before the discovery of L-3,4-dihydroxyphenylalanine (L-DOPA) suggests an increased cholinergic tone in this disease. The dopamine-acetylcholine balance hypothesis is however controversial and is revisited in this presentation with the use of optogenetics and pharmacogenetics to evaluate the specific contribution of ChIs to striatal microcircuit organization in physiological and pathological conditions. Special attention will be given to the role played by muscarinic acetylcholine receptors (mAChRs) in the regulation of striatal network which may have important implications in the development of novel therapeutic strategies for motor and cognitive impairment in PD. In our recent studies, we used optogenetics to selectively manipulate ChIs neuronal activity in ChAT-cre mice expressing channel rhodopsin and halorhodopsin to selectively activate or inhibit ChIs neurons of the striatum. We also used a pharmacological approach to determine the nature of receptors involved in the pathophysiology of PD, especially M1 and M4 mAChRs, largely expressed in the striatum. The involvement of striatal ChIs and mAChRs in the expression of the motor, cognitive and emotional symptoms measured in 6-hydroxydopamine (6-OHDA) lesioned mice, as a model of PD will be discussed. Although in small proportion (1-2% of all striatal neurons), ChIs tonic activity appears to maintain striatal function, by differentially controlling the activity of the two output medium spiny neurons direct and indirect pathways and thereby differentially
modulating animal behavior. Altered cholinergic transmission via M1 and M4 mAChRs of the dorsal striatum in PD conditions plays a pivotal role in the occurrence of motor and non-motor symptoms of PD.

**DOPAMINERGIC AND CHOLINERGIC MODULATION OF IMPULSE CONTROL**
Tommy Pattj (VU University Medical Center, Netherlands)

Impulse control disturbances are key features in several neurological and psychiatric disorders, such as attention-deficit/hyperactivity disorder, Parkinson’s disease and substance use disorders. Therefore elucidating the neural correlates of impulse control is crucial for developing novel treatment strategies to improve the symptomatology of such disorders. Preclinical translational paradigms to study impulse control have greatly enhanced understanding of the neural correlates of these cognitive processes. Using translational approaches, we and others have performed several pharmacological experiments over the last decade to study the role of dopamine and acetylcholine in impulse control. Interestingly, these experiments reveal an important role of these neurotransmitters systems in modulating impulse control and demonstrate functional interactions with other neurotransmitter systems such as the cannabinoid and opioid system. In my presentation, I will give an overview of these findings and, in addition, will briefly touch upon recent optogenetic approaches in our laboratory to study the role of acetylcholine in cognitive functioning.

**ENCAPSULATED CELL THERAPY: TARGETING DOPAMINERGIC AND CHOLINERGIC STRUCTURAL ALTERATIONS WITH GDNF AS A NEW STRATEGY IN THE PATHOPHYSIOLOGY OF NEURODEGENERATIVE DISORDERS**
Giovanna Paolone (University of Verona, Italy)

Parkinson’s disease (PD) is increasingly recognized as a multisystem neurodegenerative disorder. Loss of basal forebrain cholinergic neurons occurs as early as the loss of midbrain dopaminergic neurons and is hypothesized to contribute to the cognitive decline in PD. PD patients also suffer from a propensity for falls, freezing of gait and associated impairments in posture control and movement efficacy; these symptoms do not benefit from L-DOPA treatment. Furthermore, PD patients who falls have a greater reduction of cortical cholinergic activity relative to PD non-fallers and control subject. Delivering glial cell line-derived neurotrophic factor (GDNF) to the CNS is a potential treatment for Parkinson’s Disease (PD). To be effective, GDNF needs to be delivered selectively in a long-term and stable manner to the nigrostriatal system. We have developed an encapsulated cell technology that achieves these goals by providing a targeted, continuous, de novo synthesized source of very high levels of GDNF. Our studies demonstrated sustained, stable, and selective delivery of high levels of GDNF to the rat striatum using implanted human clonal ARPE-19 cells encapsulated into hollow fiber membranes. Long-term efficacy was evidenced by robust neuroprotection of dopaminergic neurons in the substantia nigra, preservation and regeneration of dopaminergic fibers in the striatum, and behavioral recovery in 6-OHDA lesioned rats. In the longest duration studies, these benefits were observed for over 1 year (62 weeks). Similarly impressive distribution of GDNF and positive effects on dopaminergic function were observed when larger, clinical-sized devices were implanted for 3 months into the putamen of minipigs. These results support the concept that implantation of encapsulated GDNF-secreting cells can deliver high amounts of GDNF in a sustained and targeted manner paving the way for continued evaluation of this approach in PD.
Symposium 21
The transcriptomic basis of neuronal function and behaviour

MINING THE EPITRANSCRIPTOMIC PROFILE OF THE ENDOCANNABINOID SYSTEM IN A MOUSE MODEL FOR ASPECTS OF PTSD
Anand Gururajan (Brain & Mind Centre, University of Sydney, Australia)

Post-traumatic stress disorder (PTSD) is one of the most debilitating psychiatric disorders with a lifetime prevalence of 5-10% in Australia and for which current therapies are generally ineffective. The dysregulation of the endocannabinoid system is consistently implicated in the neuropathology of PTSD. This system is comprised of endocannabinoids which suppress neurotransmitter release via presynaptic cannabinoid receptors expressed throughout the brain. Clinical evidence indicates reduced endocannabinoid tone in PTSD and this is consistent with patients reporting the therapeutic effects of natural and synthetic cannabinoids in attenuating symptomatology. As such, the endocannabinoid system is an attractive therapeutic target for the treatment of PTSD. However, for several reasons which include complex dose-response relationships and the social stigma associated with cannabinoid therapies, there is much progress to be made on the drug discovery front. To this end, we explored a novel approach to target the endocannabinoid system by focusing on upstream regulatory mechanisms, thus potentially bypassing current obstacles in the field. One such regulatory mechanism is encapsulated by the term epitranscriptomics which refers to post-transcriptional modifications of newly transcribed messenger RNAs. Of these, methylation of mRNA adenosine nucleotides (m6A) is the most common in the brain, well characterised and has been implicated in mRNA localisation, translation, degradation and splicing. In the present study, we have used a mouse model for aspects of PTSD in which adult male and female mice were fear-conditioned using a CS-US paradigm. At various time points post-conditioning, cued fear memory was assessed prior to sacrifice. Consistent with previous work, male and female mice displayed robust fear memory up to 2 weeks after fear conditioning. The amygdala was dissected out, RNA was extracted and processed. Analyses of m6A profiles for genes linked to the endocannabinoid system will be discussed.

RNA MODIFICATIONS AND TRANSLATIONAL REGULATION AT NEURONAL SYNAPSES
Dan Ohtan-Wang (Kyoto University, Japan)

Single-cell analyses have revealed that compared to other cell types in the brain, neurons not only contain higher RNA content, but also higher RNA species diversity, suggesting complex translational regulatory mechanisms that neurons actively engage to achieve their function. Our lab has focused on a cellular mechanism that physically uncouple transcription and translation through mRNA trafficking and local translation at neuronal synapses. We have found that the synaptically pre-deposited mRNA species can respond to stimuli that induce long-term synaptic plasticity and undergo synapse-, transcript-, and stimulus-specific translation. In search for the regulatory components accounting for such molecular specificity, we have found that methylation at adenosine RNA residues (m6A) can functionally mark the localized RNA species and positively regulate their translation. Reducing proteins that recognize and bind to m6A in neurons causes neuronal deficits in spinogenesis, activity-dependent spine maturation, synaptic transmission, learning, and memory retention. Furthermore, we show that RNA methylation-mediated translational mechanisms may play important roles in regulating dynamic microtubule networks that underlie building and remodeling of neuronal circuits.

PROBING THE INVOLVEMENT OF RBFOX1 IN PSYCHIATRIC DISORDERS
David Slattery (University of Frankfurt, Germany)

RBFOX1 belongs to a conserved family of RNA binding proteins (RBFOX1-3) that can function within either the nucleus or cytoplasm to control alternative splicing of primary transcripts or affect mRNA stability and translation, respectively. Importantly, RBFOX1 consensus sequences are found predominantly in introns where RBFOX1 regulates alternative splicing or in the 3’-UTR where RBFOX1 regulates mRNA stability. In silico modelling and chromatin-immunoprecipitation (CHIP) experiments have revealed that both the nuclear and cytoplasm targets of RBFOX1 are implicated in brain development and psychiatric disorders. However, because RBFOX1 lacks any polymorphic variation in its coding region, genome-wide
association studies suggest that mis-regulation of RBFOX1 as a result of polymorphic variation or DNA-methylation may be a key contributor in susceptibility to numerous disorders. Remarkably, RBFOX1 has been implicated in major depressive disorder (MDD), autism, schizophrenia, attention-deficit hyperactivity disorder (ADHD) as well as neurological disorders. However, currently, the neuropsychiatric signature of RBFOX1-dependent mechanisms and programs within the different brain regions are still elusive. Thus, to further investigate the role of RBFOX1 we have generated two mouse models, namely a neuron-specific RBFOX1 knockout line and a neuron-specific RBFOX1 overexpression line. In my presentation, I will present our findings revealing that, especially RBFOX1 deletion, leads to a wide-range of behavioural alterations. In keeping with an important role for RBFOX1 in neurodevelopment, the RBFOX1 knockout mice have a dramatically altered behavioural phenotype including hyperactivity, reduced social interest, reduced aggression, impaired auditory fear condition, impaired pre-pulse inhibition and reduced cognitive flexibility.

MITOCHONDRIAL PATHWAYS ASSOCIATED WITH ANXIETY-LIKE BEHAVIOR IN MICE AND PANIC DISORDER PATIENTS THROUGH A MULTI-OMICS ANALYSIS

Iiris Hovatta (University of Helsinki, Finland)

Genetic and environmental factors contribute to the etiology of anxiety disorders, but the underlying mechanisms are poorly understood. Chronic psychosocial stress is a well-known environmental risk factor for anxiety disorders. To identify biological pathways involved in psychosocial stress-induced anxiety, we used a well-characterized mouse model of chronic social defeat stress (CSDS) in two inbred mouse strains, C57BL/6NCrl (B6) and DBA/2NCrl (D2), which differ in their susceptibility to stress. B6 mice are innately non-anxious and mostly stress-resilient, while D2 mice are innately anxious and mostly stress-susceptible. Using a multi-omics approach, we identified differential mRNA, miRNA and protein expression changes in the bed nucleus of the stria terminalis (BNST) and blood cells after chronic stress in stress-susceptible, -resilient and control mice. Integrative gene set enrichment analysis revealed enrichment of mitochondria-related genes in the BNST and blood of stressed mice. To translate these results to human anxiety disorders, we investigated blood gene expression changes associated with exposure-induced panic attacks. Remarkably, we found reduced expression of mitochondria-related genes in D2 stress-susceptible mice and in panic disorder patients experiencing an exposure-induced panic attack, but increased expression of these genes in B6 stress-susceptible mice. Moreover, stress-susceptible vs. stress-resilient B6 mice displayed more mitochondrial cross-sections in the post-synaptic compartment after CSDS. Thus, chronic stress may critically affect cellular energy metabolism with a significant genetic background effect. Our findings demonstrate mitochondria-related alterations in gene expression as an evolutionarily conserved response in stress-related behaviors and validate the use of cross-species approaches in investigating the biological mechanisms underlying anxiety disorders.

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CHRONIC PAIN INCREASES IMPULSIVITY IN HIGH- (BUT NOT LOW-) IMPULSIVE RATS

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Body
Around 10% of CP patients develop addictive behaviors and are particularly prone to opioids misuse (Vowles et al. 2015). It has been hypothesized that trait impulsivity plays a role in this condition.

To test this hypothesis 30 male Wistar-Han rats (2 months old) performed the variable delay-to-signal (VDS) test for impulsivity (Leite-Almeida et al. 2013). Training phase consisted of 10 sessions with a maximum of 100 trials or 30 min each. Trials started with a delay period of 3s followed by the light stimulus in the response aperture for 1 min (response period). Nosepokes in response period were rewarded with the delivery of a sugar pellet and omissions and responses in the delay period (premature responses) were punished with complete darkness (3s). The test consisted of 1 session with 120 trials similar to training. It started with an initial block of 25 trials with 3s delay (3si) followed by 70 random trials with longer delays (6 or 12 s) and again a final block with 25 trials with a delay of 3s (3sf). Based on the results from the test, half of the animals were considered high-impulsive (HI) and the other half low-impulsive (LI).

Each group was then divided in Sham controls, animals with a neuropathic lesion (Spared nerve injury) in the left (SNI-L) and in the right (SNI-R) hindpaw. 5 weeks after the lesion, animals perform again the VDS test.

Results show that HI and LI equally learned the protocol, presenting similar number of correct and premature responses. In general, SNI had no effect in impulsive behavior, however, it markedly increased impulsivity in HI animals, particularly SNI-L.

In conclusion, HI rats are more affected by pain. Further studies should focus on the circuitries common to CP and impulsivity, namely the mesocorticolimbic pathway to understand the molecular basis behind these differences.

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Title
ACCUMBENS CRF AMPLIFIES DRUG ANTICIPATION: RECRUITMENT OF CRF-R2 IN COCAINE-SEEKING BEHAVIOR

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Body
Dopamine signaling within the nucleus accumbens core (NAcC) is critical to guiding motivated behavior in both appetitive and aversive contexts. The present studies examine accumbens-specific actions of the stress peptide corticotropin releasing factor (CRF) as a candidate mechanism for maladaptive arousal evoked by drug-predictive stimuli. Initial microdialysis studies in Long-Evans rats shows that CRF is released in the NAcC when animals are exposed to environmental contexts that predict an aversive outcome (i.e. social defeat) or drug-reward opportunity (i.e. cocaine availability), and moreover, intra-NAcC infusion of exogenous CRF elicits a robust increase in extracellular dopamine. We subsequently aimed to assess the behavioral impact of NAcC-CRF on instrumental responding directed towards cocaine procurement. To that end, separate rats were trained to self-administer cocaine under a heterogeneous chained schedule of reinforcement (FI-FR) in order to dissociate appetitive ('drug-seeking') from consummatory ('drug-taking') behavior. Accordingly, completion of a fixed interval (5 min.) was followed by 5 min of continuously reinforced responding (0.4mg/kg cocaine; FR1) on another lever. Under these conditions, intra-NAcC microinfusion of CRF dose-dependently increased responding during the fixed-interval component of the procedure, but notably did not affect subsequent cocaine intake. Both the behavioral and neurochemical actions of NAcC-CRF were each prevented by selective CRF-R2 blockade with Astressin-2B, but not the CRF-R1 antagonist CP376395. However, the CRF-R2-mediated effects on dopamine and reward-anticipation were absent in drug-naïve animals trained to self-administer saccharin. Taken together, these data suggest a recruitment of CRF-R2 within NAcC circuits that may contribute to maladaptive cocaine-seeking behavior, perhaps via modulation of dopamine transmission.
PO 03

Title
ALLOPREGNANOLONE DECREASES EVOKED DOPAMINE RELEASE DIFFERENTLY IN RATS BY SEX AND ESTROUS STAGE

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Body
Neurosteroids are synthesized de novo in glia and neurons and modulate both gene expression and neuronal excitability. Altered levels of neurosteroids are associated with several psychiatric disorders, such as post-traumatic stress disorder and major depressive disorder. The mesolimbic dopamine system, a pathway that extends from the ventral tegmental area (VTA) to limbic and cortical targets, is also dysregulated in many psychiatric disorders; however, dopamine is not a good therapeutic target as drugs that directly target dopamine have deleterious side effects. As the neurosteroid allopregnanolone, a metabolite of progesterone, is a potent positive allosteric modulator of the GABAA receptor, we hypothesized that allopregnanolone reduces mesolimbic dopamine neurotransmission via actions at the GABAA receptor. The present study aimed to determine whether allopregnanolone modulates dopamine release in the nucleus accumbens after stimulation of the VTA. We used fast-scan cyclic voltammetry to measure dopamine release in anesthetized male and female rats before and after IP injections of 7.5, 15, or 25mg/kg allopregnanolone or β-cyclodextrin vehicle. Allopregnanolone reduced VTA-evoked dopamine release in both male and female rats. In males, all doses of allopregnanolone decreased dopamine transmission at multiple time points after injection, with stronger effects at the 15 and 25 mg/kg doses. In females, the 15 and 25mg/kg doses significantly reduced dopamine release 30 minutes post injection, while the 7.5 mg/kg dose was no different from vehicle. Furthermore, females in proestrus were significantly less responsive to allopregnanolone than females in other estrous cycle stages. Our findings confirmed that allopregnanolone reduced VTA-evoked dopamine release in both male and female rats, supporting our hypothesis. However, allopregnanolone’s effect on mesolimbic dopamine was modulated by sex and estrous cycle. These results enrich our knowledge about the pharmacological effects of neurosteroids on DA transmission and can inform the therapeutic use of neurosteroids for psychiatric illness.
Title
ALTERED MEMORY RETRIEVAL AND REDUCED 5-HT2A RECEPTORS IN BASOLATERAL AMYGDALA IN HIGH COMPULSIVE RATS SELECTED BY SCHEDULE-INDUCED POLYDIPSIA

Authors
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Body
Compulsivity is associated with the loss of inhibitory control over a broad range of behaviours that are prone to excess. Increased repetitive acts and behavioural inflexibility, could be under an alteration in the neurobiological mechanisms of learning and memory retrieval in vulnerable individuals. The present study was designed to investigate the possible involvement of the basolateral amygdala and hippocampus NMDA and 5-HT2A receptors genes with an increased behavioural inflexibility in high compulsive rats selected by schedule-induced polydipsia (SIP).

First, after 20 sessions, Wistar male rats (approx. 250 g) were selected as either high compulsive (HD) or low (LD) drinkers according to their level acquisition of water intake (ml) on SIP (fixed time schedule of 60s). Second, we assessed memory and cognitive flexibility in HD and LD rats by Morris water maze, novel object recognition memory and learning and memory retrieval by fear conditioning test. Finally, we carried out real-time qPCR quantification of the genomic sequences from 5-HT2A and NMDA receptors promoter genes in the basolateral amygdala and hippocampus in HD and LD rats. HD rats showed an altered memory retrieval in the first trial in the reversal and in the extinction condition on the Morris water maze compared LD rats. These differences were also accompanied by a reduced fear extinction on the fear conditioned test. The neurobiological analyses revealed that the altered memory retrieval in HD rats might be related to a reduced level of 5-HT2A receptors in the basolateral amygdala compared LD rats. Future studies on SIP as a model of compulsivity, could contribute to identify the underlying mechanisms and improving the pharmacological treatments related with behavioural inflexibility and memory retrieval such as obsessive- compulsive disorder and post-traumatic stress disorder.
PO 05

Title
ALTERNATIVE SPLICING FACTOR RBFOX1 IS INVOLVED IN REGULATING AGGRESSIVE BEHAVIOUR IN MICE

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Body
RBFOX1, an alternative splicing factor, is involved in neuronal development and has been implicated in numerous psychiatric disorders including autism, attention deficit hyperactivity disorder and schizophrenia. These disorders – among multiple other interacting factors – contribute to an increased risk of pathological aggression. Recently, genetic variants or expression levels of RBFOX1 were linked to aggressive traits in humans and aggressive-like phenotypes in animal models. However, systematic investigation of association of RBFOX1 with aggressive behaviour in mice is so far lacking. Here, we aimed to do this using a two-pronged approach. First, we measured Rbfox1 expression levels in naïve mice, and after a single (acute aggression) or repeated (escalated aggression) aggressive encounters in using the inbred male BALB/cJ strain. Secondly, we characterized a transgenic mouse line with a neuronal-specific deletion of Rbfox1 for aggressive and social behaviour. We showed that Rbfox1 is upregulated in the nucleus accumbens and anterior cingulate cortex after acute aggression, and in the amygdala after escalated aggression. Neuronal-specific deletion of Rbfox1 resulted in a non-aggressive and socially-avoidant phenotype. Although further studies are required to determine the nature and underlying neurobiological mechanism of the interplay between RBFOX1 and aggressive traits, overall, our findings point to a positive association between increased RBFOX1 expression levels and aggressive behaviour.
Title
ASSOCIATION OF ENDOCRINE AND CLINICAL FACTORS WITH PHYSICAL ACTIVITY IN ANOREXIA NERVOSA

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Body
A frequent symptom of patients with anorexia nervosa (AN) is increased physical activity and excessive exercises. In recent years, this phenomenon has been investigated in rats in Activity Based Anorexia model. With a significant time-limited availability of food, animals lose weight considerably but at the same time they increase activity in the running wheels.

In this study we have focused on the relationship between activity, leptin, ghrelin, hunger and anxiety.

In 30 patients with AN (age 23, BMI = 14.93 kg.m⁻²), we measured the physical activity using Actiwatch Score, which the patients wore for non-dominant hand for three days. The patient's subjective intensity of hunger and anxiety was recorded in the watch at 2-hour intervals from 8 am to 8 pm.

In the whole group, only leptin positively correlated with physical activity (r = 0.52, p = 0.003), but this relationship was rather parabolic, suggesting a negative correlation in patients with low activity (LA) and positive correlation in patients with high activity (HA). After dividing the group according to the median of physical activity, it has been shown that in the LA group the amount of activity correlated negatively with hunger and positively with anxiety. In the HA group, the amount of activity correlated with BMI.

The different association between anxiety, hunger, activity and leptin in patients with LA and HA lead us to assume that the mechanisms of physical hyperactivity may be different in different stages of treatment. Activity in LA patients, which correlated negatively with leptin but positively with anxiety, may be more biologically determined for reduction of emotion-driven anxiety. In the HA patients, whose activity positively correlated with both leptin and BMI, motivation and cognitive functions, with the intention of deliberately limiting weight gain within the therapeutic program, may dominate.

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PO 07
WITHDRAWN

Title
AUTOMATED ANALYSIS OF PROSOCIAL AND AGGRESSIVE BEHAVIOURS USING COMPUTER VISION AND MACHINE LEARNING

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Body
Background. Disrupted social behaviour is a fundamental shared symptom of many neuropsychiatric disorders, including drug addiction, depression and PTSD. However, freely behaving mice are seldom considered in the experimental design of preclinical models. This is predominately due to technical limitations preventing high-throughput, consistent, and unbiased scoring of freely-moving complex social interactions.

Method. We developed predictive classifiers of social and aggressive behaviors during mouse dyadic encounters. Single C57BL/6J mice were placed into the home-cage of a CD-1 mouse and interactions were recorded in variable lighting conditions and different resolutions/frame-rates. We used DeepLabCut (Mathis et al., 2018, Nat Neurosci) to generate a model that tracks eight body-parts on each of the two mice. We detected and reduced tracking inaccuracies and calculated a battery of diverse features (>100) based on body-part movements, distances, angles, sizes, and their deviations across rolling windows. We used the features in sklearn-based machine learning algorithms against multiple socially-relevant targets (e.g., aggressive events, anogenital sniffing, tail rattling, pursuit, lateral threat display) and we visualized the tracking and the predictions with OpenCV.

Results. Model predictions were in excellent or good agreement with manual human frame-by-frame scoring. For example, random forest implementations based on re-sampled data predicted aggressive and tail rattling events with more than 95% accuracy. The model generalized well to new recording conditions.

Conclusion. The data support that complex social behaviors can be readily quantified in an unbiased, fast, and automated way in unmarked individual mice using DeepLabCut for feature detection and our python modules for machine learning.
PO 08

Title
AYAHUASCA DECREASES PSYCHOLOCOMOTOR AROUSAL AND 50-KHZ TRILL ULTRASONIC VOCALIZATIONS INDUCED BY LISDEXAMPHETAMINE IN WISTAR RATS

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Body
Ayahuasca (AYA) is a hallucinogen brew used in therapeutic rituals in Northwestern Amazon. It’s made from Banisteriopsis caapi, rich in beta-carboline harmala alkaloids (monoamine oxidase inhibitors), combined with Psychotria viridis containing N,N-dimethyltryptamine (DMT), a 5-HT2C agonist. AYA’s potential in treating drug addiction has been increasingly investigated. Therefore, we aimed to evaluate: (1) the AYA effect on spontaneous behavior of adult male Wistar rats (namely, emission of 50-kHz USV and locomotion) and (2): the anti-addictive effect of this brew in an animal model of hyperlocomotion and increased 50-kHz USV emission induced by lisdexamphetamine (LDX). For (1), 10 rats received water (H2O, 2.2 ml/kg, p.o.) and had the locomotion and 50-kHz USV tracked in an acrylic cage (40x40cm) with bedding, 4 lux, for 20 minutes of habituation test. After 24h, these animals received AYA (2.2 ml/kg, p.o.) 20 minutes prior testing, and had their behavior tracked in the same conditions. For (2), 40 rats underwent the same protocol, but on the testing day, they received the following treatments: CONTROL-H2O; LDX-H2O; CONTROL-AYA; LDX-AYA, LDX (10 mg/kg) or control were administered s.c. 1h before testing, 40 minutes after these treatment, animals received H2O or AYA. In (1) it was observed that AYA didn’t enhance 50 kHz (t(18)=0.56; P=0.58), nor changed locomotor activity (t(18)=1.45; P=0.16), suggesting no increase in anxiety-like behavior or impaired motor skills. In experiment (2), ANOVA showed an interaction between factors repetition and treatment for trill 50 kHz USV [F(3,35)=3,39; P=0,028] and locomotion [F(3,35)=17.9; P=0.000001], with LDX treatment increasing trill 50 kHz USV (P<0.05), corroborating its psychostimulant effect. AYA treatment selectively reduced trill (P<0.05) USVs and hyperlocomotion (P<0.05). Increase in trill subtype has been related to the rewarding effects of psychostimulants and dopamine release in the nucleus accumbens., suggesting that AYA treatment reduced the reinforcing properties and psycholocomotor activation of LDX.
Title
BED NUCLEUS OF THE STRIA TERMINALIS ENDOCANNABINOID SYSTEM MODULATES CONTEXTUAL FEAR CONDITIONING RESPONSES IN RATS

Authors
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Body
The endocannabinoid system is widely present in several brain structures involved in fear expression and anxiety-related responses, mostly mediated via CB1 and CB2 receptors. Nevertheless, the role of the endocannabinoid system role in specific brain structures is not yet completely elucidated. One structure in particular is the Bed Nucleus of Stria Terminalis (BNST). This area is a limbic structure responsible for integration of autonomic, neuroendocrine and behavioral information during aversive situations. The evidence about the presence and involvement of the endocannabinoid system in the BNST on aversive responses still no clear. Therefore, the aim of the present study was to evaluate the role of the endocannabinoid system in the BNST on the modulation of contextual fear conditioning responses. Male Wistar rats (240 – 270g) were submitted to stereotaxic surgery for bilateral guide cannula implantation directed to the BNST, for drug administration. Animals received BNST bilateral injections of vehicle, AM251 (CB1-antagonist; 0.1 – 0.3nmol/100nL), URB597 (an inhibitor of FAAH; 0.01 – 0.1nmol/100nL) or AM630 (CB2-antagonist; 0.01 – 1.0 nmol/100nL). Five days after the stereotaxic surgery, animals were submitted to the contextual fear conditioning protocol, performed in three consecutive days. On test day, both behavioral (freezing) and autonomic responses (mean arterial pressure – MAP and heart rate - HR) were recorded for 10 min during conditioned chamber re-exposition. The BNST CB1 receptors antagonism increased freezing behavior (F2,24=8.874; p<0.05) and MAP (F2,285=20.93; p<0.001). However, BNST FAAH inhibition, via CB1, reduced freezing behavior (F2,21=10.53; p<0.05) and MAP (F2,266=4.194, p<0.05). Furthermore, no changes were observed after BNST CB2 receptor antagonism on freezing behavior (F3,24=0.252, p>0.05). However, BNST CB2 receptor antagonism increased the autonomic responses (MAP (F4,336=1.907, p=0.001); HR (F4.336=2.525, p<0.001)). Thus, our finds suggest that the BNST endogenous cannabinoid system is able to modulate both freezing behavior and autonomic responses associated with contextual conditioned responses.
PO 10

Title
BINGE-LIKE MEPHEDRONE PRETREATMENT IN ADOLESCENCE INTENSIFIES THE REWARDING EFFECTS OF ETHANOL IN ADOLESCENT/ADULT RATS

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Body
Background: Mephedrone (4-methylmethcathinone), a psychostimulant ‘designer drug’, shows structural similarity to central nervous system stimulating agents such as amphetamine or 4-methylenedioxymethamphetamine (MDMA or ‘ecstasy’). It appears to be used more broadly by young adults and adolescents for recreational purposes. Mephedrone is often consumed in combination with ethanol to induce intense feelings of euphoria and well-being. The aim of the present study was to evaluate whether binge-like mephedrone administration during adolescence influences the rewarding effects of ethanol in adolescent/adult rats.

Material and methods: On postnatal day (PND) 30, male Wistar rats (OMD, Lublin, Poland), were repeatedly treated (intraperitoneal, i.p.) with saline or mephedrone (10 mg/kg x 3 for 7 days) to mimic psychostimulant ‘binge’ treatment. The animals were then randomly assigned to two experimental groups and exposed to a conditioned place preference (CPP) procedure. One of these groups was subjected to ethanol-induced CPP after 2 days, while the other encountered this 14 days after mephedrone administration. The ethanol-induced CPP was established (conditioning for 8 days) by intraperitoneal (i.p.) administration of EtOH (0.3, 1.0, 1.5 g/kg, 15% v/v, i.p.), using an unbiased procedure.

Results: Ethanol, at the dose of 1.0 g/kg, induced CPP in animals from both age groups (PND47 and PND74) previously treated with mephedrone, although it did not have such effect in the saline treated rats.

Conclusions: Mephedrone, a substance often used for recreation by young people, increases the rewarding effects of ethanol in both young adults (PND47) and adults (PND74) rats, suggesting its long-lasting effect on the brain’s reward pathway.

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PO 11

Title
BEHAVIOURAL RESPONSES TO ALCOHOL INVOLVE AMYLINERGIC PATHWAYS WITHIN BRAIN AREAS PROCESSING REWARD

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Body
Alcohol use disorder is a mortal brain disorder and the limited efficacy of current pharmacotherapy identifies the need for further exploration of potential neurochemical intervention targets for alcohol. Alcohol activates interconnected brain areas, including the laterodorsal tegmental area (LDTg), ventral tegmental area (VTA), and nucleus accumbens (NAc). This activation regulates behavioural responses through complex mechanisms. We have previously established that amylin receptors, the binding site of the anorexigenic hormone amylin, are involved in the behavioural outcomes caused by alcohol. Indeed, systemic administration of the amylin receptor agonist salmon calcitonin (sCT) reduces alcohol-related behaviours. The aim of the present studies was to break down the role of LDTg, VTA and NAc in the amylinergic regulation of alcohol behaviours. We therefore tested whether salmon sCT injected into the aforementioned brain areas affects alcohol-related behaviours in rodents. We showed that sCT injected into the LDTg did not affect alcohol-induced locomotor activity or reward memory retrieval in the conditioned place preference paradigm (CPP), but it decreased alcohol-induced accumbal dopamine release in mice. sCT injected into the LDTg attenuated alcohol intake in the intermittent alcohol access paradigm in rats. sCT into the VTA decreased alcohol-induced locomotor stimulation and dopamine release in the NAc shell, but did not alter reward memory retrieval in the CPP in mice. In the same region, sCT decreased alcohol intake in rats. Lastly, sCT into the NAc decreased alcohol-induced locomotor activity, but did not alter alcohol reward-dependent memory retrieval in the CPP paradigm in mice. sCT into the NAc tended to decrease alcohol intake in rats. Our data suggest that central amylinergic pathways regulate alcohol’s ability to activate brain areas involved in reward processing.
Depression is a leading cause of disability with more than 300 million people worldwide suffering. Contrary to popular belief, women during pregnancy and during post-partum period are at the same risk of depression as unpregnant women, with 12-15 % of them meeting the requirements for depression diagnosis. Bupropion is an atypical antidepressant and acts as a norepinephrine–dopamine reuptake inhibitor. Despite its wide use there is only a limited number of studies examining the safety of bupropion during pregnancy and lactation. The aim of our study was to evaluate the effects of pregestational stress and/or bupropion administration during gestation and lactation in rats on selected reproductive variables and behavior of juvenile offspring.

For our study, female Wistar rats were subjected to chronic unpredictable stress for three weeks prior gestation. Subsequently, the dams were treated with bupropion (30 mg/kg/day) from day 10 of gestation and throughout lactation via a cookie. There were 4 groups of dams and offspring: non-stress+vehicle, non-stress+bupropion, stress+vehicle, stress+bupropion exposure. Our preliminary results have shown no obvious morphological deformities in the pups and no differences in the duration of the pregnancy or number of pups in the litters. Regardless of pregestational stress, bupropion treatment resulted in a mild maternal intoxication manifested by decreased body weight gain of the offspring during lactation. There was an effect of treatment decreasing anxiety behavior, which may be associated with attention deficit hyperactivity like disorder in the juvenile offspring. Present study suggests, that bupropion treatment during gestation and lactation may interfere with functional development and can cause behavioral changes on the level of adaptation of animals.

Acknowledgement: This study was supported by grants VEGA-2/0124/19, APVV-15-0388, APVV-15-0308.
Title
CANNABIDIOL AND 7-NITROINDAZOL REVERSE THE BEHAVIORAL CHANGES INDUCED BY SINGLE PROLONGED STRESS

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Body
Previous results from our laboratory showed that cannabidiol (CBD), a non-psychotomimetic phytocannabinoid, can prevent the behavioral changes induced by single prolonged stress (SPS), a proposed model of PTSD, by interfering with the nitrergic system. It is unknown, however, if CBD or nitrergic interventions can reverse the SPS-induced changes once they have been established. To this aim, male Wistar rats were exposed to SPS (consisting of consecutive exposure to restraint, forced swimming, and ether anesthesia). Fear sensitization and impaired extinction of conditioned fear were evaluated one week later. In an additional protocol, SPS consequences were evaluated in the forced swimming test (FST) 7 days later. Two-h after SPS or the FST, the animals received acute [vehicle (V), 7-nitroindazol (7-NI, a nNOS inhibitor, 30mg/kg), CBD (30mg/kg, i.p)] or repeated (V, CBD (5mg/kg i.p.) daily for 7 days). Twenty-four-h after the last drug injection, the rats were submitted to the contextual conditioning fear procedure. Fear sensitization and extinction were assessed in two distinct sessions in the next 48 h. The brain levels of phosphorylated neuronal nitric oxide synthase enzyme (pnNOS) were measured at different time points after SPS stress. The SPS induced fear sensitization (increased freezing in the first context re-exposure), impaired fear extinction, and increased immobility time in the FST. Increased pnNOS levels were observed 1-h, in the ventral hippocampus, and nine days, in the prelimbic cortex, after SPS. 7-NI or CBD (either after acute or chronic administration) prevented and reversed the behavioral effect of SPS. These results suggest that CBD or nitrergic interventions could be useful in the treatment of stress associated disorders such as PTSD.

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Title
GUT-BRAIN AXIS IN YOUNG BINGE DRINKERS

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Body
Binge drinking (BD) is defined as the consumption of six or more standard drinks in one session. This pattern of consumption is highly prevalent during adolescence, which is considered to last up to 25 years of age. This developmental period involves ongoing neuromaturation that results in greater vulnerability to disruptive events in the brain such as excessive alcohol consumption. BD has been associated with both neuroanatomical impairments and neuropsychological deficits. Accumulating evidence indicates that chronic alcohol consumption induces inflammation, both from a direct interaction with the brain and the periphery, particularly from the gut. Recently, chronic alcoholism has been linked with increased intestinal permeability and alteration of microbial profile, in rodents and humans. However, no study to date has investigated the gut microbiota in young people with a repeated pattern of alcohol intoxication. The aim of this study is to investigate the potential link between alcohol-induced altered microbial profile, pro-inflammatory markers, hypothalamic-pituitary adrenal (HPA) activity and neurocognitive functioning in healthy young BDs. We will characterize both basal and stimulated immune/inflammatory markers in peripheral blood, as well as measuring the acute stress response by analysing salivary cortisol levels (cortisol awakening response [CAR]). The Cambridge Neuropsychological Test Automated Battery (CANTAB) will be used to assess neurocognitive performance. In addition, we will evaluate cognitive and affective dimensions highly linked to escalation in drinking severity such as emotional regulation. We will propose and discuss the results within a neuro-immuno-affective framework to integrate recent evidence on how central and peripheral alcohol-derived inflammation might damage the still developing young brain.

