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Symposium

SY01.
Developing a functional hippocampus: from molecules to behavior
ORIGIN OF EARLY SHARP WAVES IN THE NEONATAL RAT HIPPOCAMPUS
Guzel Valeeva¹,², Sona Janackova¹, Veronica Rychkova², Roustem Khazipov¹,², Pierre-Pascal Lenck-Santini³
¹ INMED Aix-Marseille University, Marseille, France
² Kazan Federal University, Kazan, Russia

Objectives:
The neonatal rat hippocampus generates intermittent, spontaneous activity patterns that are thought to participate in the maturation of its circuits. These patterns consist of high amplitude, short lasting, early sharp waves (eSPWs) and bouts of beta (10-30Hz) oscillations often occurring at the tail of the eSPWs. Our goal is to understand the circuits involved in their generation.

Purpose: Understand the neuronal circuits involved in neonatal hippocampal early sharp waves and beta oscillations.

Methods: In unanesthetized, head restrained pups (P1-P9), we implanted laminar silicon probes, perpendicularly across all layers of CA1, dentate gyrus and/or CA3. The origin of inputs to the hippocampus and single neuron activity during eSPWs was investigated using a combination of Current Source Density, single unit analysis and stimulation protocols, and histological reconstruction of the position of the recording/stimulating electrodes.

Results: Spontaneous eSPW emerged at P2 and increased in frequency with age. In a large majority of cases they were preceded by body startles. Spontaneous eSPWs were characterized by two co-occurring prominent sinks: one in the stratum radiatum and another around the hippocampal fissure. These CSD profiles were identical to those induced by stimulation of inputs from CA3 and entorhinal cortex, respectively. Spontaneous eSPWs triggered an increase in activation of units in CA1, CA3 pyramidal and in the granular layer of dentate gyrus.

Conclusions: These findings suggest that generation of the eSPWs in CA1 hippocampus of neonatal rats recruit two main pathways, one involving intrahippocampal connections from CA3, producing a sink in stratum radiatum, and the other involving inputs from the entorhinal cortex, which produce a sink in stratum lacunosum-moleculare. We propose that during the neonatal period, the eSPWs support activity-dependent formation of connections in the developing entorhino-hippocampal network.
INVolvement of the Dentate Gyrus in the DeveloPment of episodIc-like meMIry in Mice
Muriel Koehl
Neurogenesis and Physiopathology group, Neurocentre Magendie, Bordeaux, France

Objectives: The hippocampus is involved in episodic memory, i.e. the ability to remember personal experiences in terms of what happened, where and when, and one sub-region, the dentate gyrus, was found to be essential for the relational binding of these modalities. This specific region is a site of continuous neurogenesis persisting into adulthood, resulting in important cell heterogeneity. Despite this anatomical heterogeneity, the relationship between the different cell populations and episodic memory has not been much explored yet. The objective of our studies is thus to understand the implication of different populations of granule cells of the DG in episodic-like memory in mice.

Purpose: Analyse the respective contribution of different populations of DG granule cells in episodic-like memory across development in mice.

Methods: We have first established a time-course of memory development in C57Bl/6J mice using object recognition tasks and showed as expected that simple modalities such as what or where recognition emerge earlier than complex associations, such as what-where recollection. We then approached the role of different populations of cells, one originating from the juvenile period, the other one from adulthood, in a simple what-where task and a more complex one with an additional contextual modality, i.e. a what-where-which task. We used a functional imaging approach consisting in analyzing the proportion of cells that express the product of the IEG c-Fos in response to the different behavioral tasks. Juvenile and adult-born neurons were tagged with BrdU, a mitotic marker, 6 weeks before testing and animals were sacrificed 90 min after testing.

Results: We report that juvenile and adult-born neurons are differently implicated as a function of the specific modality of memory tested. Indeed, only juvenile neurogenesis seems to be involved in the complex task (“what-where-which”) while both juvenile and adult neurogenesis seem to contribute to the simple task (“what-where”). Ongoing studies test the causal relationship linking the different population of DG cells and episodic-like memory.