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PO 15

Title
DIFFERENTIAL REGULATION OF NIGRAL DOPAMINE NEURONS BY SK3 AND KV4.3 POTASSIUM CHANNELS: AN ELECTROPHYSIOLOGICAL AND BEHAVIORAL CHARACTERIZATION

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Body
Substantia nigra pars compacta (SNc) dopaminergic neurons display a characteristic pacemaking activity and release dopamine into the dorsal striatum and influence motor and cognitive behaviors mediated by this structure. Pacemaking relies on a large set of ion channels including the SK3 and the Kv4.3 potassium channels. Numerous studies have demonstrated that neuronal activity can be maintained in the face of chronic pharmacological treatments or genetic deletion of ion channels demonstrating the robustness of these activities. Indeed, blocking SK channels using apamin increases pacemaking irregularity, while blocking Kv4.3 channels using AmmTX3 increases pacemaking frequency. Electrophysiological and behavioral studies in mice with constitutive deletion of SK3 channels (SK3−/− mice) have suggested subtle phenotypic variations. The behavioral and electrophysiological outcomes of mice with constitutive deletion of Kv4.3 channels (Kv4.3 mice) have yet to be determined. In the present study, we first sought to exhaustively define the electrical phenotype of SNc dopaminergic neurons using a multivariate in vitro approach. Robustness of the electrical phenotype was quantified in both SK3−/− and Kv4.3−/− SNc neurons. We then evaluated the behavioral outcome of these genetic manipulations. At the single-neuron level, SK3−/− SNc dopaminergic neuron electrical phenotype displayed small variations from the WT group. In contrast, Kv4.3−/− SNc dopaminergic neurons displayed an electrical phenotype reminiscent of the effects of acute AmmTX3 application. Consistent with these observations, behavioral experiments in SK3−/− mice showed intact motor and anxiety-related traits while Kv4.3−/− mice seemed to display hyperlocomotion and motor-learning impairments. Altogether these results suggest different levels of robustness of SNc dopaminergic neurons in response to SK3 and Kv4.3 genetic deletion: while the loss of SK3 seems to be compensated for, SNc dopaminergic neurons appear unable to cope with Kv4.3 genetic deletion.
Title
CBD-INDUCED REDUCTION OF COCAINE VOLUNTARY INTAKE: CRUCIAL IMPLICATION OF NEURAL PROLIFERATION AND DIFFERENTIATION IN THE DENTATE GYRUS

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Body
The administration of cannabidiol has shown promising evidence in the treatment of some neuropsychiatric disorders, including cocaine addiction. However, little information is available as to the mechanisms by which cannabidiol reduces drug use and compulsive seeking. We investigated the role of adult hippocampal neurogenesis in reducing cocaine voluntary intake after a repeated cannabidiol treatment in mice. Cocaine intake was modelled using the intravenous cocaine self-administration procedure in CD1 male mice. Cannabidiol (20 mg/kg) reduced cocaine self-administration behaviour acquisition and total cocaine intake and enhanced adult hippocampal neurogenesis. Our results show that a 6-day repeated temozolomide treatment (25 mg/kg/day), a chemotherapy drug that blocks hippocampal neurogenesis, prevented cannabidiol-induced increment in the early stages of neuronal maturation and differentiation, without altering the basal levels of BrdU/NeuN and doublecortin immunostaining. The reduction of total cocaine intake and operant behaviour acquisition observed following cannabidiol exposure was attenuated by temozolomide treatment. Our results also show a similar effect of temozolamide on a cannabidiol-induced improvement of novel object recognition memory, a task influenced by the pro-neurogenic effects of cannabidiol (10 and 20 mg/kg). The anxiolytic effects of cannabidiol (10 and 20 mg/kg), however, remained unaffected after its pro-neurogenic effects decreased. The present study confirms that adult hippocampal neurogenesis is one of the mechanisms by which cannabidiol lowers cocaine reinforcement and demonstrates the functional implication of adult hippocampal neurogenesis in cocaine voluntary consumption in mice. Such findings highlight the possible use of cannabidiol for developing new pharmacotherapies to manage cocaine use disorders.
PO 17

Title
CHEMOGENETIC ACTIVATION OF HYPOTHALAMIC OXYTOCIN NEURONS REDUCES PEER-INDUCED COCAINE SEEKING

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Body
Re-association with drug using social peers is a common trigger for relapse. Peer-induced drug seeking can be modeled using a dual-compartment operant conditioning apparatus in which two rats are allowed to interact through a wire-screen partition. We found that systemic administration of oxytocin, a neuropeptide involved in social recognition and pair bonding, reduces peer-induced cocaine seeking. In this study, we examined peer-induced drug seeking following chemogenetic activation of oxytocin neurons in the paraventricular nucleus (PVN) of the hypothalamus. Male and female Sprague-Dawley rats underwent surgery for implantation of a jugular catheter and intra-PVN microinfusion of an adeno-associated virus that targeted the oxytocin promoter (OTp). Rats were randomly assigned to receive either the control virus (OTp-mCherry) or the activation DREADD virus (OTp-mCherry:hM3Dq). Rats then underwent 30 days of twice-daily self-administration training. Each day, one session was with cocaine (1.0 mg/kg/infusion) in the presence of one peer (S+) and the other session was with saline in the presence of a different peer (S-). After extinction, rats were tested for peer-induced reinstatement (with S+, S-, or no peer) following a pretreatment with clozapine (0.1 mg/kg) or vehicle. Collapsed across treatments, rats reinstated drug seeking in the presence of the S+ peer, but not in the presence of the S- peer. The active virus did not affect acquisition of cocaine self-administration, although rats given the active virus did respond less during the extinction period. More important, rats receiving the activation virus reinstated to the S+ peer following vehicle, but did not reinstate to the S+ peer following clozapine; the response to the S- peer was unaffected. For rats with the control virus, clozapine had no effect on peer-induced reinstatement. Thus, activation of oxytocin neurons in PVN blocks peer-induced reinstatement, suggesting that this system may be a valuable target for future drug discovery projects.
Title
CHEMOGENETIC INHIBITION OF VENTRAL TEGMENTAL DOPAMINE NEURONS PREVENTS COCAINE-INDUCED DEFICITS IN DECISION MAKING IN BOTH SEXES

Authors
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Body
Women and men can differ in their propensity to take risks and develop addiction disorders. A critical biological factor in the development of addiction is aberrant dopamine (DA) neurotransmission. Sexual dimorphisms in behavioural control by the DA system may underlie these phenomena. A better understanding of how sex differences contribute to the DAergic regulation of addiction-relevant behaviours will inform pharmacotherapy. We recently showed that when male rats were allowed to volitionally take cocaine, they developed significant deficits in decision making. We were therefore caused to probe the role of DA neurons in this cocaine-induced descent into maladaptive decision making in both sexes. Through viral-mediated gene transfer using a floxed vector, we targeted over-expression of an inhibitory DREADD (hM4) to ventral tegmental area (VTA) DA neurons in female and male rats selectively expressing cre recombinase in neurons synthesising tyrosine hydroxylase (i.e., TH:Cre rats), thereby gaining inhibitory control over the DAergic neurons projecting from the region. In the morning, rats were trained in the rGT with VTA DAergic activity inhibited. At night, rats were allowed to self-administer intravenous cocaine. During the cocaine sessions, VTA DA neurons were not inhibited. Inhibition of VTA DA neurons prevented the cocaine-induced decent into maladaptive decision making in both females and males. Paradoxically, this treatment caused male rats to consume more cocaine overall and contributed to an increased preference for risk in females, regardless of whether cocaine was consumed. These findings highlight important cross-sex similarities and dimorphisms in the DAergic control of addiction.
Title
CANNABIDIOL MODULATES SUBANESTHETIC KETAMINE – INDUCED EFFECTS ON MOTOR ACTIVITY AND SPECIFIC NEUROBIOLOGICAL INDICES IN THE ADULT RAT

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Body
Introduction: Cannabidiol (CBD) is a non-addictive ingredient of cannabis which exerts its actions mainly through the endocannabinoid system. Ketamine is a non-competitive NMDA receptor antagonist, known for its anesthetic properties. Ketamine also displays prominent central actions when administered in subanesthetic doses, including the psychotogenic action.

Aim: The purpose of this study was to investigate the modulatory role of CBD pretreatment on ketamine –induced behavioural effects and specific alterations in neurobiological parameters related to the endocannabinoid and the glutamatergic system.

Methods: Adult male Sprague-Dawley rats received low doses of CBD i.p. and 20 minutes later, they were injected with a subanesthetic dose of ketamine or saline. Open field motor activity was recorded for a one hour registration period. Protein expression of specific neurobiological indices related to endocannabinoid function, glutamatergic status and neuroplasticity were assessed, in specific rat brain regions, including the prefrontal cortex, striatum, nucleus accumbens and the hippocampus.

Results: CBD treatment at low doses did not alter motor activity, while higher doses induced a mild depressant effect. Interestingly, the low CBD doses did not affect ketamine–induced profile, while higher doses enhanced ketamine–induced motoric effects in terms of horizontal and vertical activity. Protein expression analysis following CBD and ketamine treatment revealed a neurobiological profile which accompanied the aforementioned behavioural changes.

Conclusion: CBD modulated ketamine–induced effects. These findings will potentially contribute to the understanding of the pharmacological profile of CBD, an agent with antipsychotic potential, and of the functional interplay between endocannabinoid and glutamatergic systems.

Keywords:
Cannabidiol, ketamine, rats, motor activity, behavior, glutamate, neurobiological indices

Funding:
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Title
ASSESSING REWARD PREFERENCE USING OPERANT CONDITIONING IN MALE AND FEMALE C57BL6/J AND CD1 MICE

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Body
The type of reward used in operant conditioning tasks varies between studies, and the choice of reward often seems somewhat arbitrary. No study to date has compared preferences for different reward types in mice, so we sought to compare the ability of different sucrose and/or food based pellet rewards to elicit lever press behavior in an operant conditioning task. Different flavors of the two basic types of rewards were also assessed in adult male and female mice from two commonly used laboratory strains, C57Bl6/J (Jackson Laboratory, Bar Harbor, ME, USA) and CD1 (Charles River, Wilmington, MA, USA). Each mouse was initially trained to associate each of the two levers with a separate reward and then tested on 6 consecutive free choice sessions in which they could work for rewards on a fixed ratio (FR1) schedule for 30 min. Both males and females of both strains showed significant preferences of food-based over sucrose-based rewards, regardless of flavor. In addition, when tested on food-based rewards from two different manufacturers (Purified Rodent Tablets, 5TUL, TestDiet, St. Louis, MO, USA and Dustless Precision Pellet, Purified, BioServ, Flemington, NJ, USA) both strains and sexes showed a significant preference for the TestDiet over the BioServ pellets. Both strains showed a stronger preference for banana over chocolate flavor, but C57Bl6/J mice displayed an overall stronger sensitivity to the different flavors. This study provides a ranking of 8 common reward pellets, allowing the use of weaker or stronger rewards depending on the purpose of the study.

This work was supported by the Intramural Program of the NIH, National Institute of Mental Health, ZIAMH002784 (H.A.C).
Title
CHRONIC PSYCHOSOCIAL STRESS AFFECTS EMOTIONAL RESPONSE IN ANIMALS’ EXPERIENCED EARLY-LIFE SEIZURES

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Body
Early-life stress influences emotional and cognitive development and increase risk of developing a wide range of neuropsychiatric diseases including anxiety disorders, depression, cognitive decline, but also epilepsy.

In this study, we exposed the animals with early-life seizure to psychosocial stress. After four-week chronic stress we evaluated several phenotypic markers of emotional behaviour in standard paradigms such as intra-session habituation in an open field (OF), anxiety-related behaviour in an elevated plus maze (EPM) and compared them to behavioural marker in PhenoTyper testing that enable monitoring in a complex test situation. In addition, we evaluate a widely used behavioural marker of anhedonia—the sucrose preference.

Experiment results revealed no impaired intra-session habituation in the OF test in both control and SE groups, suggesting that stress did not impaired adaptation to experimental conditions. In the EPM SE stressed animals visited the open arms of the EPM more frequently and spent more time on them. We interpreted these results in terms of behavioural disinhibition rather as a lower level of anxiety. PhenoTyper testing revealed increase in distance moved during the day and decrease distance during the night in both groups, suggesting that stress affected chronobiologic rhythms in both controls and SE animals. In addition, SE animals exposed to stress had a higher sucrose preference compared to controls, indicated that social stress triggered higher level of anxiety and not hedonic behaviour as a marker of depressive-related behaviour.

In conclusion, our results showed that four-week chronic psychosocial stress lead to higher sensitivity to anxiety and emotive behaviour in animals experienced early status epilepticus.

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Title
CHRONIC SOCIAL DEFEAT STRESS PROMOTES SELECTIVE IMPAIRMENT IN SOCIAL INTERACTION AND INCREASED MESOLIMBIC DOPAMINE FUNCTION

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Body
Chronic stress is a primary factor that promotes persistent depressive symptoms in both humans and animal models. In rodents, exposure to chronic social defeat stress (CSDS) seems to promote depressive-like behavior, such as anhedonia and social deficits. CSDS also leads to functional changes in the dopaminergic mesolimbic pathway that underlie, at least partially, the depressive-like behavioral impairments. The present study aimed to broaden the characterization and investigate the validity of CSDS as a model of emotional and motivation impairment in mice. For that, in Experiment 1, male C57BL/6J mice were exposed to a 10-day CSDS protocol, in which they were daily physically and psychologically confronted by aggressive conspecifics, and then evaluated during sucrose reinforcement, social interaction, saccharin preference, sucrose splash and forced swim tests. In addition, in Experiment 2, another cohort of mice was used to record accumbal dopamine release during a sucrose reinforcement test, using fast scan cyclic voltammetry (FSCV), a technique that provides high temporal resolution. Our data showed that CSDS induced social avoidance behavior that lasted 3 weeks after termination of defeats, but did not promote alterations in other hedonic, motivation, self-care or despair behaviors. Interestingly, although CSDS did not alter sucrose reinforcement behavior, it increased dopamine concentration in response to sucrose pellets, but not to the contextual cues associated with this reward. Taken together, our results suggest that CSDS selectively promotes social behavior impairment despite not inducing other general depressive-like behaviors. Furthermore, CSDS seems to promote increased phasic dopamine responses to an appetitive stimulus (sucrose pellets).

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There has recently been a significant worldwide rise in opioid use disorder (OUD), making the understanding of the behavioral components that contribute to OUD necessary to explore. In the current study, heterogeneous stock rats underwent various testing procedures to assess the behavioral determinants associated with vulnerability versus resilience to opioid dependence. Stress and anxiety-related behaviors were assessed via the elevated-plus maze and an open field test, while analgesic thresholds were determined using a tail-flick test. Rats then underwent 3 weeks of long-access (LgA, 12-hr sessions) heroin self-administration training, followed by a progressive ratio test. Following 4 more sessions of LgA, rats underwent a within-session extinction training and heroin-induced reinstatement (0.25 mg/kg, s.c.) test and then 6 days of extinction training. After the last day of extinction training, a test for cue-induced reinstatement was performed. The behavioral measures previously mentioned to assess stress, anxiety and analgesic threshold were repeated. Results show a correlation present between total distance travelled during the open field test and cue-induced drug-seeking behavior. Additionally, when rats are characterized based on a high level of locomotor activity (high-responders, HRs) versus a lower level of locomotor activity (low-responders, LRs) in the open field test, HRs show greater heroin-induced drug-seeking behavior compared to LRs. The HR/LR model is commonly used to examine individual variation in the acquisition of drug-taking behavior, but here we show that this model may also be relevant for predicting individual variation in drug-seeking behavior following heroin self-administration. Furthermore, we have created a composite index that encompasses behavior during self-administration, the progressive ratio test, and the reinstatement tests to classify rats into those showing overall resiliency versus vulnerability to OUD. These data highlight the value of focusing on individual variation in several addiction-related behaviors to further elucidate behavioral contributions to vulnerability versus resilience to OUD.
PO 24

Title
CONTEXTUAL FEAR MEMORY EVOCATION UNDER A NEW ODOUR STIMULUS IS NOT SUFFICIENT FOR SECOND-ORDER CONDITIONING IN WISTAR RATS

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Body
In animal models, post-traumatic stress disorder (PTSD) can be studied with aversive conditioning models. A form of aversive conditioning is the second-order conditioning (when a new second stimulus is associated to the first conditioned stimulus). Thus, the conditioned fear response can be elicited by a stimulus that was not present during the trauma. Clinical data suggests that PTSD may be maintained by second-order conditioning. The objective of this study was to investigate the occurrence of second-order conditioning in Wistar rats. The unconditioned stimulus was the foot shock and the conditioned stimulus were the context and isoamyl acetate (banana odour). The conditioned response was evaluated by freezing time in the context of the foot shock (context A) or in a neutral context in the presence of odour (context B). First, rats were fear-conditioned to the context with odour. In the next day, rats were exposed to context B with odour. Odour-conditioned rats had increased freezing time compared with controls. Next, odour was paired with context A during the contextual fear retrieval. Freezing time in context B did not differ between groups (retrieval with or without odour). In the next experiments we attempted to strengthen the association between fear response and odour without promoting aversive memory generalization. 1) Rats received yohimbine (1 mg/kg, i.p.) or vehicle after the conditioning and/or after the retrieval session. 2) Rats received yohimbine (2 mg/kg or 3 mg/kg, i.p.) after retrieval. 3) Rats received two pairings in consecutive days between the context A and odour. 4) The odour was presented in a different context immediately after contextual fear retrieval. None of these protocols increased freezing time in context B. The presentation of a new stimulus during memory reconsolidation was not sufficient to promote second-order conditioning, which might suggest a distinct mechanism between memory reconsolidation and second-order conditioning.
PO 25

Title
CONTRASTING ROLES OF VENTRAL TEGMENTAL DOPAMINE NEURONS IN INCENTIVE
MOTIVATION AND DEMAND ELASTICITY

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Body
Ventral tegmental area (VTA) dopamine (DA) neurons are known to be involved in mechanisms of reward and valuation, including effort-related aspects of motivation. However, the precise role of VTA DA neurons in these processes is still not fully understood. Here, we set out to investigate the role of VTA DA neurons in reward seeking in rats by taking a behavioural economic approach. This approach enables us to quantify the relationship between reward value, price and consumption using demand curves. This behavioural economic demand curve analysis provides a unique framework for studying incentive motivation, as it offers various useful measures of reward seeking and taking such as demand elasticity, demand intensity and essential value. We therefore designed a within-session procedure for sucrose self-administration to assess the effects of VTA DA neuron activation on sucrose demand. To do so, we used designer receptors exclusively activated by designer drugs to chemogenetically enhance neuronal activity in VTA DA neurons in TH::Cre rats. After pre-treatment with CNO or vehicle, the rats were subjected to a within-session behavioural economics procedure for sucrose self-administration, in which the response requirement ratio was sequentially increased or decreased over session blocks. In addition, the rats were tested under a classic progressive ratio schedule of reinforcement. Preliminary results show that chemogenetic activation of VTA DA neurons decreased responding in the behavioural economics procedure, while increasing responding for sucrose under the progressive ratio schedule. Demand elasticity was not affected by VTA DA neuron activation. Together, these data suggest that response requirement conditions determine how ascending midbrain DA neurons influence the vigour of reward-directed behaviour. Furthermore, these findings indicate that modulation of incentive motivation and demand elasticity depends on dissociable neural substrates.
CORTICOSTERONE AND DOPAMINE ACTIVITY IN THE NUCLEUS ACCUMBENS CHANGE IN A SEX- AND PHENOTYPE-DEPENDENT MANNER FOLLOWING APPETITIVE PAVLOVIAN CONDITIONING

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Body
Through associative learning, environmental cues become predictors of biologically relevant stimuli. When such cues, however, are attributed with incentive value, they can gain inordinate control and elicit aberrant behavior. For example, when individuals with addiction encounter drug-associated cues, they often relapse. Using an animal model that captures individual variation in the propensity to attribute incentive value to reward cues, we can examine the neural substrates that contribute to such cue-driven behaviors. Rats that undergo Pavlovian conditioning, consisting of cue-reward pairings, develop either a sign- or goal-tracking response. Both sign-trackers (ST) and goal-trackers (GT) attribute predictive value to the cue, but ST also attribute incentive value, transforming it into a “motivational magnet”. Different brain circuits are engaged in response to the cue in ST vs. GT. For example, dopamine (DA) is necessary for incentive, but not predictive cue-learning. DA interacts with corticosterone (CORT), the primary regulator of stress in rats, and mediates reward-motivated behaviors. Yet, the interaction between DA and CORT in the context of ST and GT remains to be investigated. Here, we assessed changes in CORT and DA in the nucleus accumbens (NAc) over the course of Pavlovian conditioning. To do so, CORT and DA overflow was captured via in vivo microdialysis within the NAc of male and female rats prior to acquiring a conditioned response (session 1) and following the development of sign- and goal-tracking behavior (session 6). We found that conditioning experience elicits a rise in CORT across phenotypes and to a greater extent in females. Phenotype differences were apparent in DA, with ST showing greater DA levels and lower DA metabolite ratio relative to GT. These data contribute to our understanding of the role of CORT in DA-dependent learning processes that are relevant to cue-motivated psychopathologies.
Title
DBS-LIKE OPTOGENETIC STIMULATION OF ACCUMBENS DOPAMINE D2 RECEPTOR-CONTAINING NEURONS ATTENUATES COCAINE REINSTATEMENT

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Body
Previous work indicated that deep brain stimulation (DBS) of the nucleus accumbens (NAc) shell attenuated reinstatement of cocaine-seeking in rats. However, the potential differential impact of DBS on specific populations of neurons to drive the suppression of cocaine-seeking is unknown. Medium spiny neurons in the NAc are differentiated by the expression of dopamine D1 receptors (D1DRs) or dopamine D2 receptors (D2DRs), activation of which promotes or inhibits cocaine-seeking behavior, respectively. We tested the hypothesis that DBS-like optogenetic stimulation of D1DR-containing neurons in the NAc shell would potentiate cocaine-primed reinstatement, whereas DBS-like optogenetic stimulation of D2DR-containing neurons in the NAc shell would attenuate cocaine-primed reinstatement. We used transgenic rat lines that express Cre recombinase selectively in D1DR-containing or D2DR-containing neurons in combination with a Cre-dependent AAV expressing channelrhodopsin or yellow fluorescent protein (eYFP) to deliver high frequency optogenetic stimulation selectively to each population of neurons in the NAc shell. Male and female rats self-administered cocaine (0.254 mg/infusion) in 21 daily self-administration sessions, after which lever pressing was extinguished. Cocaine seeking was reinstated by delivery of cocaine (10 mg/kg, i.p.) immediately prior to reinstatement sessions, throughout which intra-accumbens DBS-like 473nm light stimulation (130 Hz) or no stimulation (sham) was administered in a within-subjects counterbalanced design. High frequency, DBS-like optogenetic stimulation of D2DR-containing neurons attenuated reinstatement of cocaine seeking in male rats, whereas DBS-like optogenetic stimulation of D1DR-containing neurons did not alter cocaine-primed reinstatement. In rats which only expressed eYFP, intra-accumbens optogenetic stimulation did not alter cocaine reinstatement relative to sham stimulation, indicating that the effect of DBS-like stimulation to attenuate cocaine reinstatement is mediated specifically by channelrhodopsin rather than as a consequence of prolonged light delivery. Collectively, these results suggest that DBS of the NAc attenuates cocaine-primed reinstatement through the selective manipulation of D2DR-containing neurons. Supported by R01 DA015215 and T32 DA028874.
Title
DECIPHERING THE GUT FEELING: NEURONAL NETWORKS UNDERLYING GUT-BRAIN COMMUNICATION

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Body
In recent years, different lines of evidence have shown that the microbes inhabiting the gut can communicate with the brain. Alterations to, or the lack of gut bacteria, has been shown to affect molecular, anatomical and behavioural parameters, which have been linked to physiological and psychological disease. However, the mechanisms underlying these effects have not been identified thus far.

In this study we used targeted recombination in active populations (TRAP) to express mCherry in a subset of neurons activated by input coming from the vagus nerve. To set up the system vagus nerve signalling was induced by Cholecystokinin (CCK) administration (i.p.) in food deprived animals. CCK is a gut hormone released upon food intake that acts as satiety signal. CCK acts through the vagus nerve and induces neuronal activation in the nucleus tractus solitarius (NTS), the projection area of the vagus nerve. In mice, genetically modified to express Cre under the Fos promoter, stimulation with CCK results in the expression of mCherry in the NTS, which had previously been injected with virus containing floxed mCherry. These results were confirmed when allowing food deprived mice to regain access to food, which result in natural release of CCK, and showed similar patterns of mCherry expression in the NTS.

To understand whether gut bacteria could be using the activate similar vagus nerve related pathways we administered Lactobacillus reuteri by oral gavage. MCherry expression was observed in the NTS in similar areas as for CCK activation, indicating that indeed gut bacteria have the ability to stimulate these pathways.

These results indicate the capability of TRAP utilisation to further investigate neuronal networks underlying vagus nerve related gut-brain communication. It is our aim to extend this technology to understand the neuronal activation patterns and impact of live biotherapeutics on emotions and behaviour.
Title
DEEP BRAIN STIMULATION OF THE VENTRAL HYPOTHALAMUS INDUCES PANICOLYTIC-LIKE EFFECTS IN THE ELEVATED T-MAZE AND DECREASES C-FOS IMMUNOREACTIVITY

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Body
The ventromedial hypothalamus (VMH) is a hypothalamic nucleus implicated with defense and emotional behavior. Previous studies from our laboratory show that both the administration of GABA/benzodiazepine agonists and of corticotrophin type 2 receptors (CRFR2) antagonists impaired elevated T-maze (ETM) escape measurements. In clinical terms, this response has been related to panic disorder. Apart from escape, the ETM also allows the measurement of avoidance responses, in clinical terms related to generalized anxiety disorder. In this study we used the technique of deep brain stimulation (DBS) to investigate the role played by the VMH in defense. Male Wistar rats were submitted to high-frequency stimulation (100 µA, 100 Hz) in the region for 1 h and immediately after tested in the avoidance or escape tasks of the ETM. An additional group of rats was submitted to DBS of the VMH and used for quantification of c-Fos immunoreactive (Fos-ir) neurons in brain regions related to the modulation of defense. Results show that high-frequency stimulation of the VMH increased escape latencies, a panicolytic-like effect, without altering avoidance or the number of crossings in the open field, which measures locomotor activity. The immunohistochemical analysis showed that DBS decreased Fos-ir in the VMH and in the ventrolateral periaqueductal grey. These results suggest that the VMH modulates in particular a defensive response associated with panic disorder and are of relevance to the better understanding of the neural mechanisms underlying this pathological condition.
Title
DESCHLOROKETAMINE STEREOSELECTIVELY INHIBITS RAT DOPAMINE TRANSPORTER

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Body
Deschloroketamine (DCK) is categorized as a dissociative anaesthetic and together with ketamine, phenylcyclohexyline (PCP) or methoxetamine (MXE) belongs to the arylcyclohexylamine drug. To help gain deeper insight into the mechanism of action of dissociative anaesthetics we focused our research on DCK enantiomers and their effect on DAT.

Despite the fact that DCK is usually administered as a racemate (composed of two isomers S(+)- and R(-)-DCK), enantiomers often interact differently in a chiral environment and thus yield a different effect (e.g. like in the case of ketamine enantiomers). Therefore, the purpose of this study was compare two stereoisomers of DCK on inhibition of DAT, which was expressed as IC50 (= half maximal inhibitory concentration). Furthermore, we measured serum and brain levels of DCK enantiomers over 24 hours.

The results of the present study on rat striatal synaptosomes demonstrated that DAT was inhibited with both DCK enantiomers, where S(+)-DCK (IC50 = 5.6 µM) was more potent than R(-)-DCK (IC50 = 63 µM). Further, S(+)-DCK had a highest measured concentration in serum of 600 mg/mL, whereas R(-)-DCK had a highest measured serum concentration of 450 mg/mL, suggesting a faster absorption for the S(+)-enantiomer. However, in brain tissue, the highest measured concentration was 1800 mg/mL at one hour for the S(+)-DCK and 2200 mg/mL for the R(-)-DCK suggesting the R-enantiomer has better brain penetration. In summary, our results revealed that similarly like ketamine, DCK enantiomers work differently and have different potency on dopamine transporter, different absorption, and brain penetration.

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PO 31

Title
DEVELOPING PREDICTORS OF ALCOHOL USE DISORDER IN A CHRONIC ALCOHOL TAKING RAT MODEL WITH SOCIAL DEFEAT EXPERIENCE

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Body
Alcohol is a highly addictive substance; however, alcohol use does not necessarily cause alcohol use disorder (AUD). For instance, individual vulnerability to addiction exists and social stress may affect the severity of AUD. Specific personality traits (related to impulsivity, compulsivity and inability to cope with stress) are important predictors for the severity of AUD in later life. Here, we searched for potential behavioral predictors by first examining the baseline value of four different tests assessing spatial and social interaction before rats were exposed to social stress and alcohol. Long-term social stress was induced by exposing rats to the social defeat-induced persistent stress (SDPS) paradigm and long-term social isolation after which they had long-term access to alcohol using home cage two-bottle free-choice and operant self-administration paradigms. Using a 5-criteria classification of according to DSM-V, AUD severity was assessed in the control and SDPS-exposed groups. Using these 5-criteria a higher incidence of the AUD phenotype was detected in the SDPS group. Baseline affective behavior, measured as interaction with an adult conspecific (social approach avoidance, SAA), prior to stress exposure was significantly correlated with most AUD criteria and opposite in control and some in SDPS-exposed groups. Furthermore, a low SAA interaction rate correlated with protection from alcohol addiction, whereas exposure to stressful life events increased addictive behavior later on in this group. We conclude that most AUD sub-phenotypes are based on prior genetic and environmental factors that may have shaped the individual’s affective behavior. Subsequent exposure to social stress is able to transform the AUD predictive ability of affective behavior.
Title
DIET INDUCED OBESITY ALTERS EXCITABILITY OF THE ORBITOFRONTAL CORTEX AND IMPAIRS OUTCOME DEVALUATION

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Body
To make decisions, one computes the value of the outcome based on current information. This goal directed behavior, updating actions based on outcome value, is mediated via the orbital frontal cortex (OFC). While the OFC has been extensively researched in substance use disorders, little is understood on how this neural circuit might be altered in diet-induced obesity. We tested the hypothesis that obese mice have impaired ability to devalue rewards and this may be due to alterations in the OFC. Using a selective satiety and conditioned taste avoidance task we found that unlike lean mice, obese mice had impaired outcome devaluation when pre-fed with the sucrose reward or when the reward was paired with sickness. Furthermore, obese mice showed decreased latency to learn a new strategy for food seeking when the contingencies were degraded. Using in-vitro whole cell patch clamp electrophysiology, we show that diet-induced obesity reduces GABAergic release probability onto OFC pyramidal neurons. To determine if decreased inhibitory input to pyramidal neurons leads to impairment in reward devaluation in normal weight animals, we expressed an inhibitory DREADDs in VGAT-ires-cre mice. Reducing inhibitory tone onto pyramidal neurons in normal weight animals induced deficits in both selective satiety and conditioned taste avoidance reward devaluation. Furthermore, by increasing GABAergic signaling in the OFC via a GABA transporter 1 antagonist, we restored sensory specific reward devaluation in obese mice. In conclusion, decreased inhibition onto OFC pyramidal neurons in diet-induced obesity is mediated by deficits in outcome devaluation.
Title
DISCOVERY OF A NOVEL BRAINSTEM CIRCUIT INVOLVED IN ENERGY BALANCE REGULATION

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Body
The present study is inspired by our observation that the lateral parabrachial nucleus (lPBN), an anorexigenic centre in the brainstem, has abundant expression of GHSR [1], the receptor for the orexigenic stomach-derived hormone, ghrelin. Here, we sought to explore (i) whether lPBN ghrelin-sensitive neurones are involved in feeding and body weight control and (ii) the neurochemical identity and projection sites of lPBN-GHSR cells. Silencing of the lPBN-GHSR neurones was achieved using a Cre-dependent viral vector expressing tetanus toxin-light chain (Tetx-LC) in GHSR-Cre mice [1]; this resulted in a significant decrease in total energy intake (Tetx-LC group: 9.3 kcal ±0.8; controls: 13.7 kcal ±0.8) and specifically a reduction in sucrose intake when given access to a high-fat high-sugar diet (Tetx-LC group: 1.3 kcal ±0.5; controls: 2.9 kcal ±0.6), followed by a significant loss in body weight (Tetx-LC group: 96.7% ±3.7 of initial body weight) compared to control animals (112.3% ±3.4 of initial body weight; wild-type mice also injected with the viral vector). Using immunofluorescence, we found that 24% of the lPBN-GHSR cells express the calcitonin gene-related peptide (CGRP). Lastly, the expression of Tetx-LC coupled to a fluorochrome in lPBN-GHSR neurones allowed us to identify brain areas that receive projections from this population of cells; nuclei of the amygdala and the hypothalamus represented a large portion of the projection sites of lPBN-GHSR neurones. Collectively, these data demonstrate that lPBN-GHSR neurones have a key role in the regulation of energy balance and food choice and that they are, in the majority, not expressing CGRP. We also identify novel ghrelin-responsive pathways from the lPBN to the amygdala, bed nucleus of the solitary tract and to several hypothalamic areas.

Research mainly supported by Vetenskapsrådet (2016-02195).

DOPAMINE-GLUTAMATE NEURONS FACILITATE BEHAVIORAL SWITCHING UNDER CIRCUMSTANCES OF ALTERED CUE-REINFORCER CONTINGENCIES

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Body
Dopamine (DA) neurons in the ventral tegmental area (VTA) capable of glutamate (GLU) cotransmission project to the nucleus accumbens (NAc) shell (Mingote et al., J Neuroscience, 2015). In the NAc shell, they make strong GLUergic connections to cholinergic interneurons, and can control their activity (Chuhma et al., Neuron, 2014). Decreasing GLU cotransmission by reducing the expression of glutaminase (gene Gls1) in DA neurons selectively interferes with the ability of the neurons to drive cholinergic interneurons to burst fire. Behaviorally, mice with reduced Gls1 in their DA neurons show potentiated latent inhibition (Mingote et al., eLife, 2017). In this paradigm, mice initially receive multiple presentations of a tone, which in a later session are paired with a mild shock, so that animals have to switch from a tone-nothing to a tone-shock association. The delay in switching characterizes latent inhibition. We hypothesized that the DA neuron GLU signal facilitates behavioral switching. To test this further, we used the INTRSECT combinatoric viral strategy (Fenno et al., Nature Meth, 2014) that allows for selective expression of channelrhodopsin-EYFP in either DA-GLU or DA-only neurons. This revealed that DA neurons projecting to the dorsal NAc medial Shell are exclusively DA-GLU neurons; DA-GLU neurons project strongly to the NAc lateral Shell and sparsely to the NAc Core. Stimulating DA-GLU neurons in the VTA in vivo disrupted latent inhibition, thus facilitating the switching from responding to a tone-nothing to a tone-shock association. These data suggest that DA-GLU neurons projecting to the NAc shell play a crucial role in adjusting behavioral responses in situations of greater uncertainty, when cue-reinforcer contingencies are altered.
Goal-directed behaviors depend upon response-outcome associations, the response being mediated by the expectation of the outcome. For optimal performance, animals not only rely on a general representation of the goal for their actions, but must also monitor their own behavioral progress in reaching that goal. The dorsomedial striatum (DMS) is involved in the formation of associations among stimuli, actions and outcomes during goal-directed decision-making. However, how this region encodes the execution of goal-directed action sequences when animals are monitoring their own behavior remains unclear. To address this question, we trained rats to complete a sequence of at least 5 consecutive lever presses to obtain a reward. Premature visits at the reward port before the completion of the sequence were punished by resetting the lever press ratio. Therefore, rats had to monitor their own behavior to maximize their rate of reinforcement. We obtained in vivo single-unit recordings in the DMS during this task. We found that DMS activity was characterized by a ramp along the sequence, culminating after the last lever press, and followed by a switch in activity before the port entry. This switch resulted from the reorganization of population activity rather than individual neuron changes. These results suggest that DMS neurons collectively encode termination of the lever press sequence and subsequent transition to the reward port, in a task favoring sustained monitoring of ongoing behavior.
Title
DOSE DEPENDENT CPP OR CPA INDUCED BY INTRA-VTA ETHANOL: ROLE OF MU OPIOID RECEPTORS AND EFFECTS ON NR2A NMDA SUBUNIT.

Authors
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Body
The neurobiological mechanisms underlying alcohol motivational properties are still not fully understood, however the mu-opioid receptors (MORs) have been evidenced as central elements in the manifestation of the alcohol reinforcing properties. Drug-associated environmental stimuli can trigger alcohol relapse and promote alcohol consumption having N-methyl-D-aspartate (NMDA) receptors an important role in these learn-context associations. Here we sought to demonstrate, for the first time, the ethanol induction of conditioned place preference or aversion (CPP or CPA) when this drug is administered locally into the ventral tegmental area (VTA) with a special focus on the MORs involvement. Further, we analysed the changes in the expression of NMDA receptor and its subunits in the implicated brain areas. First, we characterized the expression of CPP or CPA when encompassing a broad range of doses of ethanol intra-VTA are administered (35-300 nmol), showing that either reinforcing (CPP) or aversive (CPA) effects are induced depending on the ethanol dose administered. Furthermore, the pivotal involvement of local MORs in the acquisition of CPP was revealed by their selective blockade with β-Funaltrexamine. Finally, modifications of the expression of NMDA receptor subunits in the Nucleus Accumbens (NAc) and Hippocampus after ethanol-induced CPP were analysed at the proteomic and transcriptomic levels by western blot and In Situ Hybridization RNAscope techniques, respectively. Results showed that the mRNA levels of NR2A but not NMDAR1 in NAc are higher after ethanol CPP. These novel results set the base to further analyse the mechanism by which ethanol motivational properties are associated with learned environmental cues.
PO 37

Title
DRD1 AND DRD2 IN NAC CORE ARE CRITICAL TO THE INCUBATION OF METHAMPHETAMINE CRAVING AFTER VOLUNTARY ABSTINENCE

Authors
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Body
We recently introduced an animal model to study incubation of drug craving after prolonged voluntary abstinence, mimicking the human condition of relapse after successful contingency management treatment. Here we studied the role of the nucleus accumbens (NAc) in this model. We trained rats to self-administer a palatable solution (sucrose+maltodextrin 1%, 6 h/d, 6 d) and methamphetamine (6 h/d, 12 d). We then evaluated relapse to methamphetamine seeking after 1 and 15 days of voluntary abstinence, achieved via a discrete choice procedure between the palatable solution and methamphetamine (14 d). We used RNAscope in-situ hybridization to quantify the colabeling of the neuronal activity marker Fos, and dopamine Drd1- and Drd2-expressing medium spiny neurons (MSNs) in NAc core and shell during the incubation tests. Next, we determined the effect of pharmacological inactivation of NAc core and shell by either GABAA and GABAB agonists (muscimol+baclofen, 50+50 ng/side) or selective Drd1 and Drd2 antagonists (SCH39166 1.0 μg/side, raclopride 1.0 μg/side) during the relapse tests. Incubated methamphetamine seeking after voluntary abstinence was associated with a selective increase of Fos expression in the NAc core, but not shell, and Fos was co-labeled with both Drd1- and Drd2-MSNs. NAc core, but not shell, injections of muscimol+baclofen, SCH39166, and raclopride agonists reduced methamphetamine seeking after 15 days of abstinence. Together, our results suggest that dopamine transmission through Drd1 and Drd2 in NAc core is critical to the incubation of methamphetamine craving after voluntary abstinence.
Title
EFFECT OF POSITIVE ALLOSTERIC MODULATION OF GABAB RECEPTORS ON PATHOLOGICAL ALCOHOL CHOICE.

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Body
Alcohol addiction is characterized by a progressive shift of decision making, in which alcohol is increasingly chosen over healthy non-drug rewards. Using an exclusive choice-based method to identify rats that continue to self-administer alcohol at the expense of a high-value natural reward, a sweet solution, we recently found that only about 15% of outbred rats choose alcohol over an alternative high-value reward. Furthermore, these animals display a constellation of behavioral traits that resembles those currently considered diagnostic for alcohol addiction. Among several dysregulations in GABAergic pathways, we found low amygdala expression of the GABA-transporter GAT-3 in vulnerable rats, which resulted in impaired GABA-clearance. Rescuing this impaired GABA-clearance might therefore be a successful therapeutic approach in alcohol addiction.

Recent observations indicate that presynaptic GABAB receptors inhibit GABA-release within the CeA. In a first experiment, we therefore evaluated the potential of ADX71441 (3 or 10 mg/kg), a novel positive allosteric modulator of GABAB receptors to rescue pathological alcohol choice over high value alternative rewards. We found that the GABAB PAM potently, dose-dependently and selectively normalizes choice preference in the minority of rats that choose alcohol over a natural reward. This effect is achieved at doses that are not associated with sedation or other adverse effects. In a second experiment, we asked whether ADX71441 could also rescue choice preference for alcohol when this preference is induced as a result of alcohol dependence. To this end, we characterized a population of rats for alcohol vs sweet choice preference, and exposed them to the alcohol vapor inhalation procedure. A history of physical alcohol dependence increased the proportion of rats that choose alcohol over an alternative reward to about 45% of the population. Together, our results confirm and extend previous data indicating that GABAB PAMs merit being tested clinically as a therapeutic for alcohol addiction.
PO 39

Title
EFFECT OF SOCIAL CHOICE-INDUCED VOLUNTARY ABSTINENCE ON INCUBATION OF METHAMPHETAMINE CRAVING AND AMPAR RECEPTOR EXPRESSION IN NUCLEUS ACCUMBENS CORE

Authors
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Body
Cue-induced cocaine and methamphetamine (Meth) craving progressively intensifies during forced abstinence from drug self-administration (incubation of craving). Electrophysiological studies revealed that incubation of cocaine and Meth craving is associated with accumulation of GluA2-lacking calcium-permeable AMPA receptors (CP-AMPARs). Biochemical studies on cocaine incubation suggest that CP-AMPARs are mainly homomeric GluA1, reflected by an increased cell surface of the GluA1 subunit. Here we quantified AMPARs subunits (GluA1, GluA2 and GluA3) in Meth trained rats after forced or social choice-based voluntary abstinence, the latter a procedure that attenuates incubation of Meth craving. We trained rats to lever press for a social-peer (social self-administration; 2h/d, 5 d) and subsequently to intravenous Meth (6 h/d, 12 d) or saline (control groups). We then evaluated relapse to Meth seeking after 1 and 15 days of forced or social voluntary abstinence, the latter achieved via a discrete choice procedure between the social peer and Meth (14 d). Immediately after the relapse tests on day 1 and 15, we dissected the NAc core for the quantification of AMPARs subunits. We used a BS3 crosslinking procedure, which enables the distinctive quantification of surface and intracellular proteins by Western Blotting. In agreement with our previous results, Meth seeking was higher on day 15 than day 1 (incubation of craving) after forced but not social choice-based voluntary abstinence. Neither incubation after forced abstinence nor blockade of incubation by social choice-based voluntary abstinence were associated with changes in levels of surface AMPARs subunits GluA1, GluA2 and GluA3, which were not different from those of drug-naïve control rats on abstinence days 1 and 15. Our preliminary biochemical results suggest that incubation of Meth craving after forced abstinence or the blockaded incubation of Meth craving after social choice-based abstinence are not associated with evident changes in AMPARs expression in nucleus accumbens core.
PO 40

Title
CHRONIC COCAINE-INDUCED STRUCTURAL CHANGES IN BRAINS OF Rhesus Monkeys: Lasting Changes and Areas of Recovery After 2 Years of Abstinence.

Authors
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Body
To gain insight into the observed differences in brain gray matter between human cocaine users and control subjects, we previously analyzed longitudinal changes in the gray matter density (GMD) of rhesus monkeys after a 12-month period of intravenous cocaine self-administration (n=8) and compared them to controls working for water reward (n=6). Using voxel-based morphometry and an analysis pipeline to take advantage of baseline structural scans prior to cocaine exposure, we found reduced GMD in multiple regions including the orbitofrontal cortex, thalamus, and temporal and insular cortices of the cocaine group. The decrease in GMD in some clusters correlated with the impairment in cognition in the same subjects, demonstrating the functional impact of the GMD reductions. In addition, we observed increased GMD in other regions such as the temporal pole, ventral frontal cortex, caudate, cerebellum, and occipital cortex of the cocaine group. These clusters of longitudinal GMD changes correspond well with the cross-sectional changes observed clinically in humans and suggest that chronic cocaine use likely contributes to the observed reductions in their gray matter.

After a 2-year period of abstinence, we obtained another set of structural scans from a subset (cocaine n=6, control n=5) which indicated that in many regions the changes in GMD following cocaine exposure had reversed. This is consistent with the normalization of cognitive function in these subjects after 3-5 months of abstinence from cocaine. Nevertheless, we saw no change in GMD in the caudate nucleus, and in temporal and insular cortex after this prolonged abstinence from cocaine suggesting that these regions, which are hubs in key networks of the impaired response inhibition and salience attribution model, may contribute to the lasting changes that might mediate the enhanced risk of relapse observed in drug addiction.

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Title
EFFECTS OF CHRONIC CANNABINOID EXPOSURE DURING ADOLESCENCE AND ADULTHOOD ON THE REWARD-FACILITATING EFFECTS OF COCAINE IN ADULT RATS

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Body
Marijuana is by far the most commonly abused illegal substance in the world. According to research findings, chronic exposure to cannabis and synthetic cannabinoids during adolescence increases the risk of using other addictive substances in adulthood. Along these lines, the purpose of the present study was to determine the effects of chronic administration of the cannabinoid receptor agonist WIN 55,212-2 during adolescence and adulthood on the reward-facilitating effects of cocaine in adult rats. Male Sprague-Dawley rats were divided into two groups and received chronic WIN 55,212-2 (0, 0.1, 1 mg/kg, i.p.) injections, one group in adolescence (postnatal day 30-51) and the other in adulthood (postnatal day 65-86). Rats were then assessed for potential alterations of cocaine’s (0, 2.5, & 10 mg/kg, i.p.) reward-facilitating effects by using the curve-shift variant of the intracranial self-stimulation (ICSS) procedure. Rats that were exposed to the 1 mg/kg WIN 55,212-2 dose in adolescence showed increased baseline ICSS threshold compared to the control group and the group that received the 0.1 mg/kg dose of WIN 55,212-2. Moreover the group of 1 mg/kg of WIN 55,212-2 showed decreased baseline asymptotic rate of responding, compared to the control group both in adolescence and adulthood. Administration of cocaine (2.5, and 10 mg/kg, i.p.) to drug-naïve rats induced a dose-dependent decrease of ICSS threshold in both experimental groups. Furthermore, the reward-facilitating effect of 2.5 mg of cocaine was increased in rats that were exposed to 1 and 0.1 mg/kg WIN 55,212-2 in both adolescence (greater effect) and adulthood (minor effect), compared to the control group. Overall, the present results reveal that chronic cannabinoid exposure can increase the reward-facilitating effects of other addictive substances, such as cocaine, which may explain some cases where cannabis is a gateway drug for other, more harmful, addictive substances.
Title
EFFECTS OF MAMMALIAN TARGET OF RAPAMYCIN (MTOR) INHIBITORS ON BEHAVIOR IN A RAT MODEL OF FETAL ALCOHOL SYNDROME (FAS)

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Body
Background: While the mammalian target of rapamycin (mTOR) signaling pathway has attracted much attention in recent years, the contribution of mTOR activation to the development of a rat model of FAS remains largely unknown. Still, it is recognized that chronic ethanol administration increases mTOR activation and inhibits autophagy in the central nervous system. This effect induces neurodegeneration. The purpose of the present study was to investigate whether the inhibition of mTOR signaling during the development of a rat model of FAS influences the memory and anxiety-like behavior of young adult rats with FAS.

Material and Methods: The experiment was performed in male Wistar rats. The FAS model was induced by intragastric (i.g.) administration of ethanol (5g/kg, 11.33% v/v), twice a day over postnatal days (PND)4 - 9. Rapamycin (an inhibitor of mTORC1), torin-2 (an inhibitor of mTOC1/C2) and FK-506 (a mTOR-independent inducer of autophagy) were given intraperitoneally (i.p.) at the dose of 5mg/kg, 1 h before the first ethanol dose. Subsequently, the passive avoidance (PA) and elevated plus maze (EPM) tests were conducted in young adult (PND 45 - 46) rats.

Results: Our results showed that FAS model rats have impaired long (24-h delay)-term memory in the PA test, due to decreased latency index (IL). While rapamycin, torin-2 and FK-506 increased the IL in the PA task, rapamycin was the most effective. Furthermore, rapamycin, torin-2 and FK-506 normalized FAS mediated anxiolytic and hyperlocomotor effects.

Conclusions: Taken together, the results indicate that memory impairment in FAS rats is profoundly affected by mTORC1. Furthermore, mTORC1 mitigates the anxiolytic and hyperlocomotion effects observed in FAS rats. Moreover, there is dissociation between memory impairment and anxiolytic effects in FAS rats.

Acknowledgements: This work was supported by the Statutory Funds of Medical University of Lublin (DS 22/19).
Title
EFFECTS OF THE MIXED MU OPIOID RECEPTOR AND NOCICEPTIN/ORPHANIN FQ PEPTIDE (NOP) RECEPTOR AGONIST BU08028 ON ETHANOL DRINKING IN MONKEYS

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Body
Research in rodent models has supported the potential of targeting brain receptors for the neuropeptide nociceptin/orphanin FQ (NOP) to treat alcohol use disorder (AUD). The present experiments examined the effects of the mixed mu opioid/NOP receptor agonist BU08028, a structural analog of the intermediate-efficacy mu receptor agonist buprenorphine, in two nonhuman primate models of AUD. BU08028 has a similar pharmacological profile to buprenorphine, but has higher affinity and efficacy at NOP receptors and lacks abuse potential. Five female rhesus monkeys were provided free access to a 4% ethanol (EtOH) solution in daily 6-hr sessions and self-administered food pellets under a fixed-ratio schedule. When daily EtOH intakes were stable (3.01±0.29 g/kg), BU08028 (0.001-0.01 mg/kg), buprenorphine (0.01-0.056 mg/kg) or the mu receptor antagonist naltrexone (1.7-5.6 mg/kg) were administered before the session as an i.m. injection. Next, BU08028 (0.003-0.017 mg/kg), buprenorphine (0.003-0.56 mg/kg) and naltrexone (1.0-3.0 mg/kg, p.o.) were administered daily over several weeks. Each week, the dose of treatment drug was adjusted based on presence or absence of effects on EtOH intake and food-maintained responding. Finally, the acute effects of BU08028 were examined in a model of aversion-resistant drinking in which addition of the bitter tastant quinine (0.1-0.3 mg/ml) decreased alcohol drinking. Acutely, all three drugs decreased EtOH intake in all monkeys, but naltrexone also significantly decreased food-maintained responding. When administered chronically, naltrexone did not alter EtOH intake. In contrast, chronic buprenorphine and BU08028 decreased EtOH drinking in most animals without altering food-maintained responding. BU08028 also enhanced the suppressive effect of quinine on ethanol intake. The data indicate that the ability of buprenorphine to selectively decrease EtOH drinking is shared by BU08028, a drug which may have advantages for clinical use compared to buprenorphine. The results support continued studies of BU08028 and other NOP receptor agonists as potential pharmacotherapies for AUD.
PO 44

Title
EFFECTS OF THE NOVEL DEHYDROEPIANDROSTERONE (DHEA) DERIVATIVE BNN27 IN DIFFERENT RAT MODELS OF SCHIZOPHRENIA

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Body
Consistent experimental evidence indicates that the non-competitive NMDA receptor antagonist ketamine and the mixed dopamine D1/D2 receptor agonist apomorphine induce schizophrenia-like symptoms in rodents. Neuroactive steroids, including dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulphate (DHEAS) were shown to affect brain glutamatergic and dopaminergic systems and to be implicated in schizophrenia. BNN27 is a novel DHEA derivative, which is devoid of steroidogenic activity. The neuroprotective effects of BNN27 have been recently reported. The aim of the present study was to investigate the ability of BNN27 to counteract schizophrenia-like behavioural deficits produced by ketamine and apomorphine in rats. BNN27’s ability to attenuate hypermotility, stereotypies and ataxia induced by ketamine were assessed using a motor activity cage. To evaluate the efficacy of BNN27 to reverse non-spatial and spatial recognition memory deficits caused either by ketamine or apomorphine the object recognition task and the object location task were used. Finally, the social interaction test (SIT) was utilized in order to examine the effects of BNN27 on ketamine-induced social withdrawal. BNN27 (3 and 6 mg/kg, i.p.) attenuated ketamine (10 mg/kg, i.p.)-induced ataxia and to some extent also hypermotility. BNN27 (3-6 mg/kg, i.p.) counteracted ketamine (3 mg/kg, i.p.) and apomorphine (0.5 mg/kg, i.p.)-induced non-spatial and spatial recognition memory deficits. Further, BNN27 (6 mg/kg, i.p.) reduced the ketamine (8 mg/kg, i.p.)-induced social isolation. Our findings show that BNN27 was efficacious in counteracting the schizophrenia-like behavioural deficits produced by both ketamine and apomorphine. The present results, although preliminary, support a potential therapeutic role of BNN27 in the alleviation of some behavioural alterations related to schizophrenia.
Title
EFFECTS OF TRAIT SENSITIVITY TO NEGATIVE FEEDBACK ON MOTIVATION AND
ANXIETY OF RATS FOLLOWING ACUTE ADMINISTRATION OF ANTIDEPRESSANT DRUGS

Authors
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Body
Cognitive theories of depression and a growing number of experimental evidence suggest that
cognitive biases could play an important role in the individual vulnerability to depression and
antidepressant treatment.

In the present study, we investigated, in an animal model, how biased sensitivity to negative
performance feedback assessed as a stable and enduring behavioural trait, interacts with acute
effects of 5 different antidepressant drugs (AD) on rats’ motivation and anxiety.

For this purpose, initially we identified rats displaying trait 'sensitivity' and 'insensitivity' to negative
feedback in a series of probabilistic reversal learning (PRL) tests. Subsequently, in the
progressive ratio schedule of reinforcement (PRSOR) and in the light/dark (LD) tests, we
compared the effects of acute administration of venlafaxine, clomipramine, agomelatine,
estcitalopram and mirtazapine (each administered in 3 doses) on appetitive motivation and anxiety
in feedback sensitive and insensitive animals.

We report modulatory effects of feedback sensitivity on the acute effects of AD on rats’ anxiety
measured in the LD. We also demonstrate significant, though independent of feedback sensitivity,
effects of tested AD on animals’ motivation measured in PRSOR. The results are discussed in
terms of Becks’ cognitive theory of depression, neurobiological mechanisms involved in the
observed effects, and their possible implications for treatment of depressive disorders in humans.

This work was supported by the Polish National Science Centre (Research grant
PO 46

Title
ELEVATED ANANDAMIDE VIA FAAH INHIBITION PROMOTES FEAR EXTINCTION AND PROTECTS AGAINST STRESS IN HEALTHY HUMANS

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Body
Background: Dysregulation of stress and threat-responding can lead to psychopathologies such as post-traumatic stress disorder. The endocannabinoid (eCB) system is proposed to act as a “stress buffer” and thus represents a novel therapeutic target for stress-related psychiatric disorders. Preclinical data suggests that inhibition of fatty acid amide hydrolase (FAAH), the main degradative enzyme of the eCB anandamide (AEA), facilitates fear extinction and protects against the anxiogenic effects of stress. However, no studies have yet assessed whether pharmacological inhibition of FAAH produces similar effects in humans.

Methods: Healthy adults were randomized to receive FAAH inhibitor PF-04457845 (N=16) or placebo (N =29) for 10 days. On days 9 and 10 of medication administration, participants complete a 2-day behavioral and psychophysiological laboratory paradigm. Using facial electromyography (startle EMG), we assessed fear learning, as well as emotional reactivity (corrugator, zygomatic EMG) before and after a standardized stress (or control) task. Blood samples were collected for analysis of peripheral eCB and cortisol levels.

Results: FAAH inhibition was associated with enhanced recall of fear extinction when tested 24hrs after extinction learning. Participants treated with the FAAH inhibitor demonstrated attenuated autonomic and subjective stress responses, and were protected against stress-induced increases in negative affect. There was no effect of FAAH inhibition on stress-induced cortisol responses.

Conclusions: We report the first evidence of the ability of pharmacological inhibition of FAAH to influence stress- and fear-related behaviors in humans, suggesting it may represent a novel pharmacotherapeutic target for the treatment of stress-related disorders.
ENVIRONMENTAL ENRICHMENT REVERSES THE NEUROADAPTATIONS PRODUCED BY ESCALATED COCAINE INTAKE

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Escalation of cocaine taking is associated with loss of control, excessive motivation and compulsive seeking and taking of the drug. Neurobiologically, cocaine escalation produces neuroadaptations in a network of brain areas involved in motivation, salience attribution, memory, stress, and inhibitory control, which may persist after long periods of abstinence. A promising strategy to help recovery from addiction and reduce the risks of relapse is to provide “addicted” rats with environmental enrichment (EE) during abstinence. However, little is know on the neurobiological mechanisms underlying the anti-craving effects of EE affects. Here, we combined escalation of cocaine self-administration and brain-imaging approaches using fluoro-deoxyglucose microPET in rats to investigate whether EE counteracts cocaine-induced changes in brain metabolic activity. Consistent with our previous findings, escalation of cocaine, followed by a month of abstinence, led to decreased activity in the anterior cingulate and insular cortex and the dorsal striatum (DSt) and increased activity in the amygdala, the dorsal hippocampus and the mesencephalon of rats housed in standard environments (SE) compared to naïve controls. In contrast, rats housed in EE after escalation of cocaine, showed complete recovery of brain metabolic activity. Direct comparison of EE and SE rats indicates that increased activity of DSt is a selective marker of the anti-craving effects of EE. Altogether these results demonstrate that the positive effects of EE on relapse are associated with a widespread recovery of normal metabolic activity in the brain. Moreover, these results suggest that manipulating the activity of the DSt may be a strategy to help recovery from addiction.
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Title
EVALUATION OF THE REINFORCING EFFECTS OF BENZODIAZEPINE-TYPE COMPOUNDS IN REMIFENTANIL-EXPERIENCED RHESUS MONKEYS

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Body
Opioid-use disorder is associated with a high degree of co-abuse with benzodiazepines, which complicates treatment and increases risk of overdose deaths. While the mechanisms underlying the co-abuse of opioids and benzodiazepines remain unknown, α1 subunit-containing GABAA (α1GABAA) receptors seem to have a critical role in the reinforcing effects of benzodiazepine-type compounds in monkeys with a history of benzodiazepine and stimulant self-administration. Here, we aimed to investigate the extent to which a compound lacking activity at α1GABAA receptors functioned as a reinforcer in monkeys trained to self-administer the opioid remifentanil, and whether that drug is more or less robust as a reinforcer compared with full and partial GABAA receptor positive allosteric modulators (modulators). We investigated the reinforcing effects of L-838,417, a selective compound that has partial intrinsic efficacy at α2, α3, and α5 subunit-containing GABAA receptors, but lacks efficacy at α1GABAA receptors (α1-sparing compound). Its reinforcing effects were compared with those of the non-selective benzodiazepine receptor partial modulator MRK-696, and non-selective benzodiazepine receptor full modulators, triazolam and lorazepam, in rhesus monkeys trained to self-administer remifentanil under a progressive-ratio schedule of intravenous drug injection. Neither the partial modulator nor the α1-sparing compound were self-administered above vehicle levels. The full modulators triazolam and lorazepam were self-administered significantly above vehicle levels, albeit at lower levels than remifentanil. These results suggest that while α1GABAA receptors may have a role in the reinforcing effects of benzodiazepines in opioid-experienced monkeys, because L-838,417 has modest efficacy at α2, α3, and α5 subunit-containing GABAA receptors, its lack of reinforcing effects could be due to its partial activity at the other GABAA receptor subtypes. Therefore, in contrast to monkeys with benzodiazepine or stimulant self-administration histories, relatively high intrinsic efficacy at all benzodiazepine-sensitive GABAA receptors is necessary for reinforcing effects of benzodiazepine-type compounds in opioid-experienced rhesus monkeys. Funding: USPHS grant DA011792.
Title
EXENDIN-4 REDUCES SEXUAL INTERACTION VIA ACTIVATION OF GLUCAGONE-LIKE PEPTIDE 1 RECEPTORS IN THE NUCLEUS TRACTUS SOLITARIUS

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Body
The gut-brain peptide glucagone-like peptide 1 (GLP-1) reduces food intake and energy balance. In addition GLP-1 receptor (GLP-1R) agonists attenuate reward from alcohol and drugs of abuse and a recent study show that activation of GLP-1R within the nucleus tractus solitarius (NTS) suppresses alcohol-related behaviors in rodents. As reward induced by addictive drugs and sexual behaviors involve similar circuitry, we hypothesis that activation of GLP-1R suppresses sexual behavior in sexually naïve male mice. We initially identified that systemic administration of the GLP-1R agonist, exendin-4 (Ex4), decreased the number of mounts and mounting duration in the sexual interaction paradigm. On the other hand, Ex4 did neither alter the preference for female in the sexual motivation test nor the preference for female bedding in the olfactory preference test. We further established that infusion of Ex4 into NTS decreased the number of mounts, mounting duration and increased the latency to mount in male mice tested in the sexual interaction paradigm. Ex4-NTS in mice exposed to sexual interaction test displayed increased dopamine turnover as well as enhanced serotonin levels in the nucleus accumbens (NAc), an area crucial for reward. In addition, these mice displayed higher corticosterone, but not testosterone, levels in serum. Collectively these data highlights that the activation of GLP-1R, specifically those in the NTS, reduces sexual interaction in male mice and further provide a link between NTS-GLP-1R activation and the reward system.

The study is supported by grants from the Swedish Research Council (2015-03219), Swedish Society for Medical Research, The Swedish brain foundation, LUA/ALF (grant no. 148251) from the Sahlgrenska University Hospital as well as the Brain Foundation. EJ has received financial support from the Novo Nordisk Foundation. This does not alter the authors’ adherence to any journal/conference policies on sharing data and materials. The remaining author declare no conflict of interest.
Title
EXPOSURE TO A PALATABLE DIET PRIOR TO CONDITIONED PLACE PREFERENCE BLOCKS THE STRESS-INDUCED VULNERABILITY TO THE REINFORCING EFFECTS OF COCAINE IN MICE.

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Body
Certain types of food activate, not unlike drugs of abuse, common dopaminergic pathways, which could be the mechanism by which hedonic eating affects the neural pathways associated with reward. In addition, palatable food can also act as an alternative reinforcer, decreasing the vulnerability to reinstate drug-seeking behaviour. Numerous preclinical studies have provided evidence that some models of social stress, such as social defeat (SD), increase the vulnerability to the rewarding effects of cocaine with a non-effective dose (1 mg/kg). Therefore, the present study aims to evaluate whether a limited exposure to a high-fat diet (HFD) administered before each session of the conditioned place preference paradigm (CPP) blocks the increase in the rewarding effects of cocaine induced by SD.

A total of 45 adolescent male mice of the OF1 strain were employed. Animals were divided into three groups: Exploration, SD-chow, SD-HFD. Animals were exposed to 4 sessions of social defeat (SD groups) and the control group underwent a similar condition without an aggressive opponent (exploration). Three weeks after the last episode of social defeat, all the groups underwent CPP induced by a non-effective dose of cocaine (1 mg/kg). The SD-HFD group was exposed to the HFD 1h before the cocaine injection, while the rest of the groups continued to be fed with the standard diet.

As expected, SD-chow mice developed a preference for the cocaine-paired compartment, but SD-HFD animals did not show such preference. These results suggest that a brief exposure to a highly palatable diet before cocaine administration may reduce the increase in the rewarding effects of cocaine caused by social stress.

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Title
PITFALLS OF NMDA RECEPTOR MODULATION BY NEUROACTIVE STEROIDS

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Body
NMDA receptor modulation represents a promising approach to the treatment of psychiatric disorders characterized by dysfunction of glutamatergic transmission. Direct activation of NMDA receptors by glutamate site agonists raises concerns regarding excitotoxicity. Similarly NMDA receptor antagonists acting via glutamate binding site or by blocking the ion channel may interfere with normal receptor functioning. Therefore new strategies of NMDA receptor modulation have been proposed. So, neuroactive steroids represent a unique class of NMDA receptor modulators that gradually shift the focus of drug development away from direct modulation towards safer allosteric modulation.

In our previous studies we had reported therapeutic effect of negative NMDAR modulator, pregnanolone glutamate (PA-Glu), in animal models of schizophrenia, depression and in ischemia. In the present study we compared behavioral effect of PA-Glu with positive NMDAR modulator pregnanolone butyrate (MS-249) either alone or in co-application with MK-801. We assumed that enhancement of NMDAR function by MS-249 would ameliorate deficit induced by NMDAR channel blocker MK-801. We use open field, elevated plus-maze, prepulse inhibition, passive avoidance test and Carrousel maze.

In the open field neither PA-Glu nor MS-249 administration affected locomotor activity. Co-application of MK-801 with MS-249 significantly enhanced locomotion. This potentiating effect on activity was not observed in Pa-Glu+MK-801 treated rats. Enhancement of positive schizophrenia symptoms (hyperlocomotion) after application of positive allosteric modulator to MK-801 treated rats was unexpected. Also PA-Glu shows anxiolytic potential in EPM. Contrary to PA-Glu, MS-249 did not exert anxiolytic properties. The administration of both PA-Glu and MS-249 in low and medium dose reversed the memory deficit elicited by MK-801 co-application; thus showing antipsychotic effect. The highest dose of neuroactive steroids failed to restore cognitive deficit in MK-801 treated rats. Next PA-Glu normalized cognitive impairment caused by MK-801 co-treatment. None of the MS-249 doses had therapeutic effect when administered with MK-801.

It seems the positive NMDAR modulation can influence other neurobiological processes beside memory formation, e.g. anxiety and response to stress, confounding desirable outcome of treatment with memory enhancers acting via NMDARs.
Title
FREQUENCY OF GROOMING IN THE SPLASH TEST AFTER SOCIAL DEFEAT EXPOSURE PREDICTS RESILIENCE TO THE LONG-TERM EFFECTS OF DEFEAT ON COCAINE REWARD IN MICE

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Body
Stress has been associated to the development of mental disorders, including depression and drug addiction. However, most individuals exposed to negative events deal with stress positively and do not develop such disorders. In preclinical studies, repeated social defeat (RSD) is used a model of social stress and mice exposed to RSD showed an enhanced sensitivity to the rewarding effects of cocaine in the conditioned place preference (CPP) paradigm. Here, we evaluated whether grooming behaviour in the splash test after RSD exposure may predict the subsequent resilience of mice to the long-term effects of RSD on the CPP induced by cocaine. One group of mice (n= 25) were exposed to RSD (on PND 47, 50, 53 and 56) while another was only exposed to an empty cage (control, n= 15). Forty-eight hours after the last episode of RSD or exploration, all mice underwent the splash test (squirting a 10% sucrose solution on the mouse’s dorsal coat). The latency, frequency and time spent in grooming were evaluated for 5 minutes. RSD decreased time and frequency of grooming with respect to the control group. Defeated mice were divided into two groups (normal- and low-grooming). Three weeks after RSD, the three groups of mice were conditioned with cocaine (1 mg/kg). Only the low grooming group, which had less time and frequency of grooming than control mice acquired cocaine-induced CPP. Thus, the maintenance of a normal motivational and self-care behaviour after exposure to defeat predicts resilience to the effects of stress on cocaine reward. Knowledge of the behavioural traits that confer resilience to the effects of stress may contribute to develop preventive strategies to enhance resilience to drug-related disorders in vulnerable individuals.

This work has been possible thanks to the grant PSI2017-83023 (Ministerio de Ciencia, Innovación y Universidades, Spain).
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Title
CHANGING DOPAMINE TRANSMISSION LEADS TO CHANGES IN SELECTION OF ACTIVITY BASED REINFORCERS: CORRELATION WITH DARPP32 PHOSPHORILATION PATTERNS

Authors
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Body
Motivational symptoms such as anergia, psychomotor retardation and fatigue are common seen in depression and are highly resistant to treatment. Nucleus accumbens dopamine (DA) is a critical component of the neural circuitry that regulates behavioral activation and effort-related processes. In the present work, we evaluate the effect of the VMAT-2 inhibitor tetrabenazine (TBZ), which produces DA depletion and has been reported to induce depression in humans. We also assessed the effect of Bupropion (BUP) that blocks DA uptake. CD1 male mice received TBZ (0, 4, 6 and 8 mg/kg, IP) or BUP (0, 5, 10 and 15 mg/kg, IP). Anergia was evaluated in a T-maze task developed for the assessment of preference between physical activities (running in a RW) in one arm vs. sedentary reinforcers (freely available sucrose pellets) in another arm, as well as, a non-social odor in the third arm. In addition, DA receptor-activity-related markers (pDARPP32-Thr75 and Thr34) in Nacb were assessed using immunohistochemistry. In the T-maze, control mice spent more time running and less consuming sucrose or sniffing. TBZ produced a shift in the relative preference, reducing selection of the reinforcer that involved vigorous activity, but increasing consumption of a reinforcer that required little effort (sucrose). BUP, increased time animals spent running with no effect on time consuming sucrose and sniffing the neutral odor. Moreover, BUP was able to reverse the shift in preferences induced by TBZ, restoring normal levels of performance. The behavioral effects were parallel to pDARPP32-Thr34 changes. These results indicate that DA in Nacb is involved in vigorous and sustained behavioral activation, and therefore, drugs acting on DA transmission are effective at reversing the anergia-inducing effects of TBZ.
PO 54

Title
LESION OF THE POSTERIOR CEREBELLAR VERMIS INCREASES ETHANOL INTAKE AND PREFERENCE

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Body
Introduction: It has long been known that the cerebellar outputs affect the dopaminergic system in a topographic manner and that lack of a functional cerebellar cortex leads to topographic changes in dopamine receptor and transporter levels. It is also known that the cerebellum is involved in limbic functions via the vermis of the posterior lobe.
Aim: Thus, we sought to investigate the effects of a lesion in the vermis of the posterior lobe on the manifestation of a limbic function: ethanol intake and preference.
Methods: Single-housed adult male Sprague-Dawley rats were stereotaxically injected with kainic acid or saline in the cortex of the posterior vermis. Three weeks post-surgery the rats were presented two bottles in their homecages, one containing tap water and the other containing increasing concentrations of ethanol. Ethanol intake and preference, food intake, and body weights were regularly measured for a three-week period. Six weeks post-surgery that rats were euthanized, with ethanol onboard, and selected brain areas were harvested for the evaluation of neurobiological indices related to the dopaminergic system.
Results: Lesion in the posterior cerebellar vermis led to a significant increase in ethanol intake and preference (85% in kainic acid-lesioned vs. 45% in sham-operated), in all ethanol concentrations tested. Protein expression analysis revealed specific alterations related to dopaminergic function.
Conclusion: The posterior vermis of the cerebellum is involved in the regulation of ethanol intake and preference, possibly by exerting an inhibitory effect, which is abrogated by an irreversible lesion of its cortex.

Keywords: cerebellum, posterior vermis, ethanol

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Title
HOW TO CATCH A MOUSE: TAIL VERSUS TUNNEL HANDLING

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Body
Rodent research forms an important pillar of preclinical and biomedical research. Increasing awareness of the impact of environmental factors on rodent well-being has resulted in the establishment of strict measures to ensure optimal and low-stress housing conditions. In particular, guidelines were established concerning social housing, cage enrichment, and maximal cage occupancy to reduce stress in rodent colonies and provide a more robust experimental context.

In 2010, a paper was published comparing different handling methods for mice and their effect on different behavioural readouts (Hurst & West, 2010; DOI:10.1038/nmeth.1500). The authors argued that handling mice by their tail induces stress and anxiety which may affect the robustness of behavioural readouts. The authors introduced an alternative method using a transparent tunnel for lifting and transporting mice between cages, and have since then published several studies all supporting the observation that tunnel handling would be more beneficial.

However, tunnel handling would present a major challenge in husbandry protocols and for animal care takers. In the current climate of intense focus on welfare of laboratory animals, combined with the growing number of rodents used in scientific research, a thorough investigation of a potentially superior handling method is relevant and necessary.

The Laboratory of Biological Psychology at KULeuven is a well-established expertise centre for mouse behaviour since 2003, specialized in phenotyping exploratory, emotional, social and cognitive behaviour in mouse models. We compared the effect of two handling methods (tail versus tunnel handling) on all behavioural domains, incorporating the required standards of housing at the KULeuven. We included 40 female C57BL/6 mice, and compared their emotional, social, stress related and cognitive behaviour using a well-established and validated test battery.
Title
IMPACT OF BACLOFEN, AN AGONIST OF GABAB RECEPTORS, ON MEPHEDRONE-INDUCED PLACE PREFERENCE IN RATS.