Conclusions: Overall this study highlights the role of the different neuronal populations of the dentate gyrus in episodic memory, which should shed light on some of the mechanisms involved in complex memories.
ASSOCIATIVE MEMORY DEVELOPMENT IN THE RAT AND TRANSLATION INTO A HUMAN PARADIGM
Division of Neuroscience, Ninewells Hospital& Medical School, Dundee Scotland, United Kingdom

Episodic memory is the recollection of unique autobiographical events, including rich detail of times, places and associated contextual information. In neurodegenerative diseases, such as Alzheimer’s disease, episodic memory is greatly impaired. Also, the ability to recall episodic memories is thought to develop later in childhood than other types of memory such as novelty recognition. This ontogeny in rodents is so far unconfirmed due to a lack of suitable behavioural tests. We have developed a protocol suitable for testing the development of simple novelty detection, associative memory and episodic-like memory (using memory for what, where and which) in juvenile rats. We are currently using it to investigate whether rats show a differential ontogenic profile of these types of memory and how this may relate to human memory development. We have some preliminary data on how experience may affect this developmental process.

We have also designed a screen-based version of the traditional rodent what-where-which episodic-like memory test and adapted it to mimic a gold-standard paired associate learning paradigm used clinically in episodic memory diagnostics. We are currently comparing the theoretical and procedural differences between the two paradigms and investigating how sensitive the what-were-which task is at detecting age-related changes in cognition.
INFANTILE AMNESIA: A CRITICAL PERIOD OF LEARNING TO LEARN AND REMEMBER
Cristina M. Alberini
Center for Neural Science, New York University, New York, NY, USA

Episodic memories formed during the first postnatal period are rapidly forgotten, a phenomenon associated to infantile amnesia. In spite of this apparent memory loss, early experiences influence adult behavior, raising the question of which mechanisms underlie infantile memories and amnesia. Studies in my laboratory have recently found that in rats an experience learned during the infantile amnesia period requires the dorsal hippocampus to store a long-lasting, latent memory trace. This memory storage requires mechanisms typical of developmental critical periods and matures the hippocampal system. We also found that the hippocampus reaches the highest levels of synaptic and neuronal activation during the infantile amnesia period compared to a later developmental age and to adulthood. I will discuss conclusions and implications about the hippocampus undergoing a developmental critical period to become functionally competent.
Symposium

SY02.
Memory manipulations during sleep:
Fundamental advances and clinical application
IMPOSED REPLAY MODIFIES STRENGTH AND PRECISION OF ODOR MEMORY
Donald A. Wilson
Nathan Kline Institute for Psychiatric Research
New York University School of Medicine

Objectives: During slow-wave sleep (SWS), the primary olfactory cortex becomes hypo-responsive to sensory input and more strongly coherent with top-down inputs. This shift in connectivity is necessary for accurate replay of odor memory during post-training SWS, allowing strong consolidation of precise odor memory.

Purpose: This research explores how the balance between bottom-up and top-down inputs to the olfactory cortex shifts between waking and sleep, and how this shift during post-training sleep is critical for strong, precise odor memory formation.

Methods: Freely moving Long Evans rats were used for direct optogenetic analysis of changes in network connectivity over the sleep-wake cycle. Channelrhodopsin was expressed in neurons of the olfactory bulb (bottom-up), piriform cortex or lateral entorhinal cortex (top-down) and light-evoked synaptic responses monitored at 20 sec intervals with an optotrode implanted in the piriform cortex as the animals cycled through sleep-wake states. In separate animals, electrode arrays were implanted in the olfactory bulb to evoke odor-like activity as a conditioned stimulus in a fear conditioning paradigm. The odor-like activity was replayed during SWS post-conditioning and the strength and precision of fear memory assessed 24 hr later.

Results: The efficacy of intra- and inter-cortical synapses is enhanced during SWS, while at the same time the response to sensory input is depressed. This allows replay of odor memory to occur in the absence of sensory interference. Artificially imposing odor-related activity replay during post-training SWS enhances the strength of odor memory. In contrast, bypassing the sensory gate during post-training SWS (inducing interference) induces odor memory generalization (reduced accuracy).