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Body
Preclinical studies indicate that GABAB receptors are a potential target for treatment of drug abuse. Mephedrone (4-methylmethcathinone), a psychostimulant from the designer cathinone class, enters the presynaptic neuron and promotes transporter-mediated release of dopamine and serotonin and increases extracellular level of these neurotransmitters in the nucleus accumbens of rats. However, the role of GABA-ergic system in mephedrone rewarding effects has not been evaluated so far. Therefore, to evaluate the impact of GABAB receptors on addiction-related behaviour, we tested the ability of orthosteric agonist, baclofen, to suppress conditioned place preference induced by mephedrone. Our studies revealed that mephedrone at the doses of 10 and 20 mg/kg produced a place preference in an unbiased procedure. Once established, mephedrone induced conditioned place preference was attenuated by acute administration of baclofen (3 mg/kg, i.p.). Although we are aware of side effects of baclofen in humans, we suggest that these findings may encourage further investigation of GABAB receptor positive modulators in addiction models to develop novel treatment strategies for mephedrone addiction.

This study was partially supported by grant no 2017/25/B/NZ7/02410 from the National Science Centre, Poland.
THE ANTIDEPRESSANT BUPROPION ENHANCES BEHAVIORAL ACTIVATION IN A MOUSE MODEL OF EFFORT-BASED DECISION-MAKING: COMPARISON BETWEEN CHOICE AND NON-CHOICE OPERANT TASKS

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Impairments in behavioral activation and effort-related decision-making are often seen in people with depression. These impairments lead to symptoms such as fatigue and anergia, which are very resistant to treatment. Since mesolimbic dopamine (DA) has demonstrated to be part of the circuit that regulates these processes, in the present study we administered Bupropion (BUP), a DA uptake blocker used as an antidepressant, to enhance DA function in CD1 male adult mice.

To evaluate the potential improvement of BUP (0, 5, 10 and 15 mg/kg, IP), not only on effortful behaviors, but specifically on effort-based decision making, mice were split in two groups: the first group was trained in an operant chamber under a high effort FR8 schedule that, during 5 seconds, made available a bottle with a 10% sucrose solution (no-choice condition). Second group of animals was also trained in a FR8 schedule for 10% sucrose, but additionally they concurrently had in the operant box a bottle with 3% sucrose solution (choice condition). The presence of the free 3% sucrose solution lead to a lower baseline lever pressing in the choice condition, and mice consumed the same volume of both solutions after the 15 minutes operant session. In a previous free-drinking choice test with no operant work required, mice strongly preferred and consumed significantly more of the 10% sucrose vs the 3% sucrose solution. While BUP did not change lever pressing under no-choice condition, a dose 5 mg/kg BUP significantly increased lever pressing and reduced free 3% drinking under the operant choice condition. This increase was not due to a purely effect on baseline lever pressing, since in a FR4 no-choice test that generates a lower baseline lever-pressing, BUP did not produce an increase. Thus, drugs that enhance DA transmission may be effective to improve depressive symptoms related to anergia.
PO 58

Title
ANTIDEPRESSANTS BIND TO TRANSMEMBRANE REGION OF BDNF RECEPTOR (TRKB)

Authors
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Body
The BDNF receptor TRKB, plays a crucial role in antidepressant-induced plasticity. These drugs accumulate in cholesterol-enriched domains of cell membrane. Thus we hypothesized that antidepressant drugs facilitate TRKB activation in cholesterol-dependent manner. We identified a cholesterol-binding motif (CRAC) in the transmembrane region of TRKB. In cultured cortical cells from rat embryos (E18, DIV8-14) lower doses of cholesterol (20μM) facilitate BDNF effect on TRKB (pTRKB), while higher concentrations (50μM) prevents such effect. Combination with fluoxetine partially recovered BDNF effect under 50μM of cholesterol. Molecular dynamics simulations indicate three possible states of TRKB dimers upon cholesterol increase in the membrane the TRKB dimer assumes a signaling competent arrange at intermediate levels of cholesterol (20%/mol). Simulations indicate a pocket for fluoxetine formed by the TRKB dimer and engaging lipid membrane to stabilize the complex. Then we assayed the binding of biotinylated antidepressants to immobilized TRKB. All tested compounds (fluoxetine, imipramine and 2R,6R-HNK) were found to bind to TRKB.wt and at lower level to CRAC mutant TRKB. Cholesterol promotes the binding of labeled fluoxetine or RR-HNK to TRKB, with reduced effects in mutant TRKB. Fluorescence recovery after photobleaching (FRAP) assay indicates that GFP-tagged TRKB movement in spines is promoted by fluoxetine or BDNF, but absent in mutant TRKB. TIRF/dSTORM analysis indicates that fluoxetine- or BDNF-induced clustering of TRKB is attenuated in TRKB.mutant. Finally, using animals carrying the same point mutation in TRKB CRAC motif, we observed the blockade of fluoxetine effects on object-location memory, extinction of fear conditioning and shift in ocular dominance.

Our data presents a novel mechanism for the drug-induced plasticity, where the membrane lipids provides a crucial environment for TRKB interaction with antidepressants.
INCREASED IMPULSIVITY AND BRAIN CYTOKINE ALTERATIONS AFTER STREPTOCOCCAL AND ANTIBIOTIC EXPOSURE IN RATS

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Rationale: Group A streptococcus (GAS) infection is associated with different neuropsychiatric disorders characterized by inhibitory control deficit, such as attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, and Tourette’s syndrome. Antibiotic treatment reduces GAS symptoms; however, the effects on impulsivity have not been fully assessed, thereby limiting our understanding of its causal role in neuropsychiatric disorders.

Objectives: We investigated whether GAS exposure during early adolescence might induce impulsivity in the adulthood, and if the antibiotic treatment contribute to its prevention.

Methods: Male Wistar rats were exposed to GAS antigen or vehicle plus adjuvants at postnatal day 35 (with two boosts), and were treated with either Ampicillin (supplemented in their drinking water) from PND35 to PND70 (Groups: Control/Water, Control/Ampicillin, GAS/Water and GAS/Ampicillin). Impulsivity was assessed, in the adulthood, using two different models: the 5-Choice serial reaction time task (5-CSRT task) and the Delay-discounting task. Brain cytokine levels within prefrontal cortex and nucleus accumbens were assessed in homogenates using an ELISA approach.

Results: GAS exposure increased impulsivity in both paradigms, revealing some differences due to its treatment with Ampicillin. GAS/ampicillin group showed poor inhibitory control by increased premature responses after manipulating the inter-trial interval in the 5-CSRT task. GAS exposed groups revealed a higher choice impulsivity at delay 40 s in the Delay-discounting task. Moreover, the increased impulsivity was associated with reduced interleukin levels, IL-6 and IL-17, in the prefrontal cortex; and increased TNF-alpha levels in the nucleus accumbens.

Conclusions: GAS exposure and ampicillin treatment induced inhibitory control deficit, suggesting long-term changes in frontostriatal mechanisms that might be involved in vulnerability to neuropsychiatric disorders.

This work was supported by a grant from the Ministerio de Economía y Competitividad (Spanish Government) and Fondo Europeo de Desarrollo Regional (Grant number MINECO-FEDER P12015-70037-R and PGC2018-099117-B-C21).
Title
INDIVIDUAL DIFFERENCES IN THE CONTRIBUTIONS OF NICOTINE AND A NICOTINE-ASSOCIATED CUE DURING NICOTINE SELF-ADMINISTRATION

Authors
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Body
Nicotine has been recognized as the main psychoactive compound responsible for tobacco dependence, and yet current therapeutic treatment targeting nicotine have limited efficacy. Understanding the precise psychobiological mechanisms that underlie tobacco dependence could eventually lead to the development of better therapeutic strategies. Clinical and preclinical studies have shown that nicotine seeking is a complex behavior controlled by interactions between nicotine and associated environmental cues. Nicotine can act as a primary reinforcer, and can make nicotine-associated cues become conditioned reinforcers through Pavlovian mechanisms. Nicotine can also enhance the reinforcing value of stimuli that are already reinforcing. Importantly, there is evidence that individuals may be differently responsive to these nicotine-cue interactions, and this could explain the differences in smoking behavior, withdrawal symptoms and success to a quit attempt reported in the literature. However, the exploration of the psychopharmacological mechanisms behind these differences remains largely ignored. We have evidenced two subpopulations of individuals with distinct contributions of nicotine-cue interactions that drive their seeking behavior during nicotine self-administration. Rats were first trained to self-administer nicotine paired with a discrete cue light, which is by itself mildly reinforcing, and then tested for seeking behavior when (a) the cue was omitted, but nicotine was still available and (b) when nicotine was omitted, but the cue was still present. In the first subgroup (n=34), rats would extinguish seeking behavior when either nicotine or the cue were absent, suggesting that in these individuals nicotine is enhancing the reinforcement of the cue. In the second subgroup (n=28), rats would maintain seeking behavior either with nicotine, or cue, by themselves, suggesting that nicotine acted as a primary reinforcer, while the cue had become a conditioned reinforcer. Altogether, this data supports that different psychopharmacological mechanisms in the intersection between nicotine and surrounding cues might support nicotine self-administration at the individual level.
PO 61

Title
INDIVIDUAL VULNERABILITY TO STRESS IS ASSOCIATED WITH INCREASED DEMAND FOR INTRAVENOUS HEROIN SELF-ADMINISTRATION IN RATS

Authors
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Body
Opioid use is a widespread epidemic, and traumatic stress exposure is a critical risk factor in opioid use and relapse. There is a significant gap in our understanding of how stress contributes to heroin use, and there are limited studies investigating individual differences underlying stress reactivity and subsequent stress-induced heroin self-administration. We hypothesized that greater individual vulnerability to stress would predict higher demand for heroin self-administration in a within-subjects rodent model of stress and heroin use comorbidity. Male rats were exposed to inescapable intermittent swim stress (ISS) and individual biological (corticosterone) or behavioral (open field, social exploration, and forced swim tests) measures were assessed before and after the stress episode. Individual demand for self-administered heroin (0.05 mg/kg/infusion; 12-hour sessions) was assessed using a behavioral economics approach followed by extinction and reinstatement tests triggered by stress re-exposure, non-contingent cue presentations, and yohimbine (0, 1.0, or 2.5 mg/kg). We found that behavioral, biological, and a combination of behavioral and biological markers sampled prior and after ISS and weeks before the access to heroin self-administration predicted individual demand for heroin. The non-contingent presentation of cues previously associated with heroin reinstated heroin seeking in extinction. For the first time, we show that individual biological response to an ecologically relevant stressor in combination with associated behavioral markers can be used to predict subsequent economic demand for heroin.
PO 62

Title
INTERMITTENT ACCESS COCAINE SELF-ADMINISTRATION AND PSYCHOMOTOR SENSITIZATION

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Body
The ability of drug self-administration (SA) experience to produce symptoms of addiction is critical to understanding the neural and behavioral plasticity associated with the transition from controlled to problematic use. Traditional models of cocaine SA, particularly the Long Access (LgA) model, have been shown to blunt the psychomotor activating effects of cocaine, and this has been taken as evidence that the transition to addiction is due, in part, to a hypo-dopaminergic state, and that drug-seeking is maintained to alleviate this DA deficiency. However, recent studies have established that Intermittent Access (IntA) cocaine SA is more effective than LgA at producing addiction-like behavior, and it sensitizes DA neurotransmission. We asked, therefore, whether IntA (and LgA) experience produces psychomotor sensitization, comparable to that known to be produced by intermittent experimenter-administered cocaine. When tested following one day of withdrawal, rats with IntA (but not LgA) experience expressed psychomotor sensitization, evidenced by increased locomotor activity. After extended withdrawal, however, both IntA and LgA (6 hours/day) rats expressed robust psychomotor sensitization, as indicated by focused stereotyped behavior. As reported following experimenter-administered cocaine, IntA experience produced more robust psychomotor sensitization in female than male rats. Experimenter-administered cocaine is also known to produce cross-sensitization to other drugs including amphetamine. Importantly, IntA experience also sensitized rats to the psychomotor activating effects of a subsequent injection of amphetamine. In summary, IntA cocaine SA experience is highly effective at producing changes in those brain systems that mediate the psychomotor activating effects of psychostimulant drugs, which are thought to include mesostriatal DA systems. These studies add to a growing literature that suggests IntA experience produces a hyper-responsive DA system. This is consistent with the concept of incentive-sensitization, and supports the notion that a hyper-, rather than hypo-dopaminergic state may promote the transition to addiction.
PO 63

Title
INVESTIGATION OF LONG-TERM POTENTIATION- AND DEPRESSION-INDUCED TAU PHOSPHORYLATION IN RATS WITH STARCH BASED SUGAR

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Body
Objective: A lot of evidence supports the hypothesis that the mechanism of memory trace formation at the cellular level is long-term potentiation (LTP) and long-term depression (LTD). LTP and LTD are initiated postsynaptically by the activation of N-methyl-d-aspartate (NMDA) receptors (NMDARs), resulting in Ca2+ influx and the subsequent activation of several kinases. Studies in which experimental animals were fed with fructose for a long time showed that insulin resistance occurred and this was associated with poor performance in hippocampus-dependent learning. We therefore wanted to study that LTP/LTD-related modifications of tau phosphorylation could be, or not be, changed with high-fructose Corn Syrup consumption (HFCS).

Methods: The study was performed on sixty (100 ± 15 gr; 20 / group) 21-day old male Wistar Albino rats obtained from Erciyes University Experimental Animal Research Center. On the 21st day, the male rats leaving their mothers are fed with unrestricted standard rat chow and tap water, HFCS solution (8%; 0.24 Kcal / mL) or sucrose solution (10%, 0.4 Kcal), / mL for at least 21 days. The field potentials were recorded from the right dentate gyrus with stimulation of the right medial perforant path. Long-term potentiation (LTP) and long-term depression (LTD) were induced by high and low frequency stimulation (HFS and LFS), respectively. Total and phosphorylated forms of Tau was measured in the hippocampus at least 60 min after induction of plasticity.

Conclusion: These findings suggest that high fructose-containing diets may disrupt the balance between two forms of synaptic plasticity and thus adversely affect learning processes [3]. Epitope specific tau phosphorylation had been emphasized for Alzheimer’s disease-like learning deficit due to feeding with HFSC.
Title
LATERAL HYPOTHALAMIC OREXIN PROJECTIONS TO VENTRAL TEGMENTAL AREA MODULATE DOPAMINE NEUROTRANSMISSION AND REWARD-RELATED PROCESSES

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Body
Reward and reinforcement processes are critical for individuals’ survival and propagation of genes. While a number of brain systems are involved in these processes, evidence points to a cardinal role for mesolimbic dopamine (DA). Indeed, DA projections from the ventral tegmental area (VTA) to ventral striatum, in particular the nucleus accumbens (NAcc), can modulate reward-seeking. Orexin (Ox; hypocretin) neurons from the lateral hypothalamus (LH) project to the VTA and have also been implicated in motivation and reward-seeking behaviours. Furthermore, exogenous Ox application to the VTA increases NAcc DA. Ox is co-expressed with dynorphin (DYN), a kappa-opioid receptor agonist that reduces DA neuronal activity. Therefore, it is unclear how co-release of endogenous Ox and DYN in the VTA modulate DA neurotransmission in the NAcc. We hypothesised that optogenetically-potentiated LHox/dyn input to the VTA enhances DA neurotransmission in NAcc and amplifies reward-seeking behaviour.

To test our hypothesis, we used genetic, optogenetic, fast-scan cyclic voltammetric, and behavioural approaches. Ox-cre (+/+) mice were infused with channelrhodopsin virus in LH (control mice were infused with a fluophore-tagged control virus). We performed anaesthetized FSCV during which we assessed electrically-evoke DA neurotransmission in NAcc, while optogenetically stimulating LH Ox terminals in VTA. We found that LHOx/dyn terminal stimulation in VTA potentiates electrically-evoked DA neurotransmission in NAcc. We also assessed real-time place preference to optogenetic stimulation of LHOx/dyn terminals in VTA and found that mice infused with channel rhodopsin spent more time in the stimulation area compared to controls, and to the non-stimulation side. These data show that photostimulating LHOx/dyn projection terminals on VTA DA neurons increased evoked DA neurotransmission, suggesting that Ox likely predominates over DYN on VTA to NAcc projections. Furthermore, photostimulation of the LHox/dyn projection to the VTA promotes reward seeking. Future directions will assess this circuit in reinforcer- and cue-driven behaviours.
Title
MATERNAL STRESS PRIOR GESTATION EFFECTS EXCITABILITY OF HIPPOCAMPAL CELLS IN VITRO AND IS ASSOCIATED WITH NEUROBEHAVIORAL ALTERATIONS DURING ADULTHOOD

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Body
Chronic stress during pregnancy can negatively affect offspring’s neurobehavioural development. Several studies have shown, that offspring who had experienced excessive stress during gestation had higher rates of cognitive and mood disorders later during adolescence or in adulthood. Hippocampal neurons play a crucial role in the regulation of behavior, mainly in anxiety-related behaviors and spatial learning and memory. Recently, it has been shown, that excessive stress even prior to gestation could interfere with sensitive developmental processes in the brain and may affect hippocampal functioning with severe neurobehavioural consequences in later life. The aim of this work was to investigate the effects of pre-gestational stress of the rat dams on the hippocampal excitability of the pups right after the birth. Neurobehavioural consequences of pre-gestational stress were analyzed during adolescence and in early adulthood. We have shown that pre-gestational chronic maternal stress increased resting membrane potential, suppressed depolarization-activated action potential firing, and increased spontaneous activity of hippocampal cells from newborn offspring. Altered function of hippocampus was reflected at the behavioural level. Adolescent male offspring of dams exposed stress prior to conception showed hyperactivity-like behavior in a new stressful environment and increased anxiety-like behavior during adulthood compared to adult males from non-stress group. Together, this work suggests, that chronic stress even prior to gestation can interfere with functional brain development of the offspring and can cause long-term behavioural changes at the level of neurobehavioural adaptations.

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Title
METABOLIC EFFECTS OF MEPHEDRONE

Authors
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Body
Mephedrone, a synthetic derivative of cathinone represents a group of new psychoactive substances (NPS) and exerts its effects by interacting with plasma membrane monoamine transporters proteins for dopamine (DAT), noradrenaline (NET) and serotonin (SERT) and increasing the level of abovementioned monoamines in the central nervous system. It also demonstrates reinforcing properties by activating the neuronal pathways in the brain reward system. Although, there are numerous studies published on mephedrone addictive, neurotoxic and pro-oxidative potential, its impact on metabolic effects is still unknown. Hence, the aim of our study was to evaluate mephedrone impact on metabolic effects in rats using Oxymax-CLAMS (Comprehensive Lab Animal Monitoring System) – a device capable of multi-parameter measurements, including calorimetry. In this system, heat is derived by assessment of the exchange of oxygen for carbon dioxide that occurs during the metabolic process. The relationship between the volume of gas consumed (O2) and of that produced (CO2) reveals the energy utilized by the subject. Our study showed that mephedrone (30 mg/kg) administered in binge-like regimen (4 times a day, every 2h) caused an increase of the CO2 production and O2 consumption. Moreover, mephedrone (10 and 30 mg/kg) caused an increase of body temperature. All measurements were calculated in comparison to vehicle treated group. These results suggest that mephedrone influences metabolic processes by increasing the amount of produced heat and energy. However, measuring interactions in electron transport chain will be the next crucial step to properly evaluate mechanisms underlying observed metabolic effects of mephedrone.
PO 67

Title
MGLU5 RECEPTOR AVAILABILITY IN EMERGING ADULTS AT RISK FOR ADDICTIONS: EFFECTS OF VULNERABILITY TRAITS AND CANNABIS USE

Authors
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Body
Objective:
The excitatory neurotransmitter glutamate has been implicated in experience-dependent neuroplasticity and drug-seeking behaviors. Type 5 metabotropic glutamate (mGlu5) receptors might be particularly important. The receptors are critically involved in synaptic plasticity and their availability is reported to be lower in people with alcohol, tobacco, and cocaine use disorders. Since these reductions could reflect effects of drug use or pre-existing traits, we used positron emission tomography to measure mGlu5 availability in young adults at elevated risk for addictions.

Methods:
Fifty-nine participants were recruited from a longitudinal cohort that has been followed since birth. Based on externalizing traits that predict future substance use problems, half the participants were at low risk, half were at high risk. Cannabis use histories varied markedly and participants were divided into three groups: zero, low, and high use.

Results:
Compared to low risk volunteers, those at elevated risk had lower [11C]ABP688 binding in the striatum, amygdala, insula, and orbitofrontal cortex (OFC). Cannabis use by risk group interactions were observed in the striatum and OFC. In these regions, high cannabis use was associated with low [11C]ABP688 binding in the high risk group only. When the high risk, high cannabis use individuals were compared to all other participants, [11C]ABP688 binding values were significantly lower in the striatum, OFC, and insula.

Conclusion:
Low mGlu5 receptor availability was seen in high risk, high cannabis users. The results provide the first evidence of a neurobiological mechanism by which adolescent cannabis use could lower the threshold for psychiatric disorders in vulnerable populations.

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Title
OPTIMIZATION OF AN ANIMAL MODEL OF CUE-INDUCED REINSTATEMENT OF FOOD SEEKING AS A CONTROL TO STUDY CUE-INDUCED REINSTATEMENT OF METHAMPHETAMINE SEEKING

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Body
From 2010 to 2015, methamphetamine (METH) poisoning deaths increased by 3-fold in the United States and METH seizures increased worldwide by 158%. Unfortunately, there are no FDA-approved pharmacotherapeutics for METH use disorder. Preclinical studies showed that lobeline inhibits vesicular monoamine transporter-2 (VMAT2) function, decreases METH-evoked dopamine release, and decreases METH self-administration. Phase 1b clinical trials demonstrated the safety of lobeline as a treatment for those actively using METH. However, lobeline is not selective for VMAT2. Generally, METH self-administration is used as the gold-standard animal model for evaluation of potential therapeutics for METH use disorder, and food self-administration is used to evaluate the specificity of effects on METH self-administration. Iterative drug discovery research identified several compounds, with high affinity and selectivity for VMAT2 that specifically decrease METH self-administration without altering food-maintained responding. These compounds also decrease cue-induced reinstatement of METH seeking. However, the specificity of the decrease in cue-induced responding typically is not evaluated. The current study sought to optimize cue-induced reinstatement of food seeking as a control animal model to further investigate the specificity of compounds that decrease cue-induced reinstatement of METH seeking. Results showed that increasing the number of extinction sessions prior to reinstatement testing increased cue-induced reinstatement of food seeking, which may have increased the saliency of cue light on reinstatement session due to incubation. Using a palatable food pellet, rather than a standard pellet, only increased responding during acquisition training without increasing cue-induced food seeking. Increasing the fixed ratio requirement also resulted in increased cue-induced food seeking. Thus, the current work establishes an optimized animal model to evaluate the specificity of compounds on cue-induced food seeking.

Supported by NIH U01 DA013519.
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Title
MODELLING THE INDIVIDUAL VARIABILITY TO DEVELOP HEROIN DEPENDENCE IN OUTBRED NIH HETEROGENEOUS STOCK RATS

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Body
Drug addiction is a chronic relapsing disorder characterized by compulsive drug seeking and use despite harmful consequences. In the USA the abuse of prescription opioid analgesics caused a recrudescence of heroin dependence epidemic. Drug dependence develops only in a subset of vulnerable subjects; understanding the biological bases of opioid addiction vulnerability would provide a valuable help for the development of personalized treatments. For this purpose we used outbred NIH Heterogeneous Stock (HS) rats characterized by a large genetic variability similar to the human population, to develop a behavioral preclinical model of individual vulnerability. Male and female HS rats were trained to a 1h short-access heroin (60µg/kg/infusion) self-administration and then they were switched to 12h long-access sessions. After the long-access, three criteria for heroin dependence were scored: escalation of heroin intake; motivation for heroin with the progressive ratio schedule of reinforcement and relapse induced by a priming dose of heroin. To verify that the pattern of individual vulnerability to heroin in outbred NIH-HS is different from genetically more homogeneous, inbred lines, we compared these data with two (Wistar Kyoto (W/K) and Fisher 344 (F344)) of the eight inbred rat lines that generate the HS. We performed Neuroimaging before and after heroin exposure to investigate if and how the drug can modify brain morphology and a regression tree analysis to verify if and to what extend data about heroin motivation and escalation could predict the relapse. Our data demonstrate that F344 and W/K represent respectively upper and lower propensity to develop opioid dependence and the HS rats include features of both lines. The HS show heroin-induced neuroimaging biomarkers similar to human patients and relapse ratio can be predicted by heroin history. Data indicate that the HS line is a suitable model to study the bases of individual variability for opioid dependence.
PO 70

Title
MORPHINE AS AN INTEROCEPTIVE PAVLOVIAN DISCRIMINATIVE STIMULUS IN MALE AND FEMALE SPRAGUE-DAWLEY RATS

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Body
Drug stimuli are capable of many of the same Pavlovian associations typically studied using exteroceptive stimuli, such as visual and auditory cues. Occasion setting is one type of hierarchical associative learning wherein the occasion setter (OS) disambiguates the relation between a conditioned stimulus (CS) and unconditioned stimulus (US) and becomes a discriminative guide of behaviour. The interoceptive stimulus evoked by administration of a drug can be learned as feature positive (FP) and feature negative (FN) OS for an appetitive CS-US association. The effectiveness of the interoceptive drug stimulus to activate or inhibit a response evoked by an exteroceptive stimulus appears to transcend drug class. However, this has not yet been investigated in opioids. Male and female Sprague-Dawley rats were assigned to FP or FN training. All rats were given 20-min daily intermixed morphine (3.2 mg/kg IP) or saline sessions containing eight 15-sec WN presentations. For FP rats, on morphine sessions, each WN was followed by 4-sec sucrose access; on saline sessions, no sucrose was available. For FN rats, sucrose was delivered on saline sessions and withheld on morphine sessions. The difference in the number of anticipatory head entries into the sucrose dispenser during and before the initial WN presentation was the primary measure of conditioned responding. Following conditioning, rats entered generalization testing where they were challenged with each of a series of morphine doses in a latin square order (0.0, 0.5, 1.0, 2.1, 3.2, 5.4 mg/kg). Acquisition was established sooner in females than males and FP training developed earlier than FN training. Furthermore, interoceptive guidance of behaviour was stimulus specific with increasing deviations from the training dose leading lower conditioned responding in FP rats and higher responding in FN rats. These findings open the opioid system to investigations of interactions between interoception and exteroception.
Title
MU OPIOID RECEPTORS AND NEUROINFLAMMATION IN A RAT MODEL OF ALCOHOL RELAPSE DUE TO PAIN SUFFERING

Authors
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Body
The relapse phenomenon occurs due to several factors such as stress, drug associated cues and, as it has been recently suggested, pain. However, the underlying biochemical changes that underlie relapse due to pain suffering have not been described yet. Furthermore, Mu Opioid Receptors (MOR) in the mesocorticollimbic system play a key role in alcohol addiction and relapse. Indeed, the use of Nalmefene or Naltrexone as anti-relapse therapy is based in MORs antagonism. Additionally, some studies have revealed that regulation of MORs cellular trafficking might be related to neuroinflammatory processes which are activated after ethanol exposure. However, the way in which neuroinflammation is related with MORs expression and function is still not fully understood. Therefore, biochemical assays were performed in an alcohol intermittent access animal model in combination with a CFA-induced inflammatory pain rat model to detect the levels of neuroinflammatory mediators COX2 and iNOS along with the transcriptional factor NFkB and expression of MORs in Ventral Tegmental Area (VTA), Prefrontal Cortex (PFC) and Nucleus Accumbens (NAc). Furthermore, all our studies were performed in male and female rats to analyse the sex factor. Interestingly, only females showed behavioural and biochemical changes whereas the proteins of analysis and the behaviour in males were not affected. Results showed that the neuroinflammatory mediators COX2, iNOS and NFkB were altered in PFC and NAc in the abstinence and reintroduction period, being those changes more remarkable in rats in pain. Same alterations were also observed in MORs expression agreeing with the possibility of an interaction between neuroinflammation and MORs trafficking. Very interestingly our studies also revealed that these changes observed in PFC during abstinence may be reverted after alcohol relapse contributing to the understanding of the mechanisms involved in pain induced alcohol relapse-like behaviour in female rats.

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Title
A NOVEL HYPOTHALAMIC-TO-THALAMIC CIRCUITRY CONTROLLING MOTIVATED NICOTINE SEEKING

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Body
In these studies, we set out to identify the circuits and mechanisms of Orexin (OX; hypocretin) neurons, of the lateral hypothalamus (LH), modulation of the motivational properties of nicotine. We found that rates of nicotine self-administration are markedly decreased, in a gene-dosage dependent manner, in mice with one or two null alleles, respectively, of the Hcrtr1 gene, which encodes the orexin-1 receptor (OX1R). When the work required to obtain nicotine was decreased by reducing the reinforcement schedule from a fixed ratio 5 (FR5) to FR1, deficits in intake were completely reversed in the mutant mice. Recordings of calcium dynamics in OX cell bodies during self-administration revealed that OX neural activity specifically coded the effort associated with obtaining nicotine, but not nicotine receipt. To identify brain circuits that explain this deficit in OX1R mutant mice, we assessed brain c-Fos levels after a nicotine injection in wild-type (WT) and Hcrtr1 KO mice. We found a small pocket of cells in the dorsal lateral thalamus (DLT) that were more robustly activated in KO mice than WT mice. Using a Hcrtr1-eGFP reporter line of mice, as well as GAD2-Cre mice, we identified a small population of OX1R-expressing cells in this same part of the DLT, that are GABAergic. Virus-mediated re-expression of the Hcrtr1 gene in the DLT of Hcrtr1 KO mice completely restored their nicotine responding under a FR5 schedule. Conversely, infusion of an OX1R antagonist into DLT, or inhibition of GAD2+ cell bodies in the DLT, decreased nicotine responding in rats and mice tested under a FR5 but not FR1 schedule. These results suggest that LH OX projections regulate the effortful seeking of nicotine by controlling local inhibitory transmission in the DLT via OX1Rs. This novel circuit may represent a locus of dysfunction and target for treatment of motivational deficits across neuropsychiatric conditions.
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Title
NEW PSYCHOPHARMACOLOGICAL TARGET FOR COMPULSIVE BEHAVIOURS: DIRECT AND INDIRECT MODULATION OF GLU ON SCHEDULE-INDUCED POLYDIPSIA.

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Body
BACKGROUND: Compulsive behaviour, present in different psychiatric disorders, such as obsessive-compulsive disorder, schizophrenia and anxiety, has been associated with altered levels of monoamines, but also, recent evidence shows that glutamate (GLU) pharmacotherapy may be of benefit in impaired inhibitory control. However, to date, there are few preclinical studies on the therapeutic potential efficacy of different glutamate modulators in inhibitory control deficit. OBJECTIVES: The current study investigated whether GLU manipulation through different drugs, modulates compulsive drinking in schedule-induced polydipsia (SIP). METHODS: Animals were selected as either high (HD) or low (LD) drinkers corresponding with their water intake in schedule-induced polydipsia (SIP). Subsequently, we assessed the effects of acute administration of scopolamine (0.125, 0.25, and 0.5 mg/kg), memantine (3.1 and 6.2 mg/kg) and lamotrigine (15 and 30 mg/kg) on compulsive drinking in SIP. RESULTS: This psychopharmacological study revealed that scopolamine, memantine and lamotrigine, at all doses tested, decreased dose-dependent compulsive water consumption in HD rats compared to LD rats on SIP. CONCLUSIONS: These results suggest that alterations of the GLU system could be involved in compulsive behaviour in vulnerable populations. Further studies on SIP, could elucidate the therapeutic role of GLU agents as a pharmacological target for compulsive spectrum disorders.

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Title
NIDA'S MEDICATION DEVELOPMENT PRIORITIES IN RESPONSE TO THE OPIOID CRISIS

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Body
To speed the development of pharmacotherapies for the treatment of opioid overdose and Opioid Use Disorder (OUD), the National Institute on Drug Abuse (NIDA) has created a list of medication development priorities. We feel compounds with the mechanisms-of-action listed below have the highest probability of a path to FDA approval for the treatment of some aspect of OUD in the near term. The list does not include mechanisms of existing OUD medications. While useful, these medications have problematic residual symptoms and discontinuation rates, leaving an un-met medical need that could be addressed, at least in part, by new medications. Ultimately, we anticipate multiple medications, psychosocial interventions, and devices, employed in an orchestrated fashion, will be needed to achieve truly effective treatment of OUD. Highest priority mechanisms: orexin-1 or 1/2 antagonists or negative allosteric modulator (NAMs); kappa opioid antagonists or NAMs; GABA-B agonists or positive allosteric modulator (PAMs); muscarinic M5 antagonists or NAMs; AMPA antagonists, NAMs, or PAMs; NOP/ORL agonists, antagonists, NAMs, or PAMs; mGlur2/3 agonists or PAMs; ghrelin antagonists or NAMs; dopamine D3 partial agonists, PAMs, antagonists, or NAMs; cannabinoid CB-1 antagonists or NAMs; 5HT2C agonists or PAMs, with or without 5HT2A antagonist/NAM activity; biased Mu Opioid agonists or PAMs; NOP/MOP bifunctional agonists or PAMs; and, respiratory stimulants (including nicotinic agonists). For each mechanism of action we invite: critical preclinical data that will either strengthen, sink, or revise the hypothesis; translational data which would help define the predictive validity of the preclinical data; and, clinical data that will definitively test the hypothesis in humans.
Title
NOT ALL IS AS IT SEEMS: CONTRADICTORY OUTCOMES IN DIFFERENT TESTS OF DEPRESSIVE-LIKE BEHAVIOR AFTER CHRONIC ADOLESCENT HU-210 EXPOSURE

Authors
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Body
Adolescent and adult rodents are known to have differential susceptibilities to the effects of cannabinoid receptor agonists. Indeed, chronic cannabinoid exposure has been shown to induce opposite long-lasting effects, as a function of rodent age, whereby it has prodepressant- and antidepressant-like effects in adolescent and adult animals, respectively. Interestingly, while chronic cannabinoid exposure also seems to lead to short-term antidepressant-like effects in adults, there is no equivalent data regarding adolescent animals.

Here, we report two separate experiments, designed to assess the short-term affective behavioral effects of chronic adolescent HU-210 exposure. For this, two separate series of adolescent female Sprague-Dawley rats were administered twice-daily intraperitoneal injections of HU-210, following an ascending dosing schedule (PND35-37: 25ug/kg; PND38-41: 50ug/kg; PND42-45: 100ug/kg), for 11 days. Starting 24-hours following the last injection animals were tested in Open Field Test (OFT) and mFST, or the Elevated Plus Maze (EPM) and the SPT. Furthermore, samples from the hippocampus and the PFC were collected for molecular analyses.

In line with previous adult studies, HU-210-treated animals showed a marked antidepressant-like profile in the mFST – with significantly decreased immobility, and increased climbing – without alterations of locomotor activity or anxiety-like behavior in the OFT. Contrastingly, in the SPT, HU-210-treated animals showed strong decreases in sucrose preference/intake, suggesting a marked prodepressant-like impact of treatment.

In addition to having important implications for the cannabinoid literature, our results also highlight the necessity of critically evaluating the results of behavioral tests in light of their known limitations, and of using multiple tests to perform more reliable assessments. Finally, our results also raise the need for a mechanistic explanation of how a single manipulation led to the markedly contrasting effects observed, regarding depressive-like behavior.
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Title
NUCLEUS ACCUMBENS SHELL KAPPA-OPIOIDERIC MECHANISMS PARTICIPATE IN CONTROLLING RELAPSE-LIKE ETHANOL INTAKE IN RATS

Authors
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Body
A major challenge in ethanol dependence research is to understand the mechanisms that promote relapse, as relapses frequently occur in recovering alcoholics. The kappa-opioidergic system is suggested to become overactivated as ethanol dependence evolves. The aim of this study was to clarify the role of the kappa-opioidergic system interacting with the nucleus accumbens shell on relapse-like ethanol intake using JDTic, a selective kappa-opioid receptor antagonist, and the alcohol deprivation effect (ADE) paradigm. The ADE is defined as a transient increase in ethanol intake after a forced period of deprivation.

Male Long-Evans rats were trained to voluntarily consume 10% (V/V) ethanol solution. After establishing stable ethanol intake and implantation of bilateral guide cannulas above the nucleus accumbens shell, ADE cycles were initiated. One cycle consisted of 10 days of 90 min access to ethanol followed by 6 days of ethanol deprivation. After this a new cycle began, in the beginning of which the ADE was evaluated. Following training infusions and a stable ADE, rats received JDTic either intra-accumbally (15 microg/site) or subcutaneously (10 mg/kg) 24h prior to ethanol re-access, and the effects on the ADE were measured. The non-selective opioid receptor antagonist naltrexone (0.3 mg/kg, sc, 20min prior) was used as a reference drug.

According to the results, both JDTic administered systemically and into the nucleus accumbens shell attenuated the ADE. Naltrexone inhibited the ADE and decreased ethanol intake. The results suggest that the kappa-opioidergic system participates in controlling ethanol relapse and the nucleus accumbens shell is one brain area mediating these effects. The results also suggest that selective kappa-opioid receptor antagonism could be used for ethanol relapse prevention.

This study was funded by grants from the Finnish Foundation for Alcohol Studies and the Finnish Cultural Foundation. JDTic was generously provided by RTI International. The authors declare no conflicts of interest.
Title
OPIOID ABUSE VULNERABILITY IN GENETICALLY SELECTED MARCHIGIAN SARDINIAN ALCOHOL PREFERING RATS.

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Body
Genetically selected Marchigian Sardinian alcohol preferring (msP) rats have been selected for their high ethanol preference for about 18 years starting from the 13th generation of Sardinian alcohol-prefering rats. Previous works demonstrated that msP rats exhibit genetic propensity to excessive alcohol drinking, potentially driven by an attempt to self-medicate from innate negative affect. In neuroimaging, microdialysis and behavioral studies we found that msPs show also increased response to psychostimulants suggesting that they might represent also a genetic model of vulnerability to other drugs of abuse. Here we tested the hypothesis that msP rats are more susceptible to abuse heroin compared to the parental Wistar line.

Male msP and Wistar rats were trained to self-administer heroin (20µg/infusion) under a fixed-ratio 1 (FR1) schedule of reinforcement. Then animals were switched to different doses of heroin (1, 6.7, 20 and 60µg/infusion) to evaluate their heroin sensitivity. Motivation was assessed using different heroin doses (1, 6.7, 20 and 60µg/infusion) under a progressive ratio (PR) schedule of reinforcement. We tested cue-induced reinstatement of heroin seeking after short and prolonged abstinence. Female msP and Wistar rats were used in order to investigate gender differences in response to heroin. Finally, using Wistars we evaluated the effect of Cebranopadol, a panopioid agonist that activates also the nociception receptor NOP, on heroin self-administration.

Results showed that both male and female msP rats self-administered significantly more heroin compared to Wistars. Break point for heroin reached under PR contingency was higher in msP compared to Wistars for all heroin doses, indicating increased motivation for opiates. Finally, in Wistar rats the panopioid agonist cebranopadol reduced self-administration of different doses of heroin (1, 7, 20 and 60µg/infusion).

These findings suggest that msP rats show an higher propensity to self-administer heroin compared to Wistars.
Environmental cues can guide behavior in an adaptive manner, bringing one in close proximity to valuable resources. However, for some individuals, such cues attain inordinate control over behavior. In rodents, individual differences in cue-motivated behaviors can be captured using Pavlovian conditioned approach (PavCa), wherein presentation of a cue (lever) is followed by delivery of a food reward. Following PavCa training, two distinct phenotypes emerge – goal-trackers (GT) and sign-trackers (ST). While both GT and ST attribute predictive value to the cue, ST also attribute incentive value to the cue. The attribution of incentive value transforms the cue into an attractive and desirable stimulus. ST and GT rely on distinct neurobiological mechanisms. Notably, the behavior of ST is dopamine (DA)-dependent, and cue-elicited DA in the nucleus accumbens is believed to encode the incentive value of reward cues. Here we exploited the temporal resolution of optogenetics to determine if selective inhibition of cue-elicited DA attenuates the propensity to sign-track. To do so, we utilized tyrosine hydroxylase (TH)-Cre Long Evans rats, which express Cre-recombinase in DA neurons. An optogenetic viral construct containing halorhodopsin, a light-sensitive inhibitory channel, was infused and expressed in DA neurons within the ventral tegmental area. First, we assessed the tendency of TH-Cre Long Evans rats to sign-track, and found that, out of ~45 rats, ~85% are sign-trackers. We then assessed whether laser-induced inhibition paired with lever presentation would prevent the development of sign-tracking behavior. Indeed, pairing of the laser-light with lever presentation during the first 75 trials of lever-food presentations decreased the tendency to sign-track. Those with optogenetic inhibition of cue-elicited DA exhibited a bias towards goal-tracking, rather than sign-tracking behavior. When laser inhibition was terminated, these same rats began to develop a sign-tracking response. These findings demonstrate that cue-elicited DA release is critical for incentive learning processes.
Title
PHARMACOLOGICAL BLOCKED OF CB2 RECEPTOR SIGNALING PROMOTES ANXIOLYTIC AND ANTIDEPRESSANT-LIKE EFFECTS IN CHRONICALLY STRESSED MICE

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Body
Introduction: Selective serotonin reuptake inhibitors, such as escitalopram (ESC), are the first line of treatment for major depressive and anxiety disorders. However, their prescription is often associated with delayed therapeutic response, important side effects and low rates of response due treatment-resistance. Several works have indicated facilitation of cannabinoid-mediated neurotransmission as a potential alternative for the treatment of psychiatric disorders. In the present work, we tested the hypothesis that the cannabinoid 2 (CB2) receptors could be involved in the behavioral and neuroplastic effects observed in an experimental model of depressive disorder, i.e., chronic unpredictable stress (CUS). Methods: Briefly, males C57BL6 were submitted to a 21 days protocol of CUS (CEUA/FMRP 032/2015-1) and received daily intraperitoneal injections of vehicle, ESC or AM630, a CB2 receptor inverse agonist. At the end of the treatment period, the animals were evaluated in the tail suspension test (TST) and in the novelty suppressed feeding (NSF). After behavioral tasks, the hippocampi were isolated and processed for evaluating the expression of newborn neurons using doublecortin (DCX) score and the expression of neuroplasticity markers, including brain derived neurotrophic factor (BDNF) and mammalian target of rapamycin (mTOR). Results: AM630 and ESC promoted equivalent antidepressant and anxiolytic-like effects, in the TST and NSF, respectively. ESC but not AM630 prevented the decreased of the levels of BDNF and in the number of DCX-positive neurons in the hippocampus induced by CUS. Otherwise, AM630 increased the hippocampal phospho-mTOR/mTOR expression. Conclusion: ESC and AM630 promote equivalent behavioral effects, probably in different molecular pathways. Financial support: FAPESP; L’OREAL/UNESCO/ABC.
Title
PHYSICAL EXERCISE REGIMEN MODULATES THE LONG-LASTING INCREASE IN COCAINE REWARD INDUCED BY INTERMITTENT SOCIAL DEFEAT

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Body
Social defeat (SD) in rodents has repeatedly shown to enhance the sensitivity to the rewarding properties of drugs. One of the interventions that has been used in the management of stress consequences and in drug cessation is physical exercise. However, basic research show that under certain circumstances it can act as a risk factor enhancing the rewarding potential of drugs. The present study aims to increase the knowledge about the neurobiological mechanisms that underlay the effect of physical exercise in the modulation of stress and drug response. To achieve this objective, OF1 male mice were divided into 4 different experimental groups: sedentary housing (4 adult males per cage with no physical enrichment); animals housed in groups of 4 with constant access to 1 or 4 voluntary running wheels (VWR), and animals with a regimen of intermittent VWR exercise. 21 days after the protocol of SD the conditioned place preference (CPP) paradigm induced by a sub-threshold dose of cocaine (1 mg/kg) took place. Following CPP, biological samples were taken to measure interleukin-6 (IL-6) and BDNF levels. Our results confirmed that animals that experienced SD were sensitized to hedonic properties of cocaine and developed CPP. Only the condition of intermittent exercise was effective protecting against this stress effect. Moreover, non-stressed animal housed with constant access to VWR also developed CPP. Biochemical analysis showed that BDNF and IL-6 levels in the striatum and hippocampus were elevated in physically active animals compared to sedentary animals. As these two structures are key in associative learning involved in CPP, BDNF increase may be potentiating plastic changes that underlain the enhanced drug learning that our mice displayed. Increasing the understanding about the neurobiological effects of physical exercise would help to optimize the designs of physical interventions.

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**Title**  
DIETARY INTERVENTION WITH POLYPHENOLS AMELIORATES MATERNAL SEPARATION-INDUCED DEPRESSIVE BEHAVIOURS

**Authors**  
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**Body**  
Depression is a neuropsychiatric disorder characterised by a negative impact on mood, and currently considered a major health concern. In addition, evidence suggests that early life stress induces long-lasting changes in the brain, resulting in critical consequences for behaviour. Indeed, this early adversity is associated with increased risk for developing depression in adulthood. The maternal separation model in rats is a robust paradigm to study the effects of early life stress on behaviour, which produces a consistent depressive phenotype in adult animals. Diversely, phytochemicals known as polyphenols have demonstrated therapeutic potential in treating mood disorders, but the mechanisms involved are unclear. Therefore, we decided to investigate the effects of polyphenols and their mechanism in alleviating depressive behaviour in maternally separated (MS) rats. After early maternal separation, adult male Sprague-Dawley rats underwent an 8-week dietary intervention with the polyphenols xanthohumol and quercetin, as well as with the polyphenolic-enriched fraction of a phlorotannin extract. MS rats showed increased depressive-like behaviour in the forced swim test compared to the non-separated (NS) control group. Additionally, MS rats had increased anxiety in the open field test. Intriguingly, all polyphenolic treatments prevented these depressive-like behaviours.

MS is also associated with alterations in brain neurochemistry and homeostasis in the hypothalamic-pituitary-adrenal (HPA) axis, which are involved in the development of depressive behaviour in humans and animal models. Therefore, we examined the effects of polyphenols on monoamine neurotransmitter levels and corticosterone concentration in plasma. As predicted, MS resulted in altered levels of 5-HIAA and dopamine in brainstem, accompanied by abnormal elevation of corticosterone. Although polyphenols did not reverse neurotransmitter imbalance, xanthohumol normalised corticosterone levels in MS rats. These results suggest that the observed polyphenol antidepressant effect could be partially mediated by HPA regulation. Currently, studies investigating the role that the gut microbiome plays in polyphenol-mediated antidepressant activity are ongoing.
Psilocin, an active metabolite of psilocybin, is an serotonergic agonist. Psilocybin is currently well known for psychosis and has several potential implications in treatment of psychiatric disorders. First experiments assessing brain activity after psilocybin administration in humans found contradictory results and a recent study confirmed massive inhibition of activity. The aim of our animal study was to assess psilocin-induced changes in quantitative EEG (QEEG) measures – absolute spectral power brain mapping and lagged EEG coherences – in rats.

We used psilocin in dose 4mg/kg s.c. EEG was recorded in freely moving rats implanted with 12 active electrodes onto the surface of the cortex. EEG absolute power spectra (local synchronization) and lagged coherence (long projections) were analyzed comparing the drugs' effect in time (20-30, 50-60 and 80-90 minutes post administration) to the baseline record. To avoid moving artifacts and effects of behavior on EEG, only EEG traces corresponding to behavioral inactivity were included in the analysis. The distribution of absolute spectral power among cerebral cortex of rats was counted and displayed via brain mapping. The significant lagged EEG coherences were plotted on rat’s brain.

Psilocin in rats decreased the mean absolute power in all frequency bands. However, there were lo-cal increases of absolute power in parietal and temporal areas. A decrement in fronto-temporal EEG coherences in delta / theta and decrement in bitemporal coherences in alpha / beta were observed.

QEEG after psilocin in rats showed a broadband decrement of mean power and EEG coherences, which reflects local desynchronization, disconnection and increased entropy of brain activity. The distinct increase of parieto-temporal power in theta and gamma frequency can reflect limbic hyperactivity (theta bursts) described in hippocampus.

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Title
RECOVERABLE COGNITIVE CHANGES AFTER CHRONIC ALCOHOL INTAKE.

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Body
Excess alcohol consumption is one of the leading contributors to the global burden of disease, and alcohol use disorder is characterised by behavioural patterns that may be responsible for its pervasive nature. For example, relapse to alcohol use is attributed to the salient nature of alcohol-associated cues, and to rigid, habit like behavioural patterns of people with alcohol use disorders. We wished to investigate whether consumption of alcohol itself gives rise to these behavioural traits. Rats were randomly assigned to either alcohol-exposed or control condition, and then allowed intermittent access to alcohol or a calorie matched solution over 6 months. Under this schedule, rats voluntarily consumed alcohol (on average 7g/kg/24 hours). After 6 months of drinking at this rate, behaviour was assessed in operant touchscreen chambers. Rats that had been consuming alcohol showed biased attention towards a reward-associated cue, assessed using a 5-choice serial reaction time task. They also showed impaired performance in the reversal stage of a visual discrimination task, suggesting reduced behavioural flexibility. Furthermore, stereological examination of brains revealed cell loss in the prefrontal cortex of alcohol-exposed rats which was no longer apparent after abstinence. This indicates neuropathology that is consistent with behavioural deficits observed, as well as suggesting the potential for recovery. Finally, we replicated the deficit in reversal learning in high drinkers (7g/kg/24hours) compared to low drinkers (2g/kg/24hours), and further showed that it was recovered if they were allowed access to running wheels during subsequent abstinence. These findings have important implication for treating alcohol use disorder, and future research will establish whether recovering observed changes will impact alcohol intake and relapse to alcohol-seeking behaviours.
Title
EFFECT OF CXCR4 ANTAGONISTS ON PSYCHOSTIMULANTS-INDUCED HYPERLOCOMOTION IN MICE

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Body
Repeated exposure to drugs of abuse has been a social and health concern. The lack of effective treatments has promoted new lines of research as the study of the inflammatory cytokine CXCL12 and its receptor CXCR4 on drug psychostimulant properties.

For this reason, we sought to study in mice the effect of two CXCR4 antagonists, AMD3100 and (R,R)-AS (AS), on locomotor activity. Mice were treated with an equi-effective dose of cocaine, methamphetamine, mephedrone or MDMA, once daily for 7 consecutive days. qPCR assays were performed to quantify changes in the mRNA expression of CXCL12 and CXCR4 genes in ventral tegmental area/substantia nigra. One-way ANOVA revealed a significant effect of treatment (P<0.001). Particularly, repeated cocaine and methamphetamine exposure (predominantly dopaminergic drugs) upregulated CXCL12 expression (P<0.01), whereas mephedrone and MDMA (predominantly serotonergic drugs) did not alter significantly its expression.

Next, CXCR4 antagonists (5 mg/kg, i.p.) were tested on the hyperlocomotion produced by a single cocaine (10 mg/kg, i.p.) or methamphetamine (1.5 mg/kg, s.c.). AMD3100 damped the ambulatory activity induced by methamphetamine (100%) and cocaine (53.32%). Interestingly, AS partially blocked the effect of methamphetamine, while potentiated cocaine when administered 40 min before the psychostimulant. A plausible mechanism would be a downregulation of the dopamine transporter (DAT) due to AS pretreatment, probably due to changes in DAT trafficking. To investigate this mechanism, we assessed the DAT functionalism in striatal synaptosomes of mice previously treated with cocaine or AMD/AS+cocaine 1h previous sacrifice. As expected, only AS significantly blocked DAT trafficking.

In conclusion, these results indicate that by inhibiting the effect of CXCL12 through CXCR4 antagonists, we can achieve a reduction of the locomotor activity induced by dopaminergic psychostimulants. Thus, CXCR4 could be a potential therapeutic target in drug addiction treatments, but its efficacy might depend on the mechanism of action of the abused drug.
PO 85

Title
SALIDROSIDE AS A MODULATOR OF TRANSCRIPTION OF DOPAMINERGIC RECEPTORS ENCODING GENES IN THE BRAIN OF RATS SUBJECTED TO INDUCTION OF ALCOHOL TOLERANCE - PRELIMINARY REPORT

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Body
Modern medicine has a small number of medicines that can be used to treat alcohol dependence. One source of new drugs are medicinal plants and the plants with promising properties are Rhodiola rosea and Rhodiola kirilowii, whose main active ingredient is salidroside (Sal), belonging to the group of phenylethanoids. Recently we found that both the extracts from these plants and Sal inhibited a development of ethanol tolerance. The aim of this study was to compare the mRNA level changes for dopaminergic receptors in the hippocampus and prefrontal cortex of rats with induced alcohol tolerance under the influence of Sal. From the prefrontal cortex and hippocampus of male Wistar rats, divided in the previous experiment into two control groups (receiving H2O or ethanol (30%; 3g/kg/ for 9 days; i.p.)) and four Sal administered groups [(9 days: 4.5 or 45 mg/kg, p.o.) with H2O or ethanol, i.p.], a total RNA was isolated. Changes in mRNAs levels for Drd1, 2, 4 and 5 genes were measured in a two-step relative quantification quantitative real-time PCR technique (Pfaffl method). GAPDH housekeeping gene was proposed as a potential reference one. Unexpectedly its level was affected in experimental conditions especially by Sal treatment. In hippocampus, ethanol administration lowered the mRNA level of Drd1, 4 and 5, but did not Drd2. In the case of Drd2 mRNA the effect of Sal action occurred for both doses regardless of the solvent used, while it significantly increased level of Drd1, 4 and 5 transcripts in ethanol treated rats, especially at the lower dose. In prefrontal cortex, both effects of ethanol and Sal did not reach significant differences. In conclusion, it seems that Sal eliminates the negative effects of ethanol on transcription of dopaminergic receptors in the model of ethanol tolerance.
Title
SEX AND AGE DIFFERENCES IN HIPPOCAMPAL METABOLISM FOLLOWING AROMATASE INHIBITION AND FORCED SWIM TEST

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Body
Aromatase inhibitors block the conversion of androgens to estrogens but are suspected of psychotrophic effects due to inhibited estrogen production in the brain. We have recently shown that subacute, but not chronic, treatment with the aromatase inhibitor letrozole produces an antidepressant effect in young female rats and sustained aromatase inhibition results in neurotransmitter level changes in male and female brains. Here we explore the effects of subacute letrozole treatment in young cycling females and aged female rats in senescence in comparison to young and aged males. All rats received a subacute letrozole treatment consisting of 3 injections in 24 hours. Estrous cycle and senescence were estimated in young and aged females respectively through vaginal smears. We evaluated behavioral response in the open field test and the forced swim test. Hormone levels after behavioral testing and tissue brain samples were collected for analysis. We then compared the metabolite profiles in the hippocampus of letrozole- or vehicle-treated male and female young and aged rats. We used a targeted mass spectrometry-based metabolomics platform measuring up to 300 metabolites. Data were analyzed by MetaboAnalyst. Analysis showed significant sex and age main effects and interactions in the open field and forced swim test. Letrozole treatment induced significant alterations in levels of metabolites in young females. SAM analysis revealed altered levels of 10 metabolites in the hippocampus (FDR<0.05) between letrozole- and vehicle-treated young female rats. The observed metabolite changes were blunted in the hippocampus of older females. These metabolites are involved in betaine and amino acid metabolism and letrozole treatment reduced their levels. Present findings, in light of our previous studies, show a complex sex- and age-dependent letrozole effect that possibly results not only in transient behavioral changes, but also in more permanent neurobiological alterations in the brain of rats treated with aromatase inhibitors.
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WITHDRAWN

Title
SEX-SPECIFIC BEHAVIOURAL, TRANSCRIPTOMIC AND STRUCTURAL ALTERATIONS IN ADULT RATS AFTER CHRONIC EXPOSURE TO THC DURING ADOLESCENCE: SEARCH FOR EARLY MARKERS OF VULNERABILITY.

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Body
Cannabis has been shown to interfere with adolescent development favoring the onset of psychopathology. Our goal is to understand the origins of such effects by combining RNASeq and imaging studies with behavioral profiling.

(1) Early vulnerability markers: Male and female rats were subjected to EPM and OF at PND25. On PND27 they underwent a PET study. On PND38 THC treatment (9 every other day i.p. of 3mg/kg of THC) began. Rats were submitted to a second PET at PND65. On PND95, animals began a multi-component cocaine self-administration protocol.

(2) Long-term effects of adolescent THC on addiction-like behaviours: Male and female Wistar rats with a similar THC treatment were examined at PN90 for i) addiction-related traits: pavlovian to instrumental transfer (PIT) and motor impulsivity (2CSRTT); ii) addiction-related traits: Pavlovian conditioned approach (PCA) and habit learning; iii) Multi-component cocaine self-administration; iv) NAcShell transcriptome (RNA-seq); v) Brain morphology/metabolism (MRI).

(1) Locomotion in OF was correlated with intake during escalation phase in vehicle-treated animals but lost in THC-treated rats. THC treatment augmented caudate activity and induced a cortical hypometabolism in THC-females. Cortical activity was also correlated with acquisition on firsts cocaine self-administration sessions. THC-females showed a higher positive significant correlation with cocaine intake.

(2) THC-males showed an increase in PIT but reduced impulsivity. THC-treated animals were more goal-directed. THC-females had a higher intake during escalation phase but lower cue-induced seeking of cocaine. RNAseq revealed a dramatic interaction between sex and THC in subsets of genes related to glutamatergic synapses, binding and axonal growth. MRI showed an increased volume and mean diffusivity but reduced fractional anisotropy (FA) in the striatum of THC-males, while THC females showed the opposite pattern. DTI white matter tractography showed a reduction in FA due to THC mainly in the rostral regions. Ventricular volume was decreased in THC treated rats.
Binge drinking is associated with impairments in cognitive control and with alterations in the functioning of reward and control-related brain regions (Wheelan et al., 2014; Smith et al., 2015). Noradrenaline (NA) function in prefrontal cortex (PFC), is suggested as being important for the implementation of control (Chamberlain & Robbins, 2013). Atomoxetine was used to modify NA function and examine changes in cognitive and brain function associated with severity of binge drinking. Thirty-two healthy heavy drinkers who also exhibited binge-drinking behaviours received 60mg of Atomoxetine and placebo over two separate sessions in a counterbalanced order; they underwent functional MRI whilst completing a task that examined attentional biases to alcohol-related stimuli under different levels of attentional load (high vs low) expressed with delayed reaction times in the presence of alcohol over neutral stimuli.

A Drug by Load interaction \( [F(1,31)=4.72, p<0.05] \) depicted that Atomoxetine compared to placebo, tended to reduce biases to alcohol-related stimuli relative to neutral stimuli under conditions of low attentional load \( [t(31)=1.78, p=0.085] \). Biases to alcohol-related stimuli increased under high attentional load under Atomoxetine compared to placebo, however, this effect was not statistically significant.

In the brain, Atomoxetine compared to placebo significantly increased responses to alcohol compared to non-alcohol-related stimuli in the dorso-medial PFC and the precuneus under low attentional load \( [ts(31)>2.4, ps<0.05] \), and had the reversed effect in both regions under high attentional load \( [ts(31)>2.4, ps<0.05] \). The effect in the precuneus showed a tendency to be influenced by the average weekly units consumed by participants \( [F(1,31)=2.78, p=0.10] \). Binge drinkers who consumed more alcohol per week (>24 UK units), tended to show a greater reduction in responses to alcohol relative to neutral stimuli in the precuneus under Atomoxetine. Thus Atomoxetine tends to reduce attentional biases to alcohol-related stimuli in some conditions; this effect could potentially benefit heavier drinkers.
PO 89

Title
STIMULATION OF 5-HT1A RECEPTORS IN THE DORSAL AND VENTRAL HIPPOCAMPUS CAUSES OPPOSITE EFFECT IN ANXIETY

Authors
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Body
5-HT1A receptor-mediated neurotransmission in the hippocampus has been critically associated with anxiety and depression. In the dorsal pole of the hippocampus (DH), there is evidence showing that activation of these ligand sites may cause anxiolytic and anxiogenic effects, depending on the dose of the stimulating drug and/or the experimental model used. However, the role played by ventral hippocampus (VH) 5-HT1A receptors in anxiety processing is not yet fully comprehended. In the present study, the effects caused by the injection of the 5-HT1A receptor agonist 8-OH-DPAT or the endogenous neurotransmitter 5-HT in the DH or VH were investigated in male Wistar rats submitted to the Vogel conflict test. The results showed that, whereas these agonists increased the number of punished responding in the DH, indicating an anxiogenic effect, they caused the opposite effect in the VH. The anxiolytic effect of these agonists in the VH was also evidenced in rats submitted to the elevated T-maze. Using this test, we also observed that blockade of VH 5-HT1A receptors with the antagonist WAY-100635 counteracted the anxiolytic effect caused by chronic systemic administration of the tricyclic antidepressant imipramine. Chronic imipramine did not change the expression of 5-HT1A receptors in the DH or VH. Therefore, these results suggest that 5-HT1A receptors in the DH and VH play opposite roles in anxiety processing and that these ligand sites are recruited for the anxiolytic effect of imipramine.
Title
ADULT HIPPOCAMPAL CYTOGENESIS: BEHAVIORAL CORRELATES AND FUNCTION IN THE FEMALE BRAIN

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Body
Most studies on the relevance of adult hippocampal cytogenesis have been performed in male rodents, disregarding putative sex disparities and the role of female hormones. To address this topic in the female brain, we have used a transgenic GFAP-Tk rat model in which adult cytogenesis is suppressed and performed a comprehensive behavioral and neural plasticity characterization while monitoring the estrous cycle phase.

We show that cytogenesis ablation induced anxiety-like behavior, while producing no significant effects in hedonic, depressive-like or social-interaction behaviors. Moreover, increased basal levels of serum glucocorticoids were accompanied by increased nuclear GR protein expression in the ventral DG of female rats after cytogenesis ablation, as well as increased cytosolic expression of HSP90. Interestingly, GFAP-tk females also revealed hypertrophy of the Basolateral amygdala neurons apical dendrites. Overall, we report that cytogenesis suppression induces hypercorticosteronemia in adult female rats, which is accompanied by changes in dendritic plasticity and heightened anxiety.
Title
THE EFFECT OF CAFFEINE AND SCHIZOTYPY ON WORKING MEMORY PERFORMANCE IN HEALTHY PARTICIPANTS

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Body
Background: There is evidence that a working memory (WM) deficit is one of the core dysfunctions in some people with schizophrenia. Research in nonhuman primates has demonstrated that dopamine in the prefrontal cortex exhibits an inverse-U shaped relationship with working memory performance, with an optimal concentration producing optimal performance, and deficits with decreases or increases below or above that optimal amount. Previously, our lab showed that people with a dexamphetamine-induced increase in schizotypy also had a decrease in spatial working memory, while those that failed to show an increase in schizotypy had improved spatial working memory after dexamphetamine, indicating an inverse-U relationship between psychomotor stimulant effects and working memory, with high enough levels to increase schizotypy also impaired spatial working memory. The present study aimed to study the effect of caffeine and the impact of schizotypy trait on WM to determine if the previous effects were selective for stimulants that influence dopamine or if any stimulant may influence working memory in a manner similar to dexamphetamine.

Methods: A total of 20 healthy were used for the experiment. The experiment was a randomized, double-blind, counter-balanced placebo-controlled cross-over study. The effects of 200 mg caffeine on schizotypy and on the performance of verbal and spatial WM (VWM and SWM, respectively) were examined using a range of tests assessing schizotypy and forward and backward tests of spatial span and digit span tasks.

Results: Caffeine impaired the SWM performance at 6 s delay without significantly affecting overall WM and VWM performances across a range of immediate and delay conditions. It didn’t affect schizotypy but high schizotypy individuals showed reduced performance of SWM, and VWM. Conclusion: These results indicate that caffeine and schizotypy independently affect WM performance. Caffeine impairs SWM under a delay condition, while schizotypy trait affects both VWM and SWM.
Title
THE EFFECT OF PSILOCYBIN ON MEMORY CONSOLIDATION IN HEALTHY VOLUNTEERS

Authors
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Body
Objectives: The term memory consolidation refers to events that ensure storage of newly learned information in a long term memory therefore making it more stable and less prone to interference. Serotonergic system plays important role in memory formation and many studies point to its role specifically in consolidation processes. The aim of this study was to investigate effect of psilocybin (5-HT2A/C agonist) on consolidation of auditory-verbal and visuo-spatial memory in a group of healthy volunteers using post study administration paradigm.

Methods: Each participant (10 men/10 females) completed two drug administration sessions under blinded conditions in a counterbalanced and randomized order receiving either inactive placebo or psilocybin (0.26 mg/kg) in a form of gelatin capsules. Before drug was administered participants completed 5 trials and immediate recall of Rey auditory verbal learning test (RAVLT) followed by 5 trials of Groton maze learning test (GMLT). Six hour after drug administration delayed recall for both tests was measured.

Results: Delayed recall of both RAVLT and GMLT was unaffected by psilocybin administration.

Conclusion: Present findings show that psilocybin administered in intermediate dose had no effect on consolidation of auditory-verbal and visuo-spatial memory in a group of healthy volunteers. In context of current research we could hypothesize that even if psilocybin does not affect consolidation of emotionally neutral stimuli it could affect memory processes dealing with emotionally charged material. To further elucidate effects of psilocybin on consolidation, studies focusing on emotional memory are needed. This line of inquiry could widen our understanding of potential therapeutic usefulness of psilocybin.
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Title
THE EFFECTS OF INHALED SALVINORIN A ON RESTING STATE FUNCTIONAL CONNECTIVITY IN HUMANS

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Body
Salvinorin A is a potent ☷-opioid receptor agonist and the main psychoactive constituent of Salvia divinorum, an atypical dissociative hallucinogen that is used recreationally and remains legal in many countries. Inhaled salvinorin A leads to a rapid onset and short duration of subjective effects that include a sense of depersonalization and derealization. Additionally, some evidence suggests a rapid antidepressant effect of salvinorin A like ketamine and psilocybin, drugs with noteworthy effects on default mode network (DMN) connectivity. In a single-blind, placebo-controlled design, we conducted the first functional magnetic resonance imaging study with acute administration of inhaled salvinorin A to explore its effects on resting state functional connectivity in 12 healthy participants. Participants inhaled placebo (hot air) or vaporized salvinorin A (15 μg/kg) at the beginning of two separate 20-minute resting state scans. Participants listened to ambient music and wore eyeshades during each scan. Across the whole brain, salvinorin A (compared to placebo) decreased the number of significant static functional connections. This reduction in static connectivity was especially robust within the DMN during the first half of the scan, and persisting attenuation of the DMN during the second half of the scan correlated with the duration of subjective drug strength. Salvinorin A was also found to decrease static connectivity within the frontoparietal network and a subcortical network that includes the salience network. An increase in functional connectivity was found between medial and lateral visual networks during salvinorin A scans, perhaps reflecting visual distortions. Finally, analyses on functional connectivity dynamics revealed that salvinorin A reduced variability in functional connectivity within the DMN and within the medial and lateral visual networks. These findings reflect both similarity and dissimilarity with the neural effects of other hallucinogens, suggesting neural mechanisms that are unique to the altered state produced by salvinorin A.
Title
THE EFFECTS OF THE ALPHA7 NACHR PAM ON ADULT AND JUVENILE RATS SOCIAL BEHAVIOUR IN THE NEURODEVELOPMENTAL MODEL OF SCHIZOPHRENIA

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Body
Some of the negative symptoms of schizophrenia include reduced social drive, lack of social interest, and inattention to social input. While schizophrenia is typically diagnosed during the adulthood, some social abnormalities are evident from infancy. The negative symptoms reduce the quality of patients’ life and only modest progress has been made in their treatment. The alpha 7 acetylcholine nicotinic receptors (α7 nAChRs) are one of the promising drug targets for the negative symptoms.

The aim of the present study was to evaluate the effects of CCMI, a positive allosteric modulator (PAM) of α7 nAChRs on social impairment in the neurodevelopmental model of schizophrenia symptoms in adult and juvenile rats.

We investigated schizophrenia-like impairments induced by prenatal (E17) exposure to methylazoksymethanol acetate (MAM; 22 mg/kg). The effectiveness of CCMI treatment (3.0 mg/kg) in normalising MAM-induced deficits was assessed in social play (SP) and social interaction (SI) tests in the juvenile and adult rats, respectively. The time spent on the rough-and-tumble play and on the SI was the measure of rat’s sociality.

Prenatal administration of MAM significantly reduced the time spent on SI and play behaviour by adult and juvenile rats, respectively. CCMI administration reduced SI impairment in adult rats. The tested compound specifically enhanced social exploration in MAM juveniles.

Our results support the notion that α7 nAChRs ligands may constitute a potential therapy of negative symptoms of schizophrenia in adults. To clarify whether this pharmacological approach is effective in juvenile social impairment, the further studies are warranted.

ACKNOWLEDGEMENTS
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PO 95

Title
THE INVOLVEMENT OF THE N-METHYL-D-ASPARTATE (NMDA) RECEPTOR GLYCINE SITE IN RECOGNITION MEMORY DEFICITS INDUCED BY ETHANOL WITHDRAWAL IN RATS

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Body
Chronic ethanol abuse and withdrawal affects the function of glutamatergic neurotransmission leading to learning and memory deficits. The NMDA type of glutamate receptor is essential for learning and memory. Glycine is a NMDA receptor co-agonist, and neuronal glycine transporter 1 (GlyT1) regulates the level of glycine at the synaptic cleft. The aim of the study was to investigate the effect of Org24598, a selective GlyT1 inhibitor, on recognition memory impairment following ethanol withdrawal in rats.

Ethanol (2.0 g/kg, 20% (w/v), i.g.), was given once daily for 7 days in Wistar rats. Novel object recognition test (NOR) was performed 24 and 48 h after the last ethanol administration. Org24598 (0.1, 0.3, 0.6 mg/kg, i.p.) was administered, 30 min prior to testing on the first day of abstinence. Herein, D-serine was used as a reference compound. Elevated plus maze (EPM) and locomotor activity tests were also carried out. To estimate NMDA receptor NR1 and NR2B subunit levels, brain structures (perirhinal cortex, hippocampus and striatum) were collected 48 h after the last ethanol administration.

Recognition memory was impaired after 24 and 48 h of abstinence in the NOR test. Org24598 facilitated NOR performance in ethanol-withdrawn rats at 30 min and 24 h delay after administration, as did d-serine. These effects were observed at doses that had no influence on locomotion and anxiety-like behavior. The Western blot analysis showed up-regulation of NR1 and NR2B subunits of the NMDA receptor in the hippocampus and perirhinal cortex. Org24598 normalized the expression of these subunits to the control level.

Thus, the NMDA receptor NR1 subunit plays an important role in the ethanol-induced recognition memory impairment induced by ethanol withdrawal, and there is interaction between NR1 and NR2B subunits.

Acknowledgements: This work was supported by the Statutory Funds of the Medical University of Lublin (DS22/18).
Title
THE PARTICIPATION OF GLUCAGON-LIKE PEPTIDE RECEPTORS IN MICE TOLERANT TO MORPHINE ANALGESIA

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Body
Background: Morphine, as an effective analgesic drug, is a valuable opioid medication. Its usage is limited because of its high ability for developing dependence and tolerance. In the case of morphine, tolerance is induced by adaptive changes within the mesolimbic system. Literature data confirmed the involvement of glukagon-like peptide receptors in the activity of mesolimbic system because of their presence in these structures. Moreover, it is known that glukagon-like peptide receptors occur also in the thalamus, the nucleus tractus solitarii, periaqueductal gray and the spinal cord, which suggests their participation in the transmission of nociceptive stimuli. Furthermore, literature data showed that activation of spinal GLP-1 receptors induces antinociceptive through spinal β endorphin expression and secretion. Because of that, in the present study we investigated the involvement of linagliptin, indirect modulator of glucagon-like peptide receptors, in morphine antinociceptive tolerance in mice.

Materials and Methods: The tolerance to antinociceptive effects were evaluated using hot-plate on the 1st and 7th day of the experiment. Morphine tolerance was obtained by morphine administration (10 mg/kg, ip), twice a day for 7 days. In order to evaluate the influence of linagliptin on the expression and acquisition of tolerance to antinociceptive morphine effect, linagliptin (10 and 20 mg/kg, ip) was administered in mice on the 7th or 1st-6th day of experiment, respectively, before the morphine injection.

Results: We demonstrated that linagliptin at dose of 20 mg/kg statistically significant reduced expression of tolerance to antinociceptive morphine effect. Linagliptin (10 and 20 mg/kg, ip) inhibited acquisition of tolerance to antinociceptive morphine effect.

Conclusion: Results demonstrated that the glukagon-like peptide receptors are involved in morphine tolerance.

Acknowledgments:
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PO 97

Title
THE ROLE OF ALPHA7 NICOTINIC RECEPTORS IN REINSTATEMENT OF DRUG-INDUCED CONDITIONED PLACE PREFERENCE

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Body
Introduction: Chronic exposure to drugs of abuse induces the formation and maintenance of maladaptive drug cue–context associations that can induce relapse. The ventral hippocampus (vHip) is involved in associative memory and drug-related emotional behaviours. The cholinergic system plays a key role in neuronal activity and synaptic plasticity in the vHip [1]. Inhibiting alpha7 nicotinic acetylcholine receptors (α7 nAChRs) in vHip with the antagonist methyllycaconitine (MLA) selectively attenuated priming-induced reinstatement in morphine conditioned place preference (CPP) [2]. In this study we are investigating the mechanism(s) underlying this effect, and whether it translates to other drugs of abuse.