Conclusions: State-dependent fluctuations in the balance between bottom-up and top-down inputs to the primary olfactory cortex are required for accurate odor memory consolidation.

Literature Reference 1Barnes, D.C. and Wilson, D.A. Slow-wave sleep imposed-replay modulates both strength and precision of memory. J. Neuroscience, 2014, 34:5134-5142.
EXPLICIT MEMORY CREATION DURING SLEEP: A CAUSAL ROLE OF PLACE CELLS IN NAVIGATION
Karim Benchenane
Brain Plasticity Unit, UMR 8249 CNRS ESPCI, Paris, France

Objectives: Hippocampal place cells assemblies are believed to support the cognitive map, and their reactivations during sleep are thought to be involved in spatial memory consolidation. However, while the animal is awake, it is impossible to dissociate its actual position from the associated neuronal firing, and the proposed function of place cells in navigation is based entirely on this correlation.

Purpose: We hypothesized that the transient decorrelation of place cell activity from current location during sleep could provide a way to directly test the function of place cells in navigation.

Methods: Mice were implanted with polytrodes in the CA1 pyramidal layer and stimulation electrodes in the medial forebrain bundle, known to induce reward in mice. A brain computer interface was developed to trigger automatically rewarding stimulation by the action potential of a place cells during sleep.

Results: A place cell was first identified in mice freely exploring an environment. During a 1h sleep session following this exploration, intracranial rewarding stimulations were triggered by place cell spikes. After waking up, mice headed straight for the place field of the neurons used as a trigger. The mice stayed five time longer in this location after the sleep pairing procedure compared to before. This shows that we induced, during sleep, an explicit memory trace, leading to a goal-directed behavior toward the place field.

Conclusions: Altogether, our results demonstrate that place cells’ activity during sleep still conveys relevant spatial information which is a strong support the theory of spatial reactivation during sleep. Moreover, the fact that pairing spikes of a given place cell with rewarding stimulation during sleep, when its activity was decorrelated from the actual animal position, leads to a place preference toward the related place field demonstrates that place cell activity itself functions in spatial memory and navigation.
MEMORY ENHANCEMENT OR DEPRESSION DURING SLEEP, USING PRECISE, BRAIN-WAVE GUIDED MEMORY REACTIVATION
Lucia M. Talamini¹,²
¹University of Amsterdam, Amsterdam, The Netherlands
²ABC - Amsterdam Brain and Cognition, University of Amsterdam, Amsterdam, The Netherlands

Objectives: An elegant way to manipulate the sleeping brain is through the alignment of stimuli with specific electrophysiological brain signals. We have previously developed the first closed-loop brain stimulation procedure based on signal modelling, which we used to demonstrate differential processing of real-world sounds targeted to slow oscillation (SO) up- and down-states (Cox et al., 2014, Plos One). We have now developed a new procedure for oscillatory phase targeting that is faster, more accurate and more convenient than any previously reported method.

Purpose: Using this procedure, we aimed to show that memory reactivation and consolidation are specifically linked to the SO up-state. Indeed, we hypothesised that the tight alignment of specific memory cues to SO up-states during sleep would enhance memory performance compared to SO down-state locked stimuli.

Methods: Participants were exposed to a vocabulary-learning task in the evening and tested for vocabulary acquisition. During ensuing sleep, memory reactivation was induced through subtle auditory presentation of foreign words. One group of participants received SO up-state targeted memory cues, a second groups received SO down-state locked cues. In each group only part of the pre-sleep learned items was cued, counterbalanced for pre-sleep acquisition (hit/miss). The next morning, vocabulary memory was tested again and expressed as a proportion of performance on the previous night.

Results: Using this procedure, we showed that the tight alignment of specific memory cues to SO up-states during sleep enhances performance on a pre-sleep presented vocabulary-learning task, compared to either no cueing or down-state cueing. Interestingly, down-state cueing suppresses memory performance with respect to no cueing.