Materials and Methods: Male C57BL/6J mice (6-7 weeks old) underwent heroin-induced CPP (2x conditioning with heroin (2 mg/kg, ip) and 2x with saline), followed by extinction training (4x saline ip). Drug-primed reinstatement was induced by a single injection of heroin (1 mg/kg, ip) following prior injection of MLA (4 mg/kg, sc) or saline. Immediately following reinstatement, mice were perfused for immunohistochemistry, to detect c-Fos expression in 40 μm brain slices.

Results: MLA prevented reinstatement of heroin-CPP (mean=5±16s preference for drug-paired compartment, n=8), in comparison with saline controls (61±21s, n=8; p<0.05 Student’s t-test). c-Fos expression in vHip after heroin-primed reinstatement was reduced in animals pre-treated with MLA (mean=15.47± 1.36 cells/mm², n=4), compared with vehicle (33.33 ± 1.89, n=4; p<0.001 Student’s t-test).

Conclusion: Reinstatement of heroin-CPP and c-Fos expression in the vHip in mice were inhibited by MLA. This suggests that the blockade of α7 nAChRs reduces reinstatement-induced neuronal activation in the vHip. Current experiments extend the study to cocaine-induced CPP and electrophysiological experiments will be performed to explore the mechanism by which alpha7 nAChRs modulate neuronal activity and synaptic plasticity in the vHip.

References:
Title
MILE HIGH ADDICT RATS CHOOSE HEROIN AND FOOD EQUALLY

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Body
Heroin addiction is a disorder characterized by compulsive drug seeking and can be difficult to both model and define in rodents. Recently, voluntary abstinence models have been used to reduce incubation of drug craving in rats (see Venniro et al., 2019 for review). In these models, rats are allowed to voluntarily choose between food or drug reward, and typically, the vast majority of their choices are for food. Behavioral economics can be applied to animal models of addiction to yield quantitative variables that are predictive of certain components of the addiction phenotype. Few studies, however, have combined both behavioral economics and voluntary choice between food and drug reward. In this study, we first trained rats on food self-administration on a between-session progressive fixed-ratio schedule of reinforcement to obtain behavioral economics metrics. The rats then underwent similar procedures for heroin self-administration. We found that the maximal price the rats were willing to pay (Pmax) for heroin was ~21 times higher on average than that for food, and the demand curves for heroin were significantly more inelastic (measured by alpha). Next, we allowed the rats to make a mutually exclusive choice between food or heroin and found that, on average, 50% of choices were allocated to each reward. A machine learning algorithm was applied to determine which behavioral economics variables were predictive of choice behavior, and only the essential value (EV) of heroin was implicated. We then assessed relapse in response to food vs. heroin cues, wherein only the food lever/cue or the heroin lever/cue was available at a time. Rats exhibited similar rates of relapse to these cues, but extinction was more rapid for the food cue. Analyses are ongoing to identify subpopulations of “addict” rats based on behavioral economics variables and choice preference.
Title
THE ROLE OF OXYTOCIN IN SHAPING EMPATHIC RESPONSES TOWARDS CHILDREN IN SOCIALLY PAINFUL AND REWARDING SITUATIONS

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Body
Empathy, the ability to understand and share others’ emotions, plays a fundamental role in navigating social interactions. The neuropeptide Oxytocin (OXT) has long been considered a facilitator of cognitive empathy (e.g. mind-reading and emotion recognition), however there is also recent evidence that OXT administration reduces empathy for physical pain (affective empathy). In the current functional magnetic resonance imaging (fMRI) study, we investigated the effect of a placebo controlled, within-subject, intranasal OXT (24 IU) administration in 24 healthy female subjects. In a newly developed task we measure the effect of OXT on the neural responses to images depicting children in social pain or in socially rewarding interactions compared to neutrally valanced stimuli of children. In the placebo condition we found left amygdala activation for images depicting social pain compared to neutral images, a structure important for the processing of emotional stimuli and involved in empathy for pain. Further, we found activation in the medial prefrontal cortex for images of positive social interaction compared to neutral images, an area involved in cognitive empathy abilities such as mind-reading. The effects of drug administration are currently being analyzed, but we hypothesize that in contrary to the finding that OXT decreases empathy for physical pain, where aversiveness to the experimental stimuli might have played a role, OXT increases neural activation related to empathy for social pain (e.g. amygdala, insula) in line with the social salience hypothesis. Consistent with this hypothesis, we would further expect an increase of activation in reward related areas to images with positive social interaction (e.g. ventral tegmental area, ventral striatum) after OXT. However, recent work of our own demonstrated deactivations towards infant faces after OXT, therefore an opposite effect might also be expected.

The current study was supported by a grant from the Netherlands Society of Scientific Research to P.A.B. (451-14-015).
The role of Swiprosin-1/EFHD2 in resilience to psychostimulant reward

Recently, one idea that has gained considerable support is that EFhd2 is a common genetic determinator for sensation seeking, low anxiety and alcohol addiction. The scope of our study was to investigate whether this role can be extended from alcohol to other classes of abused drugs such as cocaine and methamphetamine (METH) in mice lacking the EFhd2 protein. To this end, at the behavioral level, we examined the impact of EFhd2 on the rewarding effects of psychostimulants (cocaine: 20 mg/kg, METH: 2 mg/kg) using the conditioned place preference (CPP) paradigm. At the neurochemical level, a systemic characterization of extracellular dopamine (DA), noradrenaline (NA) and serotonin (5-HT) recovered from the Nucleus accumbens (NAc) and the prefrontal cortex (PFC) was performed using in vivo microdialysis in mice following acute cocaine (10 and 20 mg/kg) and METH (1 and 2 mg/kg) i.p. challenge. Our results demonstrate that the behaviorally rewarding effects of cocaine and METH are at the same amplitude in the absence of EFhd2 in mice in CPP acquisition. While, freely moving EFhd2 knockout mice exhibit reduced extracellular concentration of DA in both the NAc and the PFC, no significant changes are observed in the extracellular NA and 5-HT basal levels. However, the cocaine-induced increase in DA levels was much enhanced in the EFhd2 KO mice compared to WT in the NAc and the PFC. Also METH-induced DA responses were amplified, but only in the NAc and not in the PFC. Likewise, 5-HT responses were enhanced after cocaine and METH in the NAc and PFC in the EFhd2 KO mice. NA responses were predominantly enhanced after cocaine alone. Taken together these results suggest that EFhd2 might exert its resilience effects by controlling the acute monoaminergic responses to cocaine and METH in the mesocorticolimbic reward system.
PO 101

Title
THE ROSTROMEDIAL TEGMENTAL NUCLEUS: AT THE CROSSROADS OF REWARD AND AVERTION

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Body
While the reinforcing and motivational properties of natural rewards and abused drugs has been the focus of a large body of research, relatively little is known regarding how negative experiences modify the subjective value of rewards to influence future decision-making. The rostromedial tegmental nucleus (RMTg) provides dense inhibitory projections to midbrain dopamine neurons and integrates aversive signals from a diverse array of inputs. As such, the RMTg is well-positioned to influence encoding and expression of reward seeking in response to negative experiences. Recently, we found that chemogenetic inhibition of RMTg projections to dopamine neurons in the ventral tegmental area (VTA) caused a significant increase in the intensity of footshock rats were willing to endure to receive food reward or intravenous infusions of cocaine. Moreover, timing- and pathway-specific optogenetic stimulation of this RMTg-VTA pathway caused long-lasting reductions in cue-induced cocaine seeking. These data indicate that through projections to dopamine neurons, the RMTg plays a critical role in suppressing reward seeking under punishment, and RMTg activation has a profound influence on learning to avoid stimuli that are otherwise highly rewarding. Ongoing work suggests that separable inputs to the RMTg encode discrete learning and motivational signals, and the prelimbic prefrontal cortex (PL) is particularly necessary for RMTg responses to cues. Specifically, PL inactivation abolishes encoding of aversive cues by the RMTg, and chemogenetic stimulation of the PL-RMTg pathway profoundly and selectively reduces cue-induced reinstatement of cocaine seeking. Together, these findings suggest an important and previously unrecognized role for prefrontal-midbrain interactions in reinstatement, and identify the RMTg as an important target for suppressing reward seeking.
Title
VASOPRESSIN MODULATES GLUTAMATE SIGNALING IN THE LATERAL SEPTUM OF JUVENILE RATS IN SEX-SPECIFIC WAYS: IMPLICATIONS FOR SEX-SPECIFIC REGULATION OF SOCIAL PLAY BEHAVIOR

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Body
Social play is a highly rewarding behavior, is essential for the development of social skills, and is impaired in children diagnosed with autism, a disorder with a strong sex bias in prevalence. We recently showed that the arginine vasopressin (AVP) system in the lateral septum (LS) regulates social play behavior in opposite directions in male and female juvenile rats. We further showed that glutamate (glu) is involved in the sex-specific regulation of social play by the LS-AVP system. Intriguingly, males show higher LS-glu release than females at baseline and during social play while pharmacological blockade of the AVP V1a receptor (V1aR) in the LS eliminates this sex difference by increasing LS-glu release in females only. Here, we aimed to determine the origin of the sex difference in glu release as well as potential sex differences in the cell types that express the V1aR in the LS. Retrograde tracing (using cholera toxin subunit B, CtB) combined with c-Fos and vglut2 (marker for glu neurons) was used to investigate potential sex differences in social play-induced activation of glu projections to the LS. We found that females have more glu projections from hypothalamic subregions to the LS and a higher percentage of c-Fos-positive glu projections from specific prefrontal cortex subregions to the LS compared to males. CtB-positive neurons were also found in the ventral hippocampus and periaqueductal gray and we are currently examining whether these neurons are potential sources of sex-specific glu release in the LS. Finally, we will also determine if there is a sex difference in the expression of V1AR by astrocytes and by neurons. This research will help understanding the sex-specific regulation of social play, which is an important step towards better understanding the neural basis of sex-biased social disorders such as autism.
BIPERIDEN AS A POTENTIAL DRUG FOR TREATING DRUG ABUSE: EVIDENCE FROM PRECLINICAL STUDIES.

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Body
Recent studies suggest that muscarinic cholinergic receptors mediate dopamine release in the mesolimbic system and can alter the drug's reinforcing value. Here, we examine the effect of systemic biperiden, a muscarinic cholinergic (M1) antagonist receptor (at the doses 1, 5 and 10 mg/kg i.p.) on alcohol conditioned place preference (CPP). Followed, we performed an immunohistochemistry assay for Fos (neuronal activation marker), and examined the turnover of dopamine and in the nucleus accumbens of rats after the CPP test. Swiss mice were separated in 4 distinct groups, that received saline or biperiden at the doses of 1 or 5 or 10 mg/kg, thirty minutes before the CPP test. The time spent in each compartment was recorded for 15 min. At the end of the test, the rats were euthanized and their brains were processed for Fos immunohistochemistry or neurotransmitter levels analysis by high-performance liquid chromatography (HPLC). Our results demonstrated that Biperiden in different doses, blocked the alcohol CPP expression (Saline: pretest - 35.20% ± 0.02; test - 59.61 ± 0.04; Bip 1mg/Kg: pretest - 34.55% ± 0.03; test - 48.71% ± 0.14; Bip 5 mg/Kg: pretest - 35.17% ± 0.02; test - 50.51% ± 0.03; Bip 10 mg/Kg: pretest - 33.18% ± 0.03; test: 45.28% ± 0.02; p<0.05). This effect was followed by an increase in Fos positive cells (core: F3,4=32,13; shell: F3,2= 13,38;p<0,05) and serotonin levels in the nucleus accumbens (F3,4= 3,038;p<0,05). No change was observed in dopamine levels. Our results add to growing evidence that biperiden might be a promising drug for treating addiction. Financial Support: FAPESP 2017/262250. Ethics Committee: 8583220517.
Title
IMPACT OF HOUSING CONDITIONS ENVIRONMENT ON BEHAVIORAL PROFILE OF ADOLESCENT MALE RATS EXPOSED PRENATALLY TO METHAMPHETAMINE

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Body
Children prenatally exposed to methamphetamine (MA), one of the most commonly abused illicit drugs in pregnancy, are at great risk to develop psychological and/or behavioral disorders. Our previous results demonstrated that the early postnatal period in rats (twelve day after birth) is the most vulnerable to MA exposure. Adverse effects of drug exposure can be negatively as well as positively modulated by various epigenetic factors. Among them living conditions during maturations are expected to play the most important role. In the present study, the consequences of life conditions at the adolescents’ period (a time of heightened vulnerability) to environmental factors of animals exposed prenatally to MA were examined. For this reason several experiments were performed to assess behavioral responses of animals in cognitive and emotional domains. After delivery females were injected daily with MA (5 mg/kg) or saline from postnatal days (PD) 1 to PD 12. Several housing conditions were used: before weaning (standard cages vs enriched environment) and after weaning (single housing vs group housing). Animals (n=8) were tested at the following postnatal days: PD 28-32 (Habituation test), PD 35-38 (Object recognition and Object location tests) and PD 40-51 (Morris water maze). Our results suggest that housing conditions affect the behavioral profile of animals exposed prenatally to MA in both cognitive and emotional domains. Future studies will analyze molecular and cellular mechanisms underlying these effects.

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Title
OPTOGENETIC INHIBITION OF NUCLEUS ACCUMBENS NEURONAL ENSEMBLES ATTENUATED CONTEXT-INDUCED REINSTATEMENT OF ALCOHOL SEEKING

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Body
A central problem for drug addiction is the high rates of relapse during abstinence. Drug-associated cues are considered the main factors to cause relapse to drug-seeking. Learned associations between drugs and environment are hypothesized to be encoded within sparsely distributed patterns of neurons called neuronal ensembles. The nucleus accumbens is a critical brain structure involved in reward and learning behaviors. Here, we determined a causal role of context-activated neuronal ensembles in context-induced reinstatement of alcohol seeking. In one surgery session, we injected AAV (AAV-EF1a-DIO-eNpHR3.0-YFP) into nucleus accumbens and implanted optical fibers 0.5 mm above the viral injection sites. The experimental procedure consisted: alcohol self-administration training in context A (24 days), extinction in context B (10 days), induction day (1 day) in context A, additional extinction in context B (10 days), and four reinstatement tests on separate days. On induction day, one day after the 10th extinction session, we injected rats with tetracycline (5 mg/kg, i.p.) and kept them in their home cages for 2 h before placing the animals in the context A, where we exposed rats to a short 30 min extinction session. During reinstatement test days, rats were tested first in context B with and without laser activation (test days 1 and 2), and then tested in context A with and without laser activation (test days 3 and 4). Rats demonstrated reliable alcohol self-administration, as indicated by the increase in the number of infusions and active lever presses over the training. Active lever pressing decreased with repeated extinction sessions. When tested in the context A, optogenetic inhibition of nucleus accumbens putative neuronal ensembles attenuated context-induced reinstatement of alcohol seeking. No behavioral inhibition was observed when rats were tested in the context B. We demonstrated that selective inhibition of these context-encoding neuronal ensembles decreases context-induced alcohol relapse.
Title
TARGETING THE MICROBIOTA-GUT-BRAIN AXIS IN A MODEL OF CAESAREAN-SECTION

Authors
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Body
In recent years there has been a huge increase in the number of studies reporting the gut microbiota as a key factor in maintaining the health of an individual, including brain health. One of the most critical times for the establishment of the microbiota is during birth, when seeding of the infant microbiome occurs as the newborn passes along the mother’s birth canal. Delivery by cesarean-section (C-Section) disrupts this vertical transmission of microbiota from the mother to the newborn and leads to a difference in microbiota in the first months of life.

Data from our C-Section mouse model shows that mice born by C-Section have alterations in their microbiota, with concomitant deficits in social and anxiety-like behaviour later in life. In this study, we used a nutritional intervention from early life aiming to restore the deficit in microbiota of C-section born offspring and to prevent the detrimental effects on behaviour associated with this mode of delivery.

C-Section born animals were given a synbiotic in 2 different doses from postnatal day (PND) 3 onwards, while control groups (C-Section and vaginal born (VB)) received vehicle. Our results show that C-Section born animals have increased anxiety-like behaviour in early life, as indexed by increased ultrasonic vocalizations when separated from their mothers at PND9 and have decreased maternal attachment at PND10. In adulthood, these animals have deficits in social memory in the three-chamber test. Intervention with both doses of the synbiotic restores social memory in adulthood and the higher dose trended toward a reduction in anxiety-like behaviour in early life. Additionally, gut barrier integrity was compromised in C-section animals at PND7 and was improved by treatment with synbiotic.

In conclusion, restoration of microbiota with synbiotics in a C-Section model may prevent alterations/deficits in behaviour, and gut physiology associated with this mode of delivery.
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Title
BEHAVIOURAL COMPARISON OF ARIPIPRAZOLE AND HALOPERIDOL AFTER REPEATED TREATMENT IN THE RAT MODEL OF CHRONIC MILD STRESS

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Body
Antipsychotics (AP) represent a treatment of choice for psychotic and depressive disorders. The frequency of their use constantly increases. “Atypical” antipsychotics including aripiprazole (ARI) are new generation of AP with a significantly lower incidence of adverse effects. The chronic unpredictable mild stress (CMS), an animal model of depression, served as a tool to study the effect of the chronic administration of „atypical” ARI in comparison with the „typical” AP haloperidol (HAL) on the behavioural changes in rats.

The tested substances including vehicle (10%DMSO), ARI (10mg/kg), or HAL (1mg/kg), were intraperitoneally administered to Sprague-Dawley male rats daily for 4 weeks and subjected to CMS for 3 weeks. After CMS, following behavioural tests were used to assess the motor activity, cognition and the anxiety- and depression-like behaviour: the open field (OF), the elevated plus maze (EPM), the novel object recognition (NOR) and the sucrose preference test. CMS significantly reduced 1% sucrose solution intake, decreased the body weight gain and increased the spleen weight. HAL treated animals were significantly more active in OF; spent more time with a novel object in NOR, had smaller spleen size and gain more body weight in comparison with ARI in stressed conditions. HAL treated animals exhibited less anxiety-like behaviour as indicated by significantly more time spent in the open arms of EPM compared to ARI and VEH. However, CMS ameliorated the above mentioned changes. HAL administration restored the anhedonic state induced by CMS. These results demonstrate that the presented model of CMS leads to anhedonia, which was restored by both of these AP. We observed differences in the behavioural responses between ARI and HAL treated rats. HAL administration seems to induced a resilience in the stress conditions, while ARI did not reveal major impact on the CMS-induced changes.

Supported by APVV-15-0037.
Title
EFFECT OF COCAINE, METHAMPHETAMINE AND TOLUENE ON INTRACRANIAL SELF-STIMULATION IN MALE AND FEMALE C57BL/6J MICE

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Body
The facilitation of intracranial self-stimulation (ICSS) has been suggested to be a valuable tool for exploring the abuse-related effects of drugs. Despite the widespread use of mice for abuse-related studies, few ICSS studies have employed mice or compared the effects of commonly abused drugs on ICSS between male and female mice. Male and female C57BL/6J mice were implanted with chronic bipolar stimulating electrodes directed toward the medial forebrain bundle and trained to respond for ICSS using a rate-frequency operant test procedure. Response-rates of male and female mice working for ICSS under drug-free baseline conditions were not statistically different. ICSS produces similar reinforcing effects in both male and female C57BL/6J mice in the absence of drug pretreatment. Cocaine pretreatment produced dose-dependent facilitation of ICSS. d-Methamphetamine pretreatment produced facilitation of ICSS at low and intermediate doses, whereas the highest dose of d-methamphetamine had a biphasic effect in which operant responding for low frequency stimulation was facilitated whereas responding for high frequency stimulation was reduced. Exposure to toluene vapor produced less robust facilitation of ICSS than cocaine or d-methamphetamine with significant facilitation confined to low and intermediate stimulation frequencies. There were no statistically significant differences between males and females in the ICSS facilitating effects of any of the three drugs examined. These data reaffirm prior experiments demonstrating that the ICSS procedure is amenable for use in male mice and extends that finding to female mice. The study further suggests that the ICSS-reward enhancing effects of cocaine, d-methamphetamine and toluene are comparable in male and female mice under test conditions which do not incorporate hormonal cycle phase in females as a variable.
Title
EARLY LIFE STRESS-INDUCED IMMUNE ACTIVATION ALTERS THE FUNCTIONALITY OF THE VENTRAL TEGMENTAL AREA AND MEDIATES SENSITIVITY TO COCAINE

Authors
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Body
Exposure to early life stress (ELS) can alter trajectories of brain maturation and induce susceptibility to develop substance use disorder. ELS produces dysfunction in the dopamine (DA) system, which is involved in the responses to drugs of abuse. More recently, it has been shown that ELS has strong effects on the immune system, including activation of microglial cells. Microglia, the predominant immune cells of the brain, play a major role in shaping and refinement of circuits during development. Recent evidences demonstrated that microglia directly contribute to the correct development of the DA system and DA-dependent behavior.

Given this, we hypothesized that ELS-induced immune responses underlie an altered development of the DA system that confers susceptibility towards the effects of addictive drugs later in life.

To test this hypothesis, we used a murine model of early life social stress (SS), characterized by increased sensitivity to cocaine in a conditioned place preference test. At the end of the SS, we performed functional and molecular analyses in the Ventral Tegmental Area, a region sensitive to stress and central in the response to substances of abuse.

We observed that SS produced microglial activation and impairments in the functionality of DA neurons, measured respectively by immunohistochemistry and in vitro electrophysiology, compared with control pups. Moreover, we detected a massive downregulation of DAergic genes in SS vs control mice through RNA-sequencing analysis. Remarkably, inhibiting immune/microglial activation with minocycline during SS rescued DA physiological alterations and behavioral susceptibility to cocaine.

These findings show that exposure to social stress in early age influences DA neurons maturation and cocaine-induced behavior through activation of the immune system. Future experiments will be aimed at exploring: 1. the mechanisms by which microglia contribute to alteration in the DA system and 2. whether and how these DAergic deviations are responsible for cocaine sensitivity.
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Title
THE IMPACT OF PRENATAL METHAMPHETAMINE EXPOSURE AND PRENATAL HYPOXIA ON SHORT TERM MEMORY IN MALE RATS

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Body
Methamphetamine is the most commonly used drug in the Czech republic that is often used by addicted pregnant women. MA may cause abnormalities in placenta and umbilical cord that result in hypoxia and malnutrition. ADHD is a mental disorder with a heterogeneous origin. The number of patients suffering from ADHD is growing. The pathophysiological mechanisms causing ADHD has not been clarified yet. There are few rat models of ADHD - genetic models, chemically induced models (ethanol, nicotine, PCBs, 6-hydroxydopamine lesion) or environmentally induced models (anoxia). The aim of the present study was to test prenatal MA exposure as a potential novel model of ADHD in comparison with prenatal hypoxia exposure.

Pregnant Wistar rats were divided into four groups. One group was daily administered with subcutaneous injection of MA (5 mg/kg), the second was injected with saline in the same volume. Third group was affected by daily prenatal hypoxia (10% O2) for one hour. Fourth group was control (without injection). Male rat offspring were tested for their short term memory in Novel object recognition test and Object location test between 35 and 40 PND.

Differences were detected between experimental groups. Our present data showing memory impairment in MA and hypoxia offspring correspond with ADHD symptoms only partially. Other experiments have to be performed to test our hypothesis.
Title
DIFFERENT ADOLESCENT BEHAVIORAL PROFILES IN SELECTIVELY BRED HIGH COMPARED TO LOW ALCOHOL DRINKING RAT LINES – IMPACT OF REPLICATE AND SEX

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Body
Introduction. Initial contact with alcohol generally occurs during adolescence and heavy use during this period is associated with increased risk for later alcohol and other substance use disorders. Rodents selectively bred for high alcohol intake are used to identify behavioral characteristics associated with a propensity for this phenotype. The Multivariate Concentric Square Field™ (MCSF) is a multi-domain behavioral test developed to study rodents in a semi-naturalistic setting. The MCSF arena consists of zones to measure different properties to create a multivariate comprehensive, behavioral profile in a single trial. Aim. To examine the behavioral profile of two replicate lines of adolescent high alcohol drinking (HAD) and low alcohol drinking (LAD) rats of both sexes. Methods. Alcohol-naive HAD 1/2 (n=17-20/line/sex) and LAD 1/2 (n=11-12/line/sex) rats were tested once in the MCSF at postnatal day 30-35. The behavior of the animals was recorded and analyzed. Results. The replicate 1 lines display less variance than replicate 2, and fewer line-associated differences. Differences by sex vary depending on replicate; replicate 1 has moderate differences primarily in activity were females are more active than males while replicate 2 has few sex-dependent differences. HAD-2 differs markedly from LAD-2 animals by being less active and risk-taking, and more shelter-seeking. The differences between HAD-1 and LAD-1 are not as pronounced, but HAD-1 shows some increased shelter-seeking behavior while other parameters relating to exploration are increased compared to LAD-1. Conclusion. The large difference between the replicates was surprising. However, the behavioral profile of HAD-2 rats may be interpreted as relating to negative emotionality, which have been associated with vulnerability to develop substance use disorders in general and high alcohol use and development of alcohol use disorder specifically.

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Title
BOTH WT AND SERT-/- RATS HAVE A COGNITIVE BIAS ON HIGHER REWARDING IN A TOUCH-SCREEN TASK

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Body
Since the first study on genetic variance in the human serotonin transporter (SERT) gene and risk for depression in the context of early life stress, a huge amount of papers on this topic were published. However, many studies failed to find the relationship between SERT and depression in humans. Controversial findings demand the improvement of methods to assess emotional changes in animals, such as affective information processing. This can improve the validity of gene-driven-behavior hypothesis in depression. By detecting cognitive bias in depression, affective features can be measured in animals especially because it has been tested across species from insects to human. Cognitive bias is found in depressed patients and recently in rodent depression models. However, most of the rodent studies introduce a stressor (e.g. foot shock) in the task of cognitive bias. This might lead to a cofound in stress-gene effects on depression. In our task, the cognitive bias was tested in SERT-/- rats without introducing stressors by using touch-screen operant boxes. Rats were trained to discriminate two image stimuli associated with low and high sugar reward, respectively. The bias was tested by presenting ambiguous image stimuli after the training. We found out that both wild-type and knock-out rats displayed a cognitive bias towards high reward compared with low reward. Generalization of the reward value on the visual stimuli in both genotypes were similar. The behavioral outcome indicates that both of them generalized ambiguous stimuli towards high reward. Interestingly, SERT -/- rats had a short latency in action selection on both cue stimuli and choice stimuli, especially when facing high reward stimulus. The findings suggest that loss function of SERT per se may not contribute to the development of depression through processing affective information.
Title
GENETIC VARIATION SUBSTANTIALLY AFFECTS OPERANT RESPONDING FOR AN INTRAVENOUS COCAINE OR SALINE REINFORCER IN INBRED MICE

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Body
The majority of people that initiate recreational drug or alcohol misuse do not transition to a substance use disorder. This differential vulnerability is influenced by genetic variation and biological sex. Hypothetically, these factors regulate the propensity of an individual to experience drug-induced neuroadaptations that produce the disorder, or not. To address this question, we have evaluated the acquisition of cocaine self-administration in 238 adult mice (half female) from 41 genetically unique inbred strains. Mice were tested in 10 daily 2-h sessions; actuation of an active lever was reinforced by a unit dose of cocaine (0.5 mg/kg) on a FR1 schedule; infusions were accompanied by a visual conditioned stimulus. Responses on an inactive lever were recorded but had no programmed consequence. In a separate group of 239 mice from the same strains, saline self-administration sessions were conducted in an identical manner, except that the infusate contained no drug. Across training, the number of infusions earned increased monotonically in both the cocaine- and saline-reinforced groups, but the degree of increase was significantly larger in the cocaine condition. The ratio of active to inactive lever presses was significantly larger in the cocaine-reinforced group. Thus, reinforced lever pressing occurred in both groups (potentially attributed to the visual conditioned stimulus in the saline self-administration condition), but cocaine served as a more powerful reinforcer. Genetic variation exerted large effects on the number of infusions earned in both the cocaine- (heritability = 0.52) and saline-reinforced (heritability = 0.58) groups. The genetic correlation between infusions earned in the two conditions was modest ($r^2=0.27$, $p<0.001$). Notably, a strong trend for a strain $\times$ sex interaction on infusions earned was found in the cocaine-, but not saline-reinforced, condition. Overall, this data set reveals large genetic influences on cocaine-reinforced responding and a cocaine-specific pattern of sex moderation of these genetic effects.
Title
OPIOID PHARMACOLOGY OF THE KRATOM (MITRAGYNA SPECIOSA) ALKALOIDS
MITRAGYNINE AND 7-HYDROXYMITRAGYNINE IN CELL MEMBRANES AND RATS

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Body
Products containing leaves of the tropical tree Mitragyna speciosa (kratom) are increasingly used to self-treat pain and opioid dependence; however, the pharmacology of kratom alkaloids has not been established. Here, mitragynine, a major kratom alkaloid, and 7-hydroxymitragynine, a minor metabolite, were assessed for opioid receptor binding affinity in vitro and discriminative stimulus effects. In cultured membranes expressing human opioid receptors, mitragynine and 7-hydroxymitragynine inhibited [3H]DAMGO binding to mu-opioid receptors (respectively, Ki=600 and 78.1 nM) more potently than [3H]U69,593 binding to kappa-opioid receptors (Ki=1,700 and 220 nM) and [3H]DADLE binding to delta-opioid receptors (Ki=6,800 and 244 nM). 7-Hydroxymitragynine’s affinity for mu-opioid receptors was 22-fold lower than that of morphine (Ki=3.57 nM). Separate groups of rats discriminated either mitragynine (32 mg/kg, i.p.) from saline or morphine (3.2 mg/kg, i.p.) from saline; respective ED50s were 15.8 and 1.65 mg/kg. In mitragynine-trained rats, morphine (up to 32 mg/kg) and fentanyl (up to 0.32 mg/kg) produced a maximum 65% and 75% mitragynine-lever responding, respectively. 7-Hydroxymitragynine and the low efficacy μ-opioid agonist nalbuphine fully substituted for mitragynine (ED50=0.600 and 5.69 mg/kg, respectively). Mitragynine was equipotent when administered p.o. (ED50=19.4 mg/kg) and i.p. In morphine-trained rats, fentanyl, 7-hydroxymitragynine, and nalbuphine fully substituted for morphine (ED50=0.0201, 0.358, and 5.92 mg/kg, respectively). Mitragynine was equipotent when administered p.o. (ED50=19.4 mg/kg) and i.p. In morphine-trained rats, fentanyl, 7-hydroxymitragynine, and nalbuphine fully substituted for morphine (ED50=0.0201, 0.358, and 5.92 mg/kg, respectively). Mitragynine, when administered i.p. and p.o., produced up to 62% and 72% morphine-lever responding; mitragynine p.o. was 2.9-fold less potent than i.p. (ED50=34.1 and 99.0 mg/kg, respectively). The opioid antagonist naltrexone (0.032mg/kg, i.p.) shifted the dose-effect function of mitragynine rightward and downward due to the failure of naltrexone to antagonize the rate-decreasing effects of mitragynine but produced surmountable antagonism of the morphine and 7-hydroxymitragynine discrimination dose-effect functions. These results show that both mitragynine and 7-hydroxymitragynine exert μ-opioid agonist effects, including discriminative stimulus effects that overlap with prototypical, abused opioid agonists. Supported by USPHS DA25267, DA47855, and DA48353.
Title
THE SUBTHALAMIC NUCLEUS MODULATES HOW PROXIMAL SOCIAL FACTORS, AND ULTRASONIC VOCALIZATIONS IN PARTICULAR, INFLUENCE COCAINE CONSUMPTION IN RATS

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Body
Among the global social context in drug addiction, proximal social factors (PSF, i.e. those surrounding the drug exposure, such as the presence of a peer) have been shown to affect drug self-administration, but neurobiological basis of such processes still remain unclear. We studied the Subthalamic Nucleus (STN), a brain structure which lesion reduces affective responses and motivation for cocaine.

We aimed at determining the involvement of the STN in rewarding properties of social interactions in adult rats (not socially isolated) and the contribution of STN in the effects of PSF on cocaine self-administration in various conditions.

We used a conditioned place preference for the presence of the cagemate and cocaine self-administration of rats (sham or STN lesion) in presence of a peer (familiar or stranger) with or without access to cocaine or subjected to USV playback from another peer.

The results show that in sham rats, the presence of the cagemate can be rewarding only for the dominant ones, while in STN lesioned animals it is rewarding whatever the status. In sham rats, presence of a peer reduces drug intake, but in a stronger manner if the peer is a stranger, while STN lesioned rats decrease their cocaine intake in presence of a peer whatever its familiarity (familiar or stranger). The analyses of the USV emitted by each rat will be performed, they indicate a critical role of USV in the social context, especially since the playback of USV can modulate the cocaine intake in sham animals, but not in STN lesioned rats.

In conclusion, our results show that the STN is involved in the neurobiological basis of the proximal social factors’ influence on drug consumption. This interaction, resulting in a dramatic decrease in drug intake, makes the STN even more promising as a therapeutic target for drug addiction.
Previous research has indicated that individuals with pathological gambling generally have a higher body mass index and are more likely to be obese than healthy controls. In rats, obesity is associated with greater responsivity within dopaminergic reward circuitry, and prolonged exposure to a high-fat, high-sugar diet can alter the functioning of the orbitofrontal cortex leading to impairments in the devaluation of rewards. Accordingly, the present study investigated whether poor diet and obesity influences risk preference in rats, using a rodent model of cue-enhanced risky decision making.

Two cohorts of 32 male Long-Evans rats were trained on the cued version of the rat Gambling Task (rGT), a rodent analogue of the human Iowa Gambling Task. This task was designed such that the optimal strategy for earning sugar pellets is to favor options paired with lower per-trial gains, due to a higher probability of winning and shorter time-out penalties. Consistently selecting the high-risk, high-reward options results in longer and more frequent time-out penalties, and therefore less reward overall. Adding win-associated audiovisual cues to the task results in a higher proportion of rats establishing a risky decision-making profile. Following task acquisition, half of the rats were given ad libitum access to a junk-food diet for forty days, consisting of hot dogs, Doritos, Froot Loops, Kit Kats, peanut butter, and standard rat chow. Control rats had ad libitum access to chow only. cRGT performance was then reassessed for a two week period. Rats that exhibited an optimal decision-making profile prior to diet manipulation were uniquely affected in both conditions, displaying a significantly riskier phenotype following diet exposure. These results provide evidence for the role of diet in the establishment of risky decision-making patterns, and may therefore shed light on potential new therapies for individuals at risk of developing pathological gambling.
Title
INVESTIGATION OF FUNCTIONAL AND STRUCTURAL CHANGES OF THE RETINA IN THE EARLY AND LATE PHASE OF PARKINSON’S DISEASE USING TRANSGENIC MOUSE MODEL

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Body
The discovery of novel biomarkers for the early phase of Parkinson’s disease (PD) is important to diagnose more accurately at the pre-symptomatic stage, reducing the burden of the disease. Because PD affects nerve function outside of the brain, non-motor symptoms can provide a feasible clue on the exploration of the early biomarkers of PD, including visual dysfunction and retinal abnormalities that are observed in patients with PD. We aimed to investigate functional and structural changes of the retina in the early and late phase of PD using transgenic mice overexpressing human alpha-synuclein with a A53T mutation. We used six-month-old and sixteen-month-old mice with PD and control (n=8/group). After in vivo tests including visual acuity (VA), intraocular pressure (IOP), optical coherence tomography (OCT), and electroretinogram (ERG), retinas were analyzed following sacrifice. As a result, there was no significant difference in VA and IOP of early and late PD mice compared to each control. However, OCT indicated that significant thinning of inner retinal layer was aggravated over time. In addition, ERG showed amplitudes of a- and b-wave, especially in scotopic condition, were also significantly declined with age in PD mice. Consistently, immunostaining and western blot analysis detected dopamine deficiency, alpha-synuclein deposits, and inflammation in the retina with PD, worsening over time. The present study provides insight into retinal changes associated with early PD and contributes to understanding of visual disturbances experienced by PD patients. Furthermore, longitudinal inspection of retina might represent a useful and non-invasive tool to monitor the disease progression and to evaluate the therapeutic effects of drugs in PD.
Title
HOW METHAMPHETAMINE EXPOSURE AFFECTS SEXUAL BEHAVIOR AND LOCOMOTOR ACTIVITY IN MALE RATS?

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Body
Drug addiction and its consequences on social life and behavior is a current worldwide problem. Due to the fact that methamphetamine (MA) is one of the most abused psychostimulant in Czech republic, this adverse effect has to be more investigated. Previous studies demonstrated the impairing effect of MA exposure in female behavior. However, the influence on male behavior is still not clarified.

The aim of present study was to examine the effect of MA exposure on sexual behavior and spontaneous locomotor activity of adult male rats. MA was administrated subcutaneously in a dose 5mg/kg daily for period of 30 days. The control group was exposed to saline (SA) at the same time in the same volume. After the application period, exposed male rats were mated with non-treated female rats and recorded for 2 hours. Sexual mating behavior was determined by following behavioral parameters: mounting frequency, intromission frequency, ejaculation frequency, sniffing time (s) and post ejaculatory interval. Spontaneous locomotor activity of postnatally exposed male rats was examined by Laboras apparatus. Acute doses of MA (1 mg/kg) or SA were administrated for sensitizing effect prior to each testing. Afterwards, the animal was placed into unknown environment and monitored for 1 hour. The behavior was automatically evaluated by Laboras software by analyzing following parameters: duration of locomotion (s), duration of immobility (s), rearing (s), average speed (mm/s) and distance travelled (m).

Our results demonstrate that MA exposure does not significantly affect the sexual activity of adult male rats. The data from Laboras test showed that MA exposure has significant effect on locomotor activity in case of acute as well sub-chronic MA application. Our study indicates that methamphetamine exposure has negligible effect on sexual behavior. However, more experiments have to performed to examine the influence of MA on spermatogenesis and behavior of offspring.
ADDICTIVE POTENTIAL OF PSYCHOSTIMULANT DRUGS AFTER THE PRIMARY CANNABINOID EXPOSURE

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Introduction
According to Gateway drug theory, risk of the problem drug use is significantly increased if there is a previous experience with cannabis use, particular with its psychoactive component – Tetrahydrocannabinol (THC). On the contrary, cannabidiol (CBD) proved itself as antagonist of some THC effects in previous experiments. Aim of our study is to evaluate impact of primal chronic exposure to THC or CBD on development of addiction after amphetamine (AMPH) administration.

Methods
Study was carried out on animal model – male Wistar rats. Conditioned place preference (CPP) was used to evaluate (i) the addictive potential of AMPH (1 mg/kg) without cannabinoid pre-exposure, and (ii) AMPH's addictive potential following pre-treatment with escalating (every two days) doses of THC (2, 4, 8 mg/kg) or CBD (5, 10, 20 mg/kg). Data were analysed using repeated measures ANOVA.

Results
Cannabinoid pre-exposure groups spent significantly longer time in the AMPH-paired compartment than the control group and AMPH group without pre-exposure. Addictive potential of AMPH was potentiated by pre-exposure to THC or CBD.

Conclusion
In the animal model, THC and CBD have same considerable effect on the development of addiction to the psychostimulant drug. Primary exposure to both cannabinoids led to sensitisation and increased the addictive potential of AMPH. Therefore, further research is needed and we will follow with experiments at a neurotransmitter level.

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Title
DIFFERENTIAL EFFECTS OF PHARMACOLOGICAL AFFECTIVE STATE MANIPULATIONS ON DECISION MAKING IN THE RODENT JUDGEMENT BIAS TASK REFLECTS THE TIME COURSE OF REPORTING OF SUBJECTIVE MOOD CHANGE IN HUMANS.

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Body
Major depressive disorder (MDD) is one of the most common psychiatric disorders. Negative affective biases are thought to be important in the development, maintenance and treatment of the disorder (Harmer et al., 2009). Affective biases can also be measured in animals (Mendl et al., 2009). In rats, we have used a reward-based decision-making task that measures judgement bias of an ambiguous cue, and shown that this form of affective bias is sensitive to manipulations that alter affective state, both positive and negative (Hales et al., 2016, 2017). This task can dissociate between drugs with rapid onset and delayed onset antidepressant efficacy (Hales et al., 2017), as well as short and long-term effects of drugs with pro-depressant pharmacology. The time course of drug effects (both antidepressant and pro-depressant) across which affective bias is altered in this task matches the time course of subjective reporting of changes in mood in humans, suggesting this task could provide a novel method for drug development and testing of new therapeutics in MDD. Computational modelling of this behavioural data using the diffusion model reveals the dissociation between the time course of effects reflects changes in different cognitive processes: rate of information accumulation for acute drugs effects, but changes in decision starting point for chronic drug effects. I will present a summary of our findings so far using the reward-based judgement bias task, highlighting the utility of this task in affective bias research, as well as our ongoing and future research plans.

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Title
ANHEDONIA IN CLINICAL AND NON-CLINICAL POPULATIONS – AN EXPLORATORY META-ANALYSIS OF STUDIES USING THE SNAITH-HAMILTON PLEASURE SCALE

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Body
Anhedonia, defined as a reduced capacity to experience pleasure, has been associated with many clinical conditions, including major depressive disorder (MDD), schizophrenia (SCZ), substance use disorder (SUD) and Parkinson’s disease (PD). Anhedonia symptoms are rarely compared across conditions however, and it is currently unclear whether symptom severity differs between clinical groups. Reference values for hedonic capacity in healthy humans are also missing from the literature. To generate and compare reference values for anhedonia levels across healthy and clinical groups, we performed meta-analyses of self-reported anhedonia as measured with the widely used Snaith-Hamilton Pleasure Scale (SHAPS). We also calculated prediction intervals for each group, providing the range of mean SHAPS scores to be expected in future studies. We extracted baseline SHAPS scores from all available studies citing the initial scale development paper (189 papers) and used random-effects models to calculate average SHAPS scores and 95% confidence intervals separately for samples of healthy participants and samples of patients with current MDD, past/remitted MDD, SCZ, SUD and PD. We used meta-regression to compare SHAPS scores between these groups. In the available literature, patients with current MDD (Hedges’ g = 2.1, 95% CI [1.9, 2.4]), SCZ (Hedges’ g = 0.6, 95% CI [0.4, 0.7]), SUD (Hedges’ g = 0.8, 95% CI [0.6, 1.0]) and PD (Hedges’ g = 0.4, 95% CI [0.2, 0.7]) all scored higher on the SHAPS than healthy participants. SHAPS scores in SCZ, SUD and PD were nevertheless considerably lower than scores in current MDD. Our results indicate that the severity of anhedonia differs across disorders that have been associated with anhedonia. Whereas anhedonia in current MDD likely affects multiple domains of pleasure (e.g. food/drink, pastimes/hobbies, social, physical), anhedonia in SCZ, SUD and PD may instead reflect a decrease in projected enjoyment of only some of life’s many rewards.

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PO 122

Title
EFFECTS OF THE VESICULAR MONOAMINE TRANSPORTER-2 (VMAT2) INHIBITOR TETRABENAZINE ON EFFORTFUL MOTIVATION: A SYMPTOM-BRAIN CIRCUIT APPROACH STUDY.

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Body
Vesicular monoamine transporter-2 (VMAT2) inhibitors prevent monoamines vesicular accumulation at presynaptic striatal neuron terminals, and represent a class of drugs widely used for treating hyperkinetic movement disorders. Psychopharmacological and neurochemical research, suggests that monoamine transport alterations may be involved in the aetiology of motivational symptoms reported in psychiatric disorders.

The present study, investigated the pharmacodynamic/pharmacokinetic effects of the VMAT2 inhibitor Tetrabenazine on incentive motivation-related readouts. Tetrabenazine (0.5, 0.75, 1mg/kg; ip; 90min prior-test) was assessed in the effort-related choice task in rats. In this test, rats can choose to obtain a highly palatable food reward by pressing a lever under a fixed or progressive reinforcement schedule, or eat a freely available but less preferred food. In a different cohort of rats, the effect of Tetrabenazine (1.5mg/kg, ip) on extracellular striatal and accumbens dopamine levels was determined using in vivo microdialysis. To highlight neuronal activation patterns, mouse brain-wide c-fos mapping was performed, 3hrs following Tetrabenazine injection (0.25, 0.5, 1mg/kg, ip). The same dose-range of Tetrabenazine was tested in a mouse novel-environment exploration test. Rats and mouse plasma exposures were measured for all doses, and confronted to therapeutic human concentrations.

Tetrabenazine dose-dependently shifted rats' behaviour towards a low-effort/low-reward choice, and decreased extracellular striatal and accumbens dopamine at plasma concentrations close to the human therapeutic ones. An increase in c-fos expression was observed after Tetrabenazine administration (1 mg/kg, ip); computational pharmaco-mapping revealed that c-fos activation was limited to cortical activation. At the same dose, Tetrabenazine reduced mice willingness to explore a novel environment.

Interrogating behavioural, brain-wide neuronal activation as well as dopaminergic effects of VMAT2 inhibition, the present study substantiated and further expanded previous work indicating VMAT2 as a possible pharmacological target to treat motivational symptoms and associated neuronal pathophysiological alterations observed in psychiatric disorders.
DOUBLE DISSOCIATION BETWEEN ACTIONS OF DOPAMINE D1 AND D2 RECEPTORS OF THE VENTRAL AND DORSOLATERAL STRIATUM ON THE REINSTATEMENT OF COCAINE SEEKING BEHAVIOR

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Although the factors responsible for cocaine taking resumption in human addicts are not completely understood, acute re-exposure to cocaine has been identified as a major determinant of relapse. It is hypothesized that cocaine-induced plasticity at dopaminergic circuits in the brain underlies several aspects of drug seeking behavior. At dopamine (DA) receptor level, previous works from our lab and others have shown that relapse is induced by the peripheral administration of a D2, but not a D1, receptor agonists. These D1 and D2 receptors (D1R; D2R) are highly expressed in the nucleus accumbens (NAcc) and the dorsolateral striatum (DLS). We assessed the reinstating effects of intra cerebral infusions of different doses of agonists of D1R (SKF82958) or D2R (quinelorane) within the NAcc or DLS of rats after extinction of operant cocaine self-administration (COC SA). To further investigate their role on reinstatement, we infused either a D1R (SCH23390) or a D2R (raclopride) antagonist within the NAcc or DLS with the simultaneous systemic administration of a D2R agonist (quinelorane) to assess whether we could block the D2R agonist induced reinstatement. The infusion of SKF82958 induced reinstatement of operant cocaine seeking when infused into the NAcc, but not into the DLS; on the other hand, infusion of quinelorane had no effect when injected into the NAcc, but induced reinstatement when infused into the DLS. In addition, while the infusion of SCH23390 into the NAcc or DLS blocks the reinstatement induced by the peripheral infusion of the D2R agonist, raclopride administration into the NAcc blocks and in the DLS blunts, the reinstating effects of the systemic stimulation of D2R. Altogether, these results point to a double dissociation between DA receptors of the NAcc and DLS in the induction of relapse and highlight a complex interaction of D1R and D2R within both structures.
Antidepressants (AD) and nitric oxide (NO) inhibitors have been shown to induce similar behavioral effects in animal models, such as panicolytic, anxiolytic, and antidepressant effects. Interestingly, those drugs also facilitate TRKB signaling in different brain areas, which is necessary for their behavioral effects. It is unclear how those drugs activate TRKB, which lead us to question if a common molecular mechanism could be involved. We recently found that there are potential sites for NO- induced nitration in TRKB, thus we hypothesized that NO could be a primary effector acting upon TRKB. In the present study, our goals were: a) to investigate if/how nitration could affect TRKB signaling; b) if AD-induced TRKB activation could be mediated by NO inhibition.

Our data show that NO induces nitration of TRKB, which impairs its phosphorylation, increases its interaction with AP2M1 (a component of clathrin-dependent endocytosis complex) impairing cell surface positioning of TRKB, while decreases TRKB:PLCγ interaction in hippocampal neuronal culture. Fluoxetine prevents TRKB nitration induced by endogenously produced NO but is ineffective against nitration induced by NO donor sodium nitroprusside (SNP). In silico analysis revealed that nNOS may interact with TRKB through adaptor protein CAPON (carboxy-terminal PDZ ligand of nNOS) via PDZ-ligand motif and PID domain at CAPON. Fluoxetine uncouples nNOS-CAPON-TRKB complex in neuronal cultures. In vivo fluoxetine and nNOS inhibitor N-propyl-L-arginine (NPA) induced similar behavioral effects in forced swimming test, contextual fear conditioning, and in ocular dominance plasticity model, which were associated to decreased levels of TRKB nitration in hippocampus and cortex.

Concluding, NO impairs TRKB signaling through nitration, and fluoxetine counteracts this effect by uncoupling nNOS:TRKB. Thus, nNOS inhibitors and antidepressants could potentially facilitate neuronal plasticity by protecting TRKB from nitration.
Title
PHARMACOLOGICAL INHIBITION OF FKBP51 PROMOTES STRESS RESILIENCE IN A MOUSE MODEL OF CHRONIC PSYCHOSOCIAL STRESS

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Body
Stress-related psychiatric disorders such as depression are among the leading causes of morbidity and mortality. Considering that many individuals fail to respond to currently available antidepressant drugs, there is a need for new and better antidepressants. Polymorphisms in the gene encoding FK506-binding protein 51 (FKBP51), a co-chaperone of the glucocorticoid receptor, have been linked to susceptibility to stress-related psychiatric disorders. Although it’s been more than a decade since FKBP51 inhibition emerged as a potential novel antidepressant strategy, it remains largely unexplored. The aim of this work was to evaluate the effects of FKBP51 inhibition on antidepressant- and anxiety-like behaviours in a mouse model of psychosocial stress. To this end, male C57BL/6 mice were treated either with an FKBP51 inhibitor, the antidepressant fluoxetine or vehicle for 5 weeks while also undergoing a chronic psychosocial stress comprising of intermittent social defeat and overcrowding stress. Both fluoxetine and FKBP51 inhibition decreased stress-induced social avoidance in the social interaction test, anxiety in the novelty-induced hypophagia, and anhedonia in the female urine-sniffing test. Only FKBP51 inhibition increased the time stressed mice spent in the centre of an open field. This data suggest that pharmacological inhibition of FKBP5 may be a novel strategy for the treatment of stress-related disorders. Its potential therapeutic activity on regulating the hypothalamic-pituitary-adrenal axis in treatment resistant depression warrants further exploration.
Title
THE EFFECTS OF NOVEL SYNTHETIC FENTANYL COMPOUNDS IN RATS TRAINED TO DISCRIMINATE MORPHINE

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Body
Many novel psychoactive substances including opioid-like compounds have appeared on the global illicit market in the past decade. Several substances structurally related to fentanyl are being abused alone and in combination with other drugs (e.g., heroin and/or cocaine), resulting in overdoses at an alarming rate in many countries. The pharmacology of these novel fentanyl-like compounds is critical for government agencies in regulating these substances through appropriate scheduling actions, to safeguard the public, and to minimize the health consequences of the current opioid crisis. In this study, we evaluated the morphine-like stimulus effects of ortho-fluorofentanyl, crotonyl fentanyl, thiophene fentanyl, benzodioxole fentanyl, cyclopropyl fentanyl, and methoxyacetyl fentanyl, six recently identified substances structurally related to fentanyl. We compared the potencies of these new substances to schedule II opioid analgesics such as fentanyl and morphine using the preclinical abuse liability assessment model of drug discrimination. Sprague-Dawley rats were trained to discriminate between 3.2 mg/kg morphine and saline, subcutaneously, using a two-lever operant experimental chamber under a fixed ratio-10 schedule for food delivery. We evaluated saline and multiple doses of morphine, fentanyl, ortho-fluorofentanyl, crotonyl fentanyl, thiophene fentanyl, benzodioxole fentanyl, cyclopropyl fentanyl, and methoxyacetyl fentanyl. ortho-Fluorofentanyl, crotonyl fentanyl, thiophene fentanyl, cyclopropyl fentanyl, and methoxyacetyl fentanyl were similar to morphine and fentanyl in that they fully substituted for the morphine discriminative stimulus and decreased or partially decreased response rates with slightly differing potencies. Benzodioxole fentanyl failed to produce significant morphine-like responding or rate-decreasing effects at any dose although solubility issues limited testing. The opioid-like discriminative stimulus effects of ortho-fluorofentanyl, crotonyl fentanyl, thiophene fentanyl, cyclopropyl fentanyl, and methoxyacetyl fentanyl indicate that subjective effects and abuse liability of these three novel substances are likely to be similar to that of morphine and fentanyl. (Supported by DJD-17-HQ-P-0646)
Title
EXPLORING GLT1, XCT AND DELTA FOSB ALTERATIONS IN ALCOHOLISM. ARE A KEY POINT ON N-ACETYLCYSTEINE ANTI-RELAPSE EFFECT?

Authors
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Body
Alcohol Use Disorder (AUD) is a chronic, progressive and recidivant disorder which supposes a serious health as well as economic problem worldwide. Nowadays, relapse prevention is considered the main target for therapies against drug addiction, but few drugs have been developed for this purpose. In the last decades, deregulation of glutamate homeostasis has been postulated as one of the critical points in cue-induced relapse. In previous research, our laboratory evidenced that N-acetylcysteine (NAC), a safe and well-tolerated marketed drug, is able to block the Alcohol Deprivation Effect (ADE) in long-term ethanol-experienced rats, but the mechanism underlying its anti-relapse efficacy is complex and still remains unclear. Among its anti-inflammatory, glutamatergic and antioxidant properties, we hypothesized that the anti-relapse effect displayed by NAC could be due to a restoration of glutamatergic adaptations triggered by continuous ethanol experience. In the present research, we used the Western Blot technique to explore the expression of glutamate type 1 transporter (GLT-1), system xc- antiporter (xCT) and DeltaFosB (a transcription factor that plays a role in drug addiction) in the dorsolateral striatum, a region implicated in the addiction process through the control of habit formation. We used long-term ethanol-experienced rats divided in two groups: the ethanol group was subjected to chronic ethanol consumption for 5 months, while the abstinence group was subjected to the ADE paradigm for 8 months being sacrificed during the fifth abstinence period. Rats in abstinence received i.p. NAC treatment (0, 60 or 100 mg/kg NAC) once daily for 8 days. The obtained results are suggestive of a plausible mechanism for previously demonstrated NAC anti-relapse efficacy.
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Title
NICOTINE-INDUCED NEUROPLASTICITY IN STRIATUM IS SUBREGION-SPECIFIC AND REVERSED BY MOTOR TRAINING ON THE ROTAROD

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Body
Nicotine is recognized as one of the most addictive drugs, which in part could be attributed to progressive neuroadaptations and rewiring of dorsal striatal circuits. Since motor-skill learning produces neuroplasticity in the same circuits, we postulate that rotarod training could be sufficient to block nicotine-induced rewiring and thereby prevent long-lasting impairments of neuronal functioning. To test this hypothesis, Wistar rats were subjected to 15 days of nicotine treatment (0.36 mg/kg), followed by five days of training on the rotarod. Ex vivo electrophysiology was performed 1 week after the nicotine treatment period and after up to 3 months of nicotine cessation to define neurophysiological transformations in circuits of the striatum and amygdala. Our data demonstrate that nicotine alters striatal neurotransmission in a distinct temporal and spatial sequence, where acute transformations are initiated in dorsomedial striatum (DMS) and nucleus accumbens (nAc) core. Following 3 months of withdrawal, synaptic plasticity in the form of endocannabinoid-mediated long-term depression (eCB-LTD) is impaired in the dorsolateral striatum (DLS), and neurotransmission is altered in DLS, nAc shell, and the central nucleus of the amygdala (CeA). Training on the rotarod, performed after nicotine treatment, blocks neurophysiological transformations in striatal subregions, and prevents nicotine-induced impairment of eCB-LTD. These datasets suggest that nicotine-induced rewiring of stratal circuits can be extinguished by other behaviours that induce neuroplasticity. It remains to be determined if motor-skill training could be used to prevent escalating patterns of drug use in experienced users or facilitate the recover from addiction.
Title
INVESTIGATING THE INTERPLAY BETWEEN BEHAVIOUR, IMMUNITY AND THE MICROBIOME IN THE MODULATION OF THE STRESS RESPONSE IN AGING

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Body
Aging is a complex process that is associated with several debilitating behavioural problems. Exposure to stress is one of the precipitating factors for neuropsychiatric disorders across all stages of life, including aging, partially due to its shaping of peripheral and neuroinflammation. Upon an immune challenge there is a higher susceptibility to develop cognitive impairments. In addition there is a growing emphasis on the role of the microbiota (the trillions of bacteria in the gut) in mediating behavioural and physiological changes in aging. In fact, age-related inflammation has been linked to specific changes in the gut microbiota, which in turn is essential for the proper training of the immune system.

In this study we aim to understand how stress impacts behaviour and immunity parameters in aged animals and if their response to stress can be altered by positive or negative modulations of the gut microbiota. To do so, aged C57/bl6 mice (20/21 months old) underwent chronic social defeat stress (CSDS) and had their microbiota depleted using antibiotics for 1 week or were given a prebiotic enriched diet to stimulate the growth of beneficial bacteria for 3 weeks prior to stress exposure. We evaluated the social avoidance and social preference of the animals, using the social interaction and the three-chamber tests. To characterize the immune profile in the mesenteric lymph nodes, flow cytometry was used to analyse monocyte, T-helper and cytotoxic T-cell populations. Ongoing analysis is focusing on understanding the interplay between these different readouts under baseline conditions and following chronic stress.

With increased life expectancy, it is anticipated that the elderly population suffering from neuropsychiatric disorders such as depression will increase. Therefore, it is crucial to understand the mechanisms behind the stress response in aging, and how the gut microbiome might be used to modulate this process.
Title  
MUSCARINIC ACETYLCHOLINE RECEPTOR ANTAGONISM DECREASES INCENTIVE SALIENCE OF CONDITIONED CUES

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Body  
Muscarinic acetylcholine receptors (mAChRs) facilitate dopamine (DA) transmission within the mesolimbic pathway, a reward system implicated in addiction. Our laboratory uses a Pavlovian conditioned approach paradigm to investigate this system and addiction vulnerability in rats. Briefly, rats are repeatedly presented with a conditioned stimulus (CS; a lever) followed by the response-independent presentation of an unconditioned stimulus (US; a food pellet). Over multiple training sessions, two phenotypes can develop: sign-tracking (CS-directed behavior) and goal-tracking (US-directed behavior). Sign-trackers attribute incentive-motivational value to reward-related cues and are more vulnerable to addiction-like behaviors, such as cue-induced reinstatement of drug-seeking. In addition, sign-tracking behavior requires DA transmission in the mesolimbic pathway, therefore we hypothesized that mAChR antagonism would attenuate the acquisition and expression of sign-tracking behavior. In agreement with our hypothesis, scopolamine (0.3-3 mg/kg; i.p.), a nonselective mAChR antagonist, decreased the acquisition of sign-tracking behavior (and increased goal-tracking behavior) during nine daily Pavlovian conditioned approach training sessions. Also, during an expression test, previously vehicle-treated rats received scopolamine (3 mg/kg), which reduced previously learned sign-tracking behavior in rats. Taken together, these results demonstrate that mAChRs modulate sign-tracking behavior and suggest that mAChR antagonism may be a viable strategy for addiction treatment.
Title
THE ROLE OF LATERAL HYPOTHALAMIC GABAERGIC NEURONS IN LEARNING AND EXPRESSION OF REWARD ALCOHOL MEMORIES

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Body
The high rates of relapse of alcohol use following forced or voluntary abstinence are the biggest issue concerning the development of appropriate pharmacological treatment for substance addiction. Several factors play a role in relapse, such as re-exposure to the drug and drug-associated cues or contexts. As such, the encoding of reward alcohol-related contextual memories, exerts great power over addiction and relapse. Lateral hypothalamic (LH) GABAergic neurons have been shown to be critical for motivation, encoding reward memories, and most importantly for context-induced relapse to alcohol seeking after extinction and punishment, but the mechanisms underlying their involvement are still unknown. Moreover, viral targeting of specific cell-types is sometimes difficult, and genetically engineered rats costly. In this study, we aim to describe how alcohol reward memories are encoded and expressed in LH GABAergic neurons. We first aimed to achieve virally induced GABAergic cell-type specific expression of fluorescent proteins and genetically encoded calcium indicators (GECIs) in LH by employinh GAD-cre viral constructs. Then we trained rats on a Pavlovian conditioning task in which a stimulus (e.g. a clicker) was associated with the delivery of alcohol, while a different stimulus (e.g. a cue tone) was not associated with the delivery of alcohol. We used calcium imaging fibre photometry to monitor the activity of LH GABAergic neurons during learning and expression of the different associations. We aim to identify the encoding and expression patterns of LH GABAergic neurons, to advance our understanding of this area in reward related memories in health and disease.
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Title
EFFECTS OF DOPAMINERGIC COMPOUNDS INTO CEREBELLAR VERMIS OF MICE IN MOTOR COORDINATION AND BALANCE.

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Body
The cerebellum is a structure of the central nervous system related to motor coordination and balance. Dopamine acts through five types of receptors, which are divided in two groups according to functional and structural similarities: D1 and D2. The cerebellum expresses the five types of dopaminergic receptors. This study aimed to understand the role of cerebellar dopaminergic compounds in motor coordination and balance. For this, a guide cannula was implanted into the cerebellar vermis of adult swiss male mice. The experimental protocol was divided in habituation, microinjection, stage 1, stage 2 and stage 3. At habituation, the animals were placed in the Rotarod (8 r.p.m.) for up to 2 minutes, and at the balance beam until crossing. Twenty-four hours later, the animals received a microinjection of saline or drugs [Dopamine (0.29; 0.86 or 1.5 nmol/0.1ul), D1 antagonist SCH-23390 (0.31; 0.92 or 1.54 nmol/0.1ul) or D2 antagonist Eticlopride (0.26; 1.32 or 2.65 nmol/0.1ul)]. Five minutes after drug microinjection, the animals were exposed to stage 1; four hours after microinjection to stage 2; and twenty-four hours after microinjection to stage 3. At each stage the mice were placed on rota-rod (8 to 20 r.p.m.) and balance beam, each for 3 times, with 5 minutes of rest between each time. Statistical analysis was performed by analysis of variance (ANOVA). Even though the animals showed an improvement at motor performance along exposition to the behavioral tasks, there was no difference between the groups that received Dopamine [(F3,27=0.65; p=0.69) (F3,27=0.21; p=0.97)], D1 antagonist SCH-23390 [(F3,23=0.46; p=0.83) (F3,23=0.95; p=0.47)] or D2 antagonist Eticlopride [(F3,29=0.76; p=0.6) (F3,29=0.23; p=0.96)] and the control groups, which demonstrates that intravermis cerebellar microinjections of dopaminergic compounds do not affected the motor coordination and balance in mice at the doses used in this study. Financial support: São Paulo Research Foundation (FAPESP 2017/24-879-2).
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Title
A NOVEL GPR52 AGONIST, S111224, ATTENUATES ROPINIROLE-INDUCED INCREASES IN PREFERENCE FOR UNCERTAIN OUTCOMES IN RATS

Authors
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Body
Selective dopamine D2/3 agonists, like ropinirole, effectively treat Parkinson’s Disease (PD) motor symptoms, and unlike L-DOPA, do not cause problematic dyskinesias after prolonged use, making D2/3 agonists an attractive alternative to L-DOPA. However, D2/3 agonists induce impulse control and gambling disorders in a substantial minority of patients, raising concern over their use. Adjunctive medications that could be safely administered with D2/3 agonists and treat such psychiatric side-effects would therefore be highly desirable. GPR52 is a Gs-coupled g-protein coupled receptor enriched in D2-receptor expressing neurons of the striatum. Activation of GPR52 can produce a D2 antagonist-like effect without altering basal function. We have shown that ropinirole increases preference for uncertain outcomes on a rodent test of gambling-like decision making, the rodent betting task (rBT), which measures preference for certain versus uncertain rewarding outcomes of equal value. On this task, some rats increase their preference for guaranteed rewards as the wager size increases, even though the relative expected value of the two options remains constant. The choice strategy of these wager-sensitive rats has been associated with the density of D2/3 receptors in the dorsal striatum and has also been linked to the manifestation and severity of problem gambling in humans. We therefore hypothesised that the GPR52 agonist S111224 may attenuate the ability of ropinirole to promote choice of uncertain outcomes in wager-sensitive rats. Healthy male rats performed the rBT prior to implantation of an osmotic pump delivering either ropinirole or saline for 28 days. After implantation, rats received a daily injection of either vehicle or S111224. Ropinirole increased choice of the uncertain option, and S111224 blocked this effect in wager-insensitive rats. In wager-sensitive rats, the effect of ropinirole and S111224 depended on the wager size. S111224 may therefore be effective at reducing ropinirole-induced increases in preference for uncertainty. Funded by Parkinson Canada.
Title
DISRUPTION OF RECONSOLIDATION OF CONDITIONED THREAT MEMORIES IN RATS BY ELECTROCONVULSIVE SHOCK

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Body
The memory reconsolidation hypothesis posits that well-established memories become labile and susceptible to interference following reactivation or retrieval. An early study suggests that electroconvulsive shock (ECS) may disrupt the reconsolidation of threat conditioning in rats measured by the conditioned cue-controlled changes in licking behavior. However, the effects of ECS on other conditioned threat responses remain unknown. Here, we examined in rats the effects of ECS on reconsolidation of conditioned freezing responses. Rats underwent an auditory threat conditioning procedure consisting of a single 30s 5 kHz tone conditioned stimulus (CS) that terminated with a 0.6 mA 1 s electric shock to the footpads. On the following day, a group of animals was re-exposed to the CS in order to reactivate the memory and trigger reconsolidation processes. Immediately after, animals were anesthetized with isoflurane and received 50 Hz, pulse width: 0.7 ms, duration: 1 s, 50 mA ECS (Retrieval-ECS) or not (Retrieval-Sham ECS). Another group of animals after a re-exposure to the CS received isoflurane anesthesia and ECS with a 4-hour delay (Retrieval-4hr delayed ECS). An additional group of animals, on the day following threat conditioning, received either ECS (No retrieval-ECS) or sham ESC (No retrieval-sham ECS) under isoflurane anesthesia without a prior re-exposure to the CS. On the following day, all animals received the memory retention test consisting of exposures to the CS. Analysis of immobility or freezing behavior during the presentations of the CS revealed that the Retrieval-ECS group displayed significantly less freezing than other experimental groups. This pattern of findings suggests that the ECS disrupted the reconsolidation of conditioned threat memories. Ongoing experiments are focused on determining brain site-specific effects of ECS on the reactivated threat conditioned memories.
Title
TANNIC ACID, AN ALLELOCHEMICAL, INHIBITS PERIPHERAL PATHWAYS REGULATING THE LOCOMOTION AND FEEDING OF THE POND SNAIL, LYMNAEA STAGNALIS

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Body
1. The effect of tannic acid (TA), a dominant component of plant allelochemicals was investigated on locomotion and feeding of the pond snail, Lymnaea stagnalis. The effect of TA on the neuronal background underlying feeding activity was also analysed.
2. TA (10, 100 microM) affected the spontaneous locomotion of juvenile snails in a concentration dependent way. Low (10 microM) TA concentration resulted in an increased (sliding or swimming) activity compared to the control and also increased the frequency of sucrose-evoked feeding of intact animals.
3. High (100 microM) TA concentration inhibited the locomotion of animals and resulted in significantly longer feeding latency and decreased feeding rate. The feeding changes proved to be partially irreversible, as after 48 hours maintained in clear water, the animals tested in 100 microM TA previously, still showed lower feeding rate in sucrose.
4. Electrophysiological experiments on semi-intact preparations showed that application of 100 microM TA to the lip area inhibited the fictive feeding pattern of central neurons, the cellular response to sucrose.
5. On isolated CNS preparation 100 microM TA applied in the bathing solution, however, failed to inhibit activation of the central feeding (CPG) interneurons following application of extracellular dopamine.

Our results suggest that TA affects both afferent and efferent peripheral functions in Lymnaea. TA reduces feeding activity by primarily blocking feeding sensory pathways, and its negative effect on locomotion may imply sensory pathways and/or sole ciliary activity.
Title
THE NEUROD6 SUBTYPE OF VTA NEURONS CONTRIBUTES TO PSYCHOSTIMULANT SENSITIZATION AND BEHAVIORAL REINFORCEMENT

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Body
Reward-related behavior is complex and its dysfunction correlated with neuropsychiatric illness. Dopamine (DA) neurons of the ventral tegmental area (VTA) have long been associated with different aspects of reward function, but it remains to be disentangled how distinct VTA DA neurons contribute to the full range of behaviors ascribed to the VTA. Here, a recently identified subtype of VTA neurons molecularly defined by NeuroD6 (NEX1M) was addressed. Among all VTA DA neurons, less than 15% were identified as positive for NeuroD6. In addition to dopaminergic markers, sparse NeuroD6 neurons expressed the vesicular glutamate transporter 2 (Vglut2) gene. To achieve manipulation of NeuroD6 VTA neurons, NeuroD6(NEX)-Cre-driven mouse genetics and optogenetics were implemented. First, expression of vesicular monoamine transporter 2 (VMAT2) was ablated to disrupt dopaminergic function in NeuroD6 VTA neurons. Comparing Vmat2lox/lox;NEX-Cre conditional knock-out (cKO) mice with littermate controls, it was evident that baseline locomotion, preference for sugar and ethanol, and place preference upon amphetamine-induced and cocaine-induced conditioning were similar between genotypes. However, locomotion upon repeated psychostimulant administration was significantly elevated above control levels in cKO mice. Second, optogenetic activation of NEX-Cre VTA neurons was shown to induce DA release and glutamatergic postsynaptic currents within the nucleus accumbens. Third, optogenetic stimulation of NEX-Cre VTA neurons in vivo induced significant place preference behavior, while stimulation of VTA neurons defined by Calretinin failed to cause a similar response. The results show that NeuroD6 VTA neurons exert distinct regulation over specific aspects of reward-related behavior, findings that contribute to the current understanding of VTA neurocircuitry.
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Title
SEX- AND TIMING-SPECIFIC EFFECTS OF ANTIBIOTIC-INDUCED MICROBIOTA DEPLETION DURING MURINE EARLY LIFE: ARE THERE CRITICAL WINDOWS IN MICROBIOTA-GUT-BRAIN AXIS DEVELOPMENT?

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Body
Childhood psychiatric and neurodevelopmental disorders are alarmingly common, yet current gold-standard treatments fall short in creating lasting, meaningful improvements for many individuals. To improve outcomes, it is imperative to enhance our understanding of pathways to disordered neurodevelopment. The current study is based on two hypotheses regarding possible pathways. The first is that problems arise due to disruption of sensitive periods of neuroplasticity. The second is that psychiatric health is closely intertwined with gastrointestinal health and immunity, and more specifically, that the microorganisms resident in the gastrointestinal tract (the gut microbiota) can influence neural, immune and behavioral outcomes.

To identify critical windows of microbial influence on neurodevelopmental outcomes, an antibiotic cocktail (ABX) was administered during one of three developmental time windows (postnatal: postnatal days [P]2-9; pre-weaning: P12-18; post-weaning: P21-27). The ABX consisted of ampicillin, gentamicin, vancomycin and imipenem to provide broad-spectrum depletion of the microbiota. Following treatment in early life, behavioral outcomes were assessed in adulthood. In terms of learning and memory, the novel object recognition test showed that pre- or post-weaning ABX, but not postnatal ABX, enhanced recognition memory in males only. In the 3 chamber social interaction test, preference for a novel social partner was decreased by postnatal ABX only in males, but by pre- or post-weaning ABX in females.