Conclusions: These results provide strong evidence for the notion that sleep-related memory consolidation occurs during slow oscillation up-states. Moreover, they show that declarative memory can be either enhanced or suppressed during sleep, depending on the alignment of reactivating cues to specific neural activity patterns.
ASSOCIATIVE LEARNING DURING HUMAN SLEEP: INTERPLAY BETWEEN SLEEP STAGES, SLOW WAVE OSCILLATIONS AND BEHAVIOUR
Anat Arzi
Department of Psychology, University of Cambridge, Cambridge, UK

Objectives: Recent finding suggests that humans can learn novel information during sleep, and that this information can modulate behavior during wakefulness in a sleep stage dependent manner. Specifically, new associations learned during non-rapid-eye-movement sleep (NREM) had larger and longer lasting influence on behavior than associations learned during rapid–eye-movement (REM) sleep.

Purpose: We set out to test whether slow oscillations which are highly prevalent in NREM but not in REM sleep, are part of the mechanism underlying sleep stage dependent associative learning during human sleep.

Methods: We recorded electroencephalogram (EEG) during partial-reinforcement conditioning in NREM and REM sleep. On reinforced trials (two-thirds of trials), the conditioned stimulus (tone or odor) was paired with an unconditioned stimulus (odor). On non-reinforced trials (one-third of trials), the conditioned stimulus was presented without an ensuing odor, which enabled us to measure learning without the interference of the unconditioned stimulus.

Results: We found an increase in slow oscillations (0.5-5Hz) power following the conditioned stimulus offset in non-reinforced trials during NREM sleep, compared to REM and to a control experiment in which the same stimuli were presented in a random order during NREM. Moreover, during NREM the increase in slow oscillations following the conditioned stimulus offset was significantly larger when the conditioned stimulus was previously paired with an unpleasant odor than with a pleasant odor. This difference was not evident during REM sleep.

Conclusions: Our results demonstrate that new associations learned during sleep increased slow oscillation activity during NREM sleep but not during REM sleep. Furthermore, these findings imply that the increase in slow oscillations might depend on the unconditioned stimulus properties. This work suggests a mechanistic link between sleep stage dependent associative learning during human sleep and slow oscillations.
Symposium

SY03.
Exploring the bases of physiological and pathological behaviour: thinking out of the brain box
THE ROLE OF BRAIN ENERGY METABOLISM IN VULNERABILITY TO STRESS-INDUCED PSYCHOPATHOLOGIES
Carmen Sandi
Brain Mind Institute, Swiss Federal Institute of Technology Lausanne (EPFL), Switzerland

Objectives: To understand how mechanisms related to the functioning of mitochondria and energy metabolism in different brain regions, and particularly in the mesolimbic system, affect brain structure, function and behaviour.

Purpose: To understand the link between bioenergetics and brain and behaviour.

Methods: We phenotype animals for anxiety, sociability and social dominance, as well as for physiological metabolism (CLAMS) and evaluate fat content and composition in the periphery (EchoMRI). We investigate several features of mitochondrial function (respiration, membrane potential, ATP and ROS production) and structure (EM and confocal analyses). We manipulate mitochondrial function pharmacology (brain micro-infusions) and genetically (AAV-induced and genetically driven changes).

Results: Anxiety affects the functioning of the mesolimbic system by affecting mitochondrial function in the nucleus accumbens. This reverts in behavioral changes, particularly in coping behaviors (e.g., social hierarchy establishment and forced swim test). Early life stress induces a neurobehavioral and metabolic programming. We underscore a role for Sirtuin 1 in the mediation of early life stress effects.

Conclusions: We obtain strong evidence implicating a key role for variation in mitochondrial function, due to natural differences or to early life stress, on the programming of coping behaviors and on the neuronal architecture and function.

Literature Reference:
ROLE OF DIETARY LIPIDS IN THE MODULATION OF NEUROINFLAMMATORY PROCESSES AND ASSOCIATED BEHAVIOUR IMPAIRMENT
Sophie Layé
NutriNeuro, Bordeaux, France

Objectives:
The role of unbalanced diets in diabetes, cardiovascular disease and obesity is well established. In this work, we reveal an unprecedented role of a poor lipid nutrition in brain disorders. Unbalanced intake of essential n-3 polyunsaturated fatty acid (PUFAs) is a hallmark of westernized dietary habits, which occur in both developed and developing countries. We previously showed that low maternal intake of n-3 PUFA triggers their decrease in the offspring brain and behavioral deficit, but the cellular mechanisms governing the link between n-3 PUFA and brain development are still uncharacterized. Here, we show that the effect of dietary PUFA on brain PUFA accretion regulate neuroinflammatory processes, in particular microglia cell activity and behavior in mice.

Purpose:
The purpose of the work conducted in our team is to understand how dietary lipids influences neuroinflammatory processes and associated mood and cognitive disorders

Methods:
To do so, we use state-of-art lipidomics and transcriptomics analyses, super resolution imaging, electrophysiology and behavior in mice fed with a n-3 PUFA deficient or an isocaloric n-3 PUFA balanced diet

Results:
N-3 PUFA deficient diet consumption leads to a decrease in docosahexaenoic acid (DHA), the main brain n-3 PUFA and the impairment in spatial memory and emotional behaviour (anxiety-like and social behaviour). These modifications were accompanied by an altered neuroinflammatory process and hippocampal and prefrontal cortex dendritic length reduction. N-3 PUFA deficiency-induced microglia impairment leads to impaired neuronal network in the hippocampus and memory impairment at weaning.

Conclusions:
Our results here show that PUFA finely tuned microglia phagocytic activity which confers proper neuronal network functioning, which paves the way for considering these lipids in brain disorders. In this context, we believe that our findings are of a particular interest for the neuroscientist scientific community.

Literature References:
GUT MICROBIOTA: A KEY REGULATOR OF SOCIAL BEHAVIOURS
Daniela Felice, Timothy G Dinan and John F. Cryan
APC Microbiome Institute, University College Cork, Cork, Ireland

Objectives: Demonstrate an understanding of the growing emphasis on the relationship between the brain and the gastrointestinal tract, and more specifically the microbes within, in the modulation of behaviour including social behaviours.

Purpose: The presentation will discuss how the microbiota-gut-brain axis plays a key role in behaviour including social behaviour.

Methods: The effects of gut microbiota manipulation on behaviour and social behaviour have been investigated across several mouse models such as Germ Free mice and mouse models of autism spectrum disorders (BTBR and Maternal immune activation mouse models) and following treatment with prebiotics and probiotic treatment strategies. Neurochemical and immune mechanisms are investigated.

Results: Mice growing up without bacteria in their gut have altered neurodevelopmental trajectories including altered amygdala and hippocampal morphology, increased prefrontal myelination and deficits in social and anxiety behaviour. These effects are more pronounced in males compared with females. Germ free mice also have deficits in microglia activation and adult hippocampal neurogenesis that also may underlie some of their phenotypes. Mouse models of autism also have deficits in microbiota and associated behaviours. The mechanism of this altered communication are being unravelled and include vagal pathways, immune system and via microbial metabolites.

Conclusions: Together these data support the concept of appropriate microbiota composition for normal social behavior. Future studies must now confirm how much of this animal data translates into humans and perhaps lead to microbiome-based strategies for disorders of altered social behavior.

Literature Reference
ENVIRONMENT AND BRAIN PLASTICITY: LIVING CONDITIONS DRIVE THE EFFECTS OF ANTIDEPRESSANT DRUGS

Igor Branchi
Center for Behavioral Sciences and Mental Health, Istituto Superiore di Sanità, Rome, Italy

**Rationale:** Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed treatment for Major Depressive Disorder (MDD). However, their efficacy is variable and incomplete. One of the main reasons for such incomplete efficacy is the poor comprehension of their mechanism of action (Branchi, 2011).

**Purpose:** To test the interplay among SSRIs, neural plasticity and the living environment, demonstrating that drug administration increases susceptibility to the environment, leading to a reduction of symptoms in favourable conditions, while leading to a worse prognosis in stressful conditions.

**Methods:** We exploited the STAR*D dataset and selected a subpopulation of 591 patients treated with citalopram with similar MDD severity and overlapping treatment history. We therefore analyzed treatment efficacy according to the dose received, either 20 or 40 mg/d, in relation to sociodemographic characteristics. Logistic regression models and ANOVAs were used to analyse the data.

**Results:** Sociodemographic characteristics affected treatment response in the same direction in the two dose groups, but these effects reached statistical significance only in the 40 mg/d dose group. In the latter, higher improvement rate was associated with having a working employment status, longer education, high income or a private insurance, and higher remission rate was associated with having a working employment status or longer education. The variation in the depressive score was affected accordingly (Chiarotti et al., 2017).

**Conclusions:** Overall, our results indicate that citalopram amplifies the influence of the living conditions on mood in a dose-dependent fashion. These findings show that, according to the undirected susceptibility to change hypothesis, SSRIs do not affect mood per se but, by increasing brain plasticity, render the individual more susceptible to the influence of the living conditions. In addition, they provide a potential explanation for the variable efficacy of SSRIs and might lead to develop personalized strategies aimed at enhancing their efficacy.

**Literature Reference:**
Branchi I (2011) The double edged sword of neural plasticity: Increasing serotonin levels leads to both greater vulnerability to depression and improved capacity to recover. Psychoneuroendocrinology 36:339-351.
Symposium

SY04.
Thalamocortical bases of adaptive behaviors
THALAMOCORTICAL INTERACTIONS INVOLVING THE MEDIODORSAL THALAMUS SUPPORT RAPID LEARNING AND ADAPTIVE DECISION-MAKING

Anna S Mitchell
Department of Experimental Psychology, University of Oxford

Distributed neural networks across the brain govern cognitive processes and guide our behavioural outputs. Typically, cortical structures including the temporal lobes are investigated in these cognitive processes. Recent behavioural and cognitive neuroscience evidence from my laboratory demonstrates that communication between the cortex and mediodorsal thalamus supports the ability of primates to learn rapidly, make dynamic choices under changing circumstances and allow cognitive flexibility in responding. This behavioural evidence demonstrates that the mediodorsal thalamus, a higher-order thalamic neural structure actively contributes to rapid information processing, complementing the contribution of the frontal cortex itself. Analyses documenting the resting state functional neuroimaging of the primate brain after circumscribed damage to the mediodorsal thalamic will also be presented.
Oscillatory synchrony between the hippocampus and medial prefrontal cortex (mPFC) has been shown to increase in tasks with high spatial working memory demand. However, the mechanisms and circuitry supporting hippocampal-mPFC interactions during these tasks is unknown. The midline thalamic nucleus reuniens (RE) is reciprocally connected to both the hippocampus and the mPFC and has been shown to be critical for a variety of working memory tasks. Therefore, it is likely that hippocampal-mPFC oscillatory synchrony is modulated by RE activity. In this talk, I will review recent work from my lab that supports the hypothesis that the RE is a critical orchestrator of hippocampal-prefrontal synchrony during spatial working memory.
THALAMIC AND CORTICAL DETERMINANTS OF ADAPTIVE BEHAVIORS
Mathieu Wolff
Institut de Neurosciences Cognitives et Intégratives d’Aquitaine, CNRS UMR5287, Université de Bordeaux

In highly volatile environments, engaging in actions that effectively address current need and desires is an ongoing challenge for living organisms. Presumably, evolution has therefore favored the emergence of brain networks capable of promoting fast learning and adaptive decision-making in highly distributed circuits. Within these circuits, specific limbic thalamic nuclei play a critical role in these processes, challenging the view that the thalamus only acts as a relay station for the cortical stage. Data will be presented along two lines to support this latter claim. First we will reveal the neuroanatomical and functional properties of the thalamocortical architecture centered on the medial prefrontal cortex and the mediodorsal thalamus. In particular, chemogenetic inhibition of projections defined cortical or thalamic neurons suggest complementary but at least partially dissociable roles for thalamocortical and corticothalamic pathways when rats are required to perform adaptive actions. Second, we will reveal a new role for a little known thalamic region, the submedius thalamic nucleus, when rats are engaged in behaviors guided by predictive cues. At this occasion, we will show that the functional importance of this thalamic region is comparable to that of the orbitofrontal cortex, suggesting the existence of a functional circuit based on the strong reciprocal projections between these two regions. Altogether, the data to be presented contribute to shape a general and consistent role for limbic thalamic nuclei in adaptive processes supported by specific