Overall, these results provide evidence that disturbance of the microbiota during specific early-life windows has long-lasting effects on behavioral outcomes, in a sex-dependent manner. Ongoing research is focusing on the neurobiological and neuroimmune basis of such effects. This supports the hypothesis that there are sensitive periods in the microbiota-gut-brain axis and sets the stage for further research to explore the neural and psychological implications of these effects.
PO 138

Title
MOLECULAR MECHANISMS OF POST-ANESTHESIA COGNITIVE DEFICITS AND TAU PROTEIN

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Body
General anesthetics (GA) are widely used due to their multiple surgical applications. However, single as well as repeated exposure to general anesthesia has been reported to cause cognitive impairment and increase the risk for Alzheimer’s disease (AD) but the underlying mechanisms remain poorly understood. Accumulating evidence suggests Tau protein as a key regulator of neuronal plasticity & function while Tau hyperphosphorylation and synaptic missorting is causally related with synaptic malfunction and NMDA receptor excitotoxicity under different pathological conditions in and beyond AD. Despite the fact that Ketamine, a widely used anesthetic drug and NMDA antagonist, is recently shown to have neuroplastic properties, there is lack of information about the cumulative effect of ketamine on neurobehavioral profile. Using detailed molecular, structural and behavioral evidence in normothermic wild-type and Tau-KO animals, we hereby monitor: i) the impact of repeated exposure to ketamine on neuronal structure as well as the cognitive and mood behavioral profile and ii) the potential role of Tau protein in these ketamine-driven morphofunctional effects on brain. We found that repeated exposure to ketamine triggers Tau hyperphosphorylation and synaptic missorting in hippocampus of normothermic animals. In parallel, 3D-neurostructural analysis showed that ketamine administration induced neuronal atrophy in CA1 hippocampal neurons and hypertrophy in dentate gyrus of mice leading to short-term memory deficits. Note that these ketamine effects were not found in Tau-KO animals. Altogether, these novel findings suggest that repeated exposure to ketamine-driven anesthesia cause Tau-dependent morphofunctional deficits in adult brain adding to the mechanistic understanding of the detrimental effects of repeated ketamine exposure that should be taken into account in clinical applications of ketamine.
Title
OPIOID-ETHANOL INTERACTIONS IN MALE Rhesus Monkeys Are Dependent on OPRM1 Genotype

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Body
Opioid and alcohol use disorders separately are widespread public health problems that are associated with opioid neurotransmission. A single nucleotide polymorphism, A118G, in the human mu opioid receptor gene may change the way in which the receptor mediates reward via the mesolimbic circuitry. The 118G variant is linked to higher levels of alcohol-induced euphoria and increased risk of opioid and alcohol addiction, compared to the A118 variant. A polymorphism in rhesus monkeys (C77G) parallels the human mutation and its corresponding physiological and behavioral phenotypes. There is growing evidence that opioids are co-abused with alcohol and that this polydrug abuse can increase lethality of the individual drugs, as well as decrease the effectiveness of opioid maintenance therapy. However, the extent to which genotype influences the interaction remains unknown. Here, male rhesus monkeys genotyped for the C77G polymorphism (N’s: 4 C/C; 4 G/G) were given limited, daily, concurrent access to 4% w/v ethanol solution and water under a fixed-ratio schedule. Once intake was stable, monkeys received pretreatments of saline, morphine or fentanyl prior to the session. Compared to vehicle (saline), both opioids failed to enhance ethanol drinking in C/C animals and suppressed ethanol intake at their highest doses. In G/G animals, morphine enhanced ethanol drinking, while fentanyl did not alter consumption. The results indicate a clear effect of genotype in that C/C animals were more sensitive to the suppressing effects of opioids compared to G/G animals. To the extent that the decreases reflect non-specific behavioral effects, this result suggests that these drug combinations could have more severe side effects in A118-carrying humans. In the G/G animals, the results indicate a clear effect of drug on modulation of ethanol consumption. Although the reasons underlying the observed differences are not clear, they could reflect differences in drug efficacy, duration of action, or signaling bias.
Title
SELF-ADMINISTRATION OF TRIAZOLAM AND PREGNANOLONE COMBINATIONS: BEHAVIORAL ECONOMIC ANALYSIS

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Body
We have shown previously that combinations of the benzodiazepine triazolam with the neuroactive steroid pregnanolone resulted in supra-additive anxiolytic-like effects relative to either drug alone. However, the combined reinforcing effects of triazolam and pregnanolone were infra-additive, suggesting that some combinations of these drugs might retain anxiolysis but have reduced abuse potential. To explore the reinforcing effects of the combinations further, male rhesus monkeys (N=4) were implanted with i.v. catheters and trained to self-administer midazolam under a 5-response, fixed-ratio schedule of reinforcement (2 hr/day, 5 days/week). Both triazolam (0.00001-0.001 mg/kg/injection) and pregnanolone (0.01-0.3 mg/kg/injection) maintained mean numbers of injections/session above vehicle levels in all 4 monkeys. Based on the relative potencies of the two drugs in individual monkeys, fixed proportions (triazolam:pregnanolone, 1:100 or 1:300) were made available, resulting in a leftward and upward shift in the dose-response function compared with either drug alone. Peak doses of the drugs alone or combined were made available to three monkeys, and response requirements were varied from 1 to 320. Consumption (mean number of injections/session) was analyzed as a function of price (FR) using the economic demand analysis of Koffarnus et al. (2015). For each monkey, consumption decreased exponentially with price, and in 2/3 subjects, demand was more sensitive to price for the combinations relative to triazolam alone. Analysis of economic variables revealed that the Pmax (price at maximum response output) for the combinations was significantly lower than Pmax values for triazolam alone. These findings suggest that although combining triazolam and pregnanolone enhanced consumption relative to either drug alone, the combinations were more sensitive to price than the constituent drugs. However, these findings also raise the possibility that reduction in reinforcing effects by combining triazolam and pregnanolone reflects differences solely in the price that maintains maximum response output, rather than changes in overall reinforcer value.
Maternal separation in mice causes deep effects in the sensitivity to cannabinoids.

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Body
The childhood is a critical period for a healthy developmental. In fact, the maternal neglect increases the risk of psychiatric diseases, such as anxiety and substance use disorders during life of the offspring. In our laboratory we have develop a reliable model for maternal neglect named maternal separation with early weaning (MSEW) in CD-1 mice. Using this rodent model, we evaluated the long-term effects on anxiety-like behaviours (elevated plus maze), nociception (tail withdrawal and hot-plate test) and sensitivity of cannabinoids (conditioning place preference, CPP, and physical dependence). Our results indicate that the MSEW protocol not only promotes anxiety-like behaviours but also decrease the threshold sensitivity to nociceptive responses in comparison with control group (Standard Nest). We have also found that the rewarding effect of WIN 55,212-2 (0.5mg/kg) is not affected by the MSEW in the CPP paradigm. Additionally, we have examined several responses induced by cannabinoid agonist WIN 55,212-2 (1mg/kg) related with its addictive properties, including development of physical dependence after the administration of a selective antagonist of CB1 receptor SR141716A (10mg/kg). The antagonist injection precipitated different somatic signs, such as ataxia, mastication, wet dog shakes among others related with the withdrawal syndrome. The results suggest that the MSEW group take more days to recover the basal conditions in locomotor activity and body temperature induced by the cannabinoid treatment. Moreover, the MSEW mice showed higher scores of physical dependence comparing with the control group. To understand these differences, we evaluated alterations in the expression in the CB1 and vesicular transporter of GABA in MSEW in comparison with SN. Thus, MSEW model could be explaining differential responses in emotional and cannabinoid withdrawal responses.

This study was supported by the Ministerio de Economia y Competitividad (grant number SAF2016-75966-R-FEDER), Ministerio de Sanidad (Retic-ISCIII, RD16/017/010 and Plan Nacional sobre Drogas 2018/007).
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Title
The live biotherapeutic mrx0006 (blautia sp.) Attenuates autistic-like behaviour in genetic and environmental mouse models.

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Body
Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterised by deficits in social behaviour, increased repetitive behaviour, anxiety and gastrointestinal symptoms. The aetiology of autism is complex and most likely involves both genetic and environmental factors. Recent evidence suggests that microorganisms resident to the gastrointestinal system play a fundamental role in regulating brain function and behaviour across the lifespan via the microbiota-gut-brain axis. Emerging preclinical and clinical studies have documented a potential role for gut bacteria in ASD, and consequently, the microbiota represents a potential target in the development of novel therapeutics for this neurodevelopmental disorder. In this study, we investigate the efficacy of a live biotherapeutic strain of the genus Blautia, MRx0006, in positively modulating behaviour and gut function in two animal models of autism, the BTBR and maternal immune activation (MIA) models, representing genetic and environmental aetiologies of autism, respectively.

We demonstrate that chronic treatment with MRx0006 attenuated social deficits in the three-chamber test while also decreasing repetitive and anxiety-like behaviour as assessed in the marble burying test and open field test respectively in BTBR and MIA animals. Furthermore, repeated administration of MRx0006 increased intestinal motility in the BTBR model, and 16S sequencing analysis demonstrated that these effects are associated with changes in the gut microbiota in both ASD mouse models. Taken together, these findings further support evidence for a role in microbiota-driven therapies in regulating mood and behaviour. MRx0006 may represent a viable option in the management of the behaviour and gastrointestinal symptoms of ASD.
PO 143

Title
Individual differences in gambling strategies in male lister hooded rats

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Body
Gambling disorder (GD) was recently reclassified along-side the substance use disorders (SUDs). Phenomenologically, SUDs and GD share many features but relative to SUDs, less is known about underlying neurobiology, individual trajectories and endophenotypes, as well as response to pharmacological treatment in problem gambling and GD. The aim of this preclinical study was to evaluate individual differences in emotionality and risk-taking behavior, and associations with impulsivity and gambling strategies in adult, outbred male Lister Hooded rats. Naïve rats were first behaviorally profiled in the multivariate concentric square field™ (MCSF) test, followed by an ethological assessment using the novel cage test. Thereafter the rats were trained in operant chambers to perform the rat Gambling Task (rGT), a rodent analog to the Iowa gambling task. In this test the subjects choose between four options with different probabilities for reward or punishment. Protocols were kindly provided by Professor Catharine A. Winstanley. The results revealed a stable and evident pattern in the rGT already from the second week of gambling. The majority of animals preferred the most strategic choice, while a subset of animals preferred the less optimal, safest option and another subset displayed stable risky gambling strategies. No association between emotionality or risk-taking behavior in the behavioral profiling and later gambling strategies were found. The strategic group made more omissions than both other groups while the risky group made more perseverative responses than the other groups. In conclusion this study demonstrates individual differences in impulsivity and gambling strategies, including a valid number of rats choosing a risky gambling strategy. Further analyses will shed light on number and strength of connections in various brain areas using fMRI and brain neurotransmitter patterns using mass spectrometry imaging.

Funding from the Facias and the Swedish Brain Foundations as well as the Svenska spel Research Council is gratefully acknowledged.
Title
Modulation of dietary lipids reverses early-life stress-induced alterations of the gut-brain axis and behaviour in the rat.

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Body
Rationale: Early life stress (ELS) impacts negatively upon gastrointestinal tract (GIT) function and structure and increases risk for development of disorders of the gut-brain axis. Dietary interventions are emerging as efficacious methods in reducing the impact of ELS on the GIT. Milk fat globule membrane (MFGM) is a complex and unique structure composed primarily of lipids and proteins that surround milk fat globules originating from mammary gland epithelia and has been identified along with docosahexaenoic acid (DHA) as potentially promoting beneficial health effects.

Objectives: To investigate the effect of maternal separation (MS) on offspring behaviour and gut physiology and determine if MS-induced changes could be ameliorated through co-administration of MFGM and DHA.

Methods: MS (between postnatal day 2-12/9am-12pm) was implemented as a model of ELS. MFGM+DHA was administered from birth as follows: Non-Separated[DHA], Non-Separated[MFGM+DHA], MS[DHA], MS[MFGM+DHA]. Visceral hypersensitivity (VH) to colorectal distension, learning and memory (Morris water maze (MWM)) and stress-induced corticosterone levels were assessed in adulthood and gut barrier permeability was assessed in adolescence and adulthood. Enteric neuronal structure was analysed by immunohistochemistry in colonic sections.

Results: MS resulted in VH, spatial memory deficits and increased stress-induced corticosterone levels in adulthood and increased colonic barrier permeability in adolescence. MFGM+DHA ameliorated MS-induced increases in colonic barrier permeability in adolescence and VH in adulthood. MFGM+DHA decreased latency to find the platform in the MWM. MFGM+DHA decreased intensity of βIII-tubulin staining in colonic muscle layer of MS adolescent rats and increased intensity of βIII-tubulin and HuC/D staining in colonic myenteric ganglia of NS adult rats.

Conclusion: This study provides novel insights into the effect of MFGM+DHA given from birth on offspring gut physiology following exposure to ELS. Furthermore, these findings show that MFGM+DHA may have beneficial effects in disorders associated with VH.

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Title
Effects of the selective orexin 1 receptor antagonist act-335827 on conditioned reward processing in rats

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Body
Objective: The brain orexin system is involved in reward processing and can modulate the reaction of mammals to natural and synthetic conditioned rewarding stimuli such as highly palatable food (HPF) or drugs of abuse. The pharmacological blockade of orexin receptor type 1 (OXR1) is being explored as a novel concept for treating addiction. Most investigations in animals have so far, however, relied on the OXR1 antagonist SB-334867, which has additional off-target effects that might contribute to its mechanism of action. We investigated the effects of a structurally different, brain-penetrating, and orally available, selective OXR1 antagonists, ACT-335827, with a clean off-target screening profile, in rat models of conditioned reward.

Methods: Rats were trained to binge on HPF through intermittent exposure to defined periods of dieting and alternating HPF access. One hour before the actual binge eating test, where HPF intake was measured during 2 h, and after a preceding 15 min stress exposure, rats were orally treated with vehicle or different doses (100, 300 mg/kg) of ACT-335827. Other rats were trained to display conditioned place preference (CPP) for a compartment that was previously paired with exposure to either cocaine (15 mg/kg; ip) or morphine (10 mg/kg; ip). The effect of ACT-335827 (300 mg/kg; po) on the expression or acquisition of conditioned reward to those drugs of abuse was investigated.

Results: ACT-335827 reduced binge eating behavior in a dose-dependent manner. ACT-335827 itself did not produce any conditioned rewarding effects in the CPP paradigm. It had also no effects on the acquisition or expression of CPP to either morphine or cocaine.

Conclusions: The OXR1 antagonist ACT-335827 was able to reduce conditioned rewarding behavior (binge eating) to a natural reward (HPF) but failed to do so in the case of synthetic rewards such as morphine or cocaine.
Title
Identifying brain areas involved in punishment-resistant and punishment-sensitive alcohol use

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Body
In humans, alcohol use disorder (AUD) is characterized by loss of control over alcohol use and continued alcohol use despite negative consequences. However, the neurobiological factors underlying these main aspects of AUD are not well understood. In order to further identify neural circuits involved, we are using a recently developed behavioural procedure to model alcohol use despite negative consequences in rats.

During this behavioural procedure, rats are first trained to self-administer alcohol, and then undergo sessions where alcohol seeking is coupled with an aversive experience (a mild electric shock). This behavioural paradigm for rats can reliably distinguish between animals that stop drinking alcohol in the face of punishment (punishment-sensitive rats), from those that continue drinking alcohol despite negative consequences (punishment-resistant rats), highlighting individual differences in response to negative consequences of drinking also observed in humans.

Here, we have implemented this behavioural rat procedure in male and female Long-Evans outbred rats (n=24). Firstly, we have observed differences in the response to punished alcohol use between males and females. Furthermore, using cFos expression (an immediate early gene expressed in recently activated neurons), we have identified neural activity related to both punishment-sensitive and punishment-resistant alcohol use. Identifying the neural circuits underlying punishment-resistant as well as punishment-sensitive alcohol use will provide us with a greater understanding of the neurobiological underpinnings of alcohol use disorder.
Title
A NOVEL RNA-TARGETED THERAPEUTIC APPROACH FOR TAU PATHOLOGY

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Body
Hyperphosphorylation and accumulation of the cytoskeletal protein Tau as well as the imbalance on its splicing isoforms are key pathological mechanisms in Alzheimer’s disease (AD) brain as they are connected to synaptic malfunction, neuronal atrophy and related cognitive impairments. Moreover, experimental studies suggest Tau as a key trigger of neuronal malfunction in a broader spectrum of insults/neuropathologies such as environmental stress, glutamate-driven excitotoxicity and stress-driven depression. The recent FDA approval of usage of antisense oligonucleotides (ASOs) in humans opens a novel window of therapeutic opportunities but their efficacy against Tau protein in neuronal milieu is poorly explored. Hereby, we monitor 25 ASOs with different chemical modifications against total Tau protein as well as splicing imbalance of Tau using N2A cells and primary neurons. We identify that specific modifications of ASOs exhibit more than 80% reduction of Tau mRNA and protein levels in both N2A cells and primary neurons. ASOs-based reduction of aberrantly accumulated Tau provides a novel therapeutic tool against Tau-driven brain pathology in and beyond AD.
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Title
NETWORKS OF IMPULSIVITY – PREFRONTAL-STRIATAL ENCODING OF BEHAVIORAL INHIBITION

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Body
Impulsivity is an adaptive response allowing fast reaction to stimuli. However, its dysregulation is associated with disorders such as substance abuse or attention deficit/hyperactivity disorder (ADHD). Several prefrontal and subcortical areas are known to play a relevant role in response inhibition. How these areas interact across the temporal window preceding the execution of timed vs premature actions is yet to be described.

We have therefore assessed local field potentials (LFPs) bilaterally in frontal and striatal areas: prelimbic and orbital prefrontal (OPF) cortices, caudate and nucleus accumbens (NAcc) during performance of the Variable Delay-to-Signal (VDS) task. During training, the animals learn that nosepoking in an orifice while its light is on is considered a timed response and is rewarded with a sugar pellet, while nosepokes performed within the 3 s delay before the light turning on are considered premature and punished with a timeout. The number of premature responses at the end of training is associated with action impulsivity.

We determined that all these regions play a role in behavioral inhibition at specific time frames up to 3 seconds before the response (timed or premature). Three to 2 seconds before a nosepoke, all left regions, as well as the right NAcc, associate with the type of response (i.e. show different activation before a timed or a premature response). Interaction of this left lateralized network with the right hemisphere then culminates with differential activation of the right OPFC immediately before the response.

In conclusion, brain activity in the studied network is markedly different in the temporal window preceding timed and premature responses. Evidence of behavioral (dis)inhibition can be found up to 3 seconds before the actual response and evolves in a time- and hemisphere-specific fashion.
Title
CFOS BASED NETWORK ANALYSIS REVEALS PROFOUND DIFFERENCES IN THE REPRESENTATION OF MEMORIES FOR ALCOHOL AND SWEET REWARD

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Body
Cue-reward associations form distinct memories that can drive appetitive behaviours and are involved in craving for both, drugs and natural rewards. Such memories may be represented in distinct groups of local neurons, also called ensembles, which are functionally involved in the processing of distinct memories and distributed throughout the brain. We recently used cFos activity mapping to identify functional ensembles involved in memory retrieval associated with seeking for alcohol or sweet rewards under reinstatement conditions. We found that within the infralimbic area, a subregion of the medial prefrontal cortex, the two ensembles (alcohol vs saccharine) are structurally highly similar and largely overlapping. Here we expanded this investigation towards a network of reward-related brain regions and assessed the correlation structure of cFos activation patterns. We used tools from graph analysis to assess basic communication properties of networks composed of local neuronal ensembles.

Here, we trained 28 male Wistar rats on a concurrent two-reward operant conditioned self-administration task. Reinstatement-induced neuronal activity was determined in 12 distinct, reward-related brain regions by cFos-immunohistochemistry. Although both contingencies activated neuronal populations of similar size in all brain regions examined, graph analysis of the region-by-region correlation matrices showed significantly higher global communication efficiency and greater robustness against degradation in the saccharine compared to the alcohol-related network. Furthermore, we found distinct connectivity modules, particularly formed by ensembles of the prefrontal cortex, in the saccharine network. This connectivity structure disappeared in the alcohol condition, in part due to a stronger participation of amygdala nuclei, the latter shifting from strong negative to a largely positive correlation with most other network nodes in the saccharine vs alcohol condition, respectively.

In conclusion, graph analysis provides a powerful tool for gaining insights into the differential organisation of neuronal networks involved natural and drug reward memories.
PO 150

Title
ASSESSING SORTING NEXIN 27 ROLE IN COGNITIVE PERFORMANCE AND IN MOOD MODULATION

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Body
Population ageing and stress exposure are increasingly present in our societies and are linked to endocytic dysregulation, cognitive decline, glutamatergic and synaptic dysfunction. Recently, the sorting nexins (SNXs) emerged as a family of proteins that plays pleiotropic roles in protein trafficking and that have been associated with endocytic events underlying neurodegeneration, synaptic plasticity and cognitive decline. Specifically, SNX27, a brain-enriched protein, was shown to impact on synaptic plasticity, learning and memory by regulating the trafficking of the ionotropic NMDA and AMPA class glutamate receptors. Distinct studies also highlighted SNX27 association with Alzheimer’s disease (AD) and Down’s syndrome (DS). Despite this, not much is known about SNX27 role in the nervous system and how it is modulated by ageing and/or chronic stress exposure. We have shown that SNX27 expression levels are altered in the brain during ageing, and that those alterations strongly correlate with cognitive performance in rodents. Moreover, by exposing rodents to a chronic stress protocol, we found SNX27 expression to be significantly decreased in the pre-frontal cortex (PFC), and its levels to correlate strongly with corticosterone levels. Additionally, by performing a multidimensional behavioral analysis of the SNX27+/− mouse model, during ageing and under exposure to stress we have validated the role of Snx27 in learning and memory throughout age, and unraveled its impact on mood modulation in younger rodents. Altogether, the present work provides evidences of SNX27 prominent role in the nervous system.
Title
A TWO-HIT STORY: SEIZURES AND GENETIC MUTATION INTERACTION SETS PHENOTYPE SEVERITY IN SCN1A EPILEPSIES.

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Body
SCN1A (NaV1.1 sodium channel) mutations cause Dravet syndrome (DS) and GEFS+ (which is in general milder), and are risk factors in other epilepsies. Phenotypic variability limits precision medicine in epilepsy, and it is important to identify factors that set phenotype severity and their mechanisms. It is not yet clear whether SCN1A mutations are necessary for the development of severe phenotypes or just for promoting seizures. A relevant example is the pleiotropic R1648H mutation that can cause either mild GEFS+ or severe DS. We used a R1648H knock-in mouse model (Scn1aRH/+) with mild/asymptomatic phenotype to dissociate the effects of seizures and of the mutation per se. The induction of short repeated seizures, at the age of disease onset for Scn1a mouse models (P21), had no effect in WT mice, but transformed the mild/asymptomatic phenotype of Scn1aRH/+ mice into a severe DS-like phenotype, including frequent spontaneous seizures and cognitive/behavioral deficits. In these mice, we found no major modifications in cytoarchitecture or neuronal death, but increased excitability of hippocampal granule cells, consistent with a pathological remodeling. Therefore, we demonstrate for our model that an SCN1A mutation is a prerequisite for a long term deleterious effect of seizures on the brain, indicating a clear interaction between seizures and the mutation for the development of a severe phenotype generated by pathological remodeling. Applied to humans, this result suggests that genetic alterations, even if mild per se, may increase the risk of second hits to develop severe phenotypes.
Title
PAIN ALTERS ALCOHOL-REINFORCING PROPERTIES AND INDUCES RELAPSE-LIKE BEHAVIOUR IN FEMALE RATS THROUGH KOR/DYN SYSTEM

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Body
Pain affects the processing of reward leading to an anhedonic state that may impact the development of addiction. Clinical studies have shown that pain increases the risk of alcohol relapse, but the mechanisms underlying this pain-alcohol interaction remain unknown.

In our study, we first analysed inflammatory pain effect on alcohol-reinforcing properties. 48h after injection of Complete Freund Adjuvant (CFA) our microdyalisis study in male rats showed that pain impairs alcohol-induced dopamine release in the NAc. Moreover, alcohol-induced place preference was blunted in pain animals. Then, we tested pain effect on relapse-like behaviour by using the alcohol deprivation effect model to study. Five alcohol drinking periods were alterned with four abstinence periods. CFA was introduced in the fourth abstinence period 48h before the last period of alcohol intake. Pain did not alter the relapse-like behaviour showed by the animals.

Finally, we developed a new alcohol intermittent access model to study the influence of pain on relapse in male and female rats. This model has three periods: alcohol intake, abstinence and alcohol reintroduction. The CFA was introduced during the abstinence 7 days before the reintroduction of the bottles. These results revealed that only female rats in pain increased alcohol intake in the reintroduction period. Moreover, female pain rats showed alterations in kappa opioid receptor (KOR) and dynorphin (dyn) expression in NAc that indicated an increase of the KOR/dyn tone.

In conclusion, inflammatory pain may constitute a risk factor to increase the vulnerability to relapse in alcohol consumption only in female rats through the activation of the KOR/dyn system in the NAc. Further research should help us to understand how pain alters alcohol addiction-like behaviours to better design therapies for these patients.
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Title
THE EMERGENCE OF A STABLE NEURONAL ENSEMBLE FROM A WIDER POOL OF ACTIVATED NEURONS IN THE DORSAL MEDIAL PREFRONTAL CORTEX DURING APPETITIVE LEARNING IN MICE

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Body
Animals selectively respond to environmental cues associated with food reward to optimize nutrient intake. Such appetitive CS-US associations are thought to be encoded in select, stable neuronal populations or neuronal ensembles, which undergo physiological modifications during appetitive conditioning. These ensembles in the medial prefrontal cortex (mPFC) control well-established, cue-evoked food seeking, but the mechanisms involved in the genesis of these ensembles are unclear. Here, we utilized Fos-GFP mice that express the green fluorescent protein (GFP) in recently behaviorally-activated neurons, to reveal how dorsal mPFC neurons are recruited and modified to encode CS-US memory representations using an appetitive conditioning task. In the initial conditioning session, animals did not exhibit discriminated, cue-selective food seeking, but did so in later sessions, indicating that a CS-US association was established. Using microprism-based in vivo 2-Photon imaging, we revealed that only a minority of neurons activated during the initial session was consistently activated throughout subsequent conditioning sessions and during cue-evoked memory recall. Notably, using ex vivo electrophysiology we found that neurons activated following the initial session exhibited transient hyper-excitability. Chemogenetically enhancing the excitability of these neurons throughout subsequent conditioning sessions interfered with the development of reliable cue-selective food seeking, indicated by persistent, non-discriminated performance. We demonstrate how appetitive learning consistently recruits a subset of neurons to form a stable neuronal ensemble that represents a CS-US association and underlies optimal cue-evoked food seeking. This ensemble may arise from a subset of hyper-excitabile neurons activated prior to the establishment of this behavior.
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Title
AP2GAMMA TRANSCRIPTION FACTOR AS A MODULATOR OF ADULT HIPPOCAMPAL NEUROGENESIS IN AN ANIMAL MODEL OF DEPRESSION

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Body
Depression is a multidimensional psychiatric disorder that poses a significant burden in society nowadays. Despite the importance of this disease in modern societies and the large investment of resources already made in its study, the processes underlying its pathophysiology remain poorly understood. Moreover, about 65% of patients fail to respond to current first-line therapies, making this field of research a priority. Hippocampal neurogenesis has been proposed to participate in a wide range of behavioral responses, both in basal states and in the context of neuropsychiatric disorders. Several studies have shown how adult neural-plasticity becomes compromised in depressed patients and in animal models of depression. We have identified the AP2gamma transcription factor as a key regulator of hippocampal neurogenesis and we wanted to further explore its impact in a depressive-like context.

To study the impact of AP2gamma in depression, we exposed both constitutive and conditional KO animal models (males and females) to a chronic mild stress protocol, which efficiently induced core depressive-like symptoms, since different weight-gain patterns and a disruption of the hypothalamic-pituitary axis were observed. Through a multidimensional behavioral analysis, we observed that reduced expression of AP2gamma (constitutive KO mice) produced significant deficits in cortico-dependent cognitive tasks. However, this deletion since embryonic development proved to be beneficial for hippocampal-dependent cognitive functions. Possibly, the improvement observed was due to a compensatory increase of several genes (Sox2, Pax6, and Tbr2) important to promote the hippocampal niche, ameliorating the deleterious effects induced by chronic stress. This compensatory mechanism is further supported by the fact that these genes were normally expressed, and cognitive deficits were found in the conditional KO mice, in which the AP2gamma deletion occurs in an adult phase only.

Altogether, these findings open new perspectives in understanding the role of specific sub-populations of newborn neurons in the pathophysiology of neuropsychiatric disorders affecting hippocampal neuroplasticity and highlight the potential of AP2gamma as a future therapeutical target.
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Title
LDT TO NUCLEUS ACCUMBENS INPUTS DRIVE PREFERENCE AND INCREASE MOTIVATION

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Body
The brain circuits that underlie cue-reward associations are essential for survival to ensure individuals obtain food, sex and other rewards. Deficits in this circuit underlie several neuropsychiatric disorders, like depression or addiction. Neurons of the laterodorsal tegmentum (LDT) send specific inputs that tightly modulate the activity of dopaminergic neurons of the VTA, controlling the release of dopamine in the NAc. Until recently, striatal acetylcholine was believed to originate exclusively from striatal cholinergic interneurons. Recently, a novel pathway emerged, encoding direct projections from the laterodorsal tegmentum (LDT), to the nucleus accumbens (NAc), the core region of the reward circuit, suggesting both a direct and indirect role in modulating accumbal activity. Yet, nothing is known about its role in reward processing. The possibility of this external novel direct control over NAc neurons highlighted a major gap in our understanding of how neuromodulators regulate striatal activity and how reward circuits encode and control the development and expression of cue-reward associations relevant to normal functioning or maladaptive effects leading to depression or addiction. Here we investigate the biological role of LDT-NAc projections using a combination of anatomical, molecular and functional studies. The majority of LDT-NAc inputs are cholinergic, although there is also GABAergic and glutamatergic innervation. We show, for the first time, that the LDT is recruited and that the mainly excitatory LDT-NAc projections are essential for reward value and play an important role in motivation: Non-selective optogenetic activation of LDT-NAc projections in rats enhances motivational drive and shifts preference to an otherwise equal reward; whereas inhibition of these projections induces the opposite. Additionally, specific activation of LDT-NAc cholinergic inputs (not glutamatergic nor GABAergic inputs) is sufficient to shift preference, increasing motivational drive. These results extend the study of how reward information is encoded, advancing the understanding of the pathophysiological mechanisms underlying neuropsychiatric disorders with reward deficits.
Title
INFLAMMATORY PROFILE OF HEALTHY AGING INDIVIDUALS WITH DISTINCT COGNITIVE PROFILES

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Body
Understanding how the immune mediators interact with the central nervous systems and influence cognition is of great relevance to provide clues on potential strategies to reduce or delay aging-associated cognitive decline in an increasingly aged population. Evidences associating peripheral T lymphocytes and their cytokine production with cognitive performance, both in humans and in animal models, are constantly being demonstrated. Furthermore, a more pro-inflammatory profile, frequent in older individuals, has been associated with worse cognitive performances. In a cohort established in the context of a multidisciplinary project aiming to understand the correlates of healthy cognitive aging (55+) we are dissecting the associations between peripheral inflammatory profiles and cognitive performance. We measured up to 40 analytes in plasma. We observed that individuals with worse cognitive performance have a more pro-inflammatory profile than individuals with better performance, even when controlling for factors known to influence cognitive performance.
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Title
BRAIN FUNCTIONAL NETWORKS ABNORMALITIES AS NEUROPHYSIOLOGICAL BIOMARKER OF FUTURE ALCOHOL BINGE DRINKERS

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Body
In recent years, adolescent alcohol Binge Drinking (BD) has become an increasing health and social concern. Adolescence is a critical neurodevelopmental period, entailing important neurobiological changes, which makes the brain particularly vulnerable against alcohol neurotoxicity. However, evidences for neurophysiological and neuropsychological binge drinking predisposition profiles remains unveil. In this research, we evaluated a cohort of initially alcohol-naive adolescents in a two-year longitudinal study with magnetoencephalography (MEG). Participants’ neurophysiological cortical activity was recorded while performing a classical inhibition task in order to characterize the control functional networks of teenagers who will transit into intensive alcohol consumers two years later. Complementarily, they fulfilled a battery of tests to assess impulsivity and dysexecutive traits. For the first time, we detected abnormalities in MEG functional connectivity networks of those adolescents who, two years later, engaged in BD consumption, and, additionally, higher scores in impulsive and dysexecutive behaviors. These results seems to evidence the existence of abnormalities in brain functional networks prior to alcohol consumption onset, reflecting potential neurobiological vulnerabilities towards the engagement in risky behaviors. We hypothesize that these abnormalities are due neurodevelopmental and neurobiological differences, involving neurotransmission pathways, which, in turn, would cause the functional networks dysfunctions.

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Title
A GLUCOCORTICOID RECEPTOR-DEPENDENT MECHANISM OF BILE ACID ACTION WITH THERAPEUTIC IMPACT IN POLYGLUTAMINE DISEASE

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Body
Spinocerebellar ataxia type 3 (SCA3) is an autosomal dominant neurodegenerative disorder caused by a polyglutamine expansion within the protein ataxin-3, leading to protein dyshomeostasis and aggregation, neuronal dysfunction and ultimately neuronal demise. Clinically, it is characterized by gait imbalance, oculomotor and speech difficulties, with a mid-life onset. Despite growing efforts, no directed treatments are currently available for this invariably fatal disease. In this work we tested bile acids as potential therapeutic agents for SCA3, since these molecules have been shown to be neuroprotective in other conditions, such as Parkinson’s and Huntington’s diseases. Using a C. elegans model of SCA3 we observed that tauroursodeoxycholic acid (TUDCA) was the most efficient bile acid in improving the animals’ motor phenotype. A significant improvement was also observed in a pre-clinical trial using CMVMJD135 mice: chronically treated mice showed markedly improved performance in several tests measuring motor behavior, as well as reduced neuropathology and neuroinflammation markers. After establishing the potential of TUDCA for treatment of SCA3, we dissected the mechanism of action of this drug using the C. elegans SCA3 model. Surprisingly, we observed that the effect of TUDCA was independent of its canonical nuclear receptor, the farnesoid X receptor (FXR), but fully dependent on the glucocorticoid receptor (GR). Moreover, GR protein levels were markedly decreased in the CMVMJD135 mouse model, and fully recovered by an acute treatment with TUDCA. Finally, and most importantly, we have also observed a decrease in GR levels in the pons, a highly disease-affected brain region, of SCA3 patients. In sum, we identified TUDCA, a drug with a high translational potential, as a contender compound for the treatment of SCA3, and propose a novel mechanism of action that could be of high interest in the future, including for other neuromuscular disorders currently treated with glucocorticoids.
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Title
INVOlVEMENT OF NUCleUS ACCUMBENS NEURONAL ENSEMBLES IN CUE-INDUCED CRAVING AFTER PROLONGED ABSTINENCE.

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Body
Exposure to environmental stimuli previously associated with drug use can induce cocaine relapse by an associative learning process. Associative learning is encoded by a small specific pattern of activated neurons, now called neuronal ensembles. Neuroplasticities are fundamental for associative learning, however, most of them, especially those related to drug addiction, are still unknown. It was demonstrated that some of the addiction-related plasticities are modified during the abstinence period and these modifications appear to be pivotal for the increase of the cue-induced cocaine craving after prolonged abstinence. This phenomenon has been termed incubation of drug craving. Our goal was to investigate the role of nucleus accumbens neuronal ensembles and its neuroplasticities in the incubation of cocaine craving. For that, jugular vein of male Wistar rats was catheterized for cocaine self-administration. Rats were trained to self-administer cocaine 6h/day, for 12 days in a specific context. Then, we assessed relapse to cocaine seeking after 1 or 30 abstinence days (AD) and performed histological analysis (Animal Research Ethical Committee number: 4183030918). Following 30 days of abstinence, rats exposed to cocaine related context, presented a robust increase on active lever presses compared to day 1 of abstinence. After 1 or 30 days of abstinence, rats exposed to drug context, compared with home cage group, presented a higher activation of nucleus accumbens core and shell neurons. Interestingly, the number of accumbens activated neurons following drug context exposure was not different between 1 and 30 days of abstinence. Our data suggest the involvement of nucleus accumbens neuronal ensembles on incubation of cocaine craving.

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Title
FUNCTIONAL CONNECTIVITY AND ALCOHOL CONSUMPTION ARE ASSOCIATED IN YOUNG BINGE DRINKERS: A MEG STUDY

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Body
Neurofunctional studies have shown that binge drinking patterns of alcohol consumption during adolescence and youth are associated with anomalies in the brain functioning. Recent evidence suggests that functional connectivity may be an appropriate index of neurofunctional damage associated with hazardous alcohol intake. The purpose of the present study was to examine brain functional connectivity abnormalities of young adults binge alcohol drinkers. Participants were asked to cover a record of daily consumption indicating what they drank, the quantity and for how long (hours). Their blood alcohol concentration (BAC) was calculated based on the information of each drinking episode of the last 6 months. We considered the BAC value as a rough index representing the BD’s level of each subject. We have carried out an eyes-closed resting state magnetoencephalography (MEG) study and analyzed the brain functional connectivity of 25 young binge drinkers by assuming that those with a higher BAC would present greater FC disruption. The results indicated that the higher BAC value, the higher functional connectivity disruption on the frontal areas of the BDs. This findings are in line with previous studies showing that frontal areas are affected by alcohol binge drinking in comparison to peer controls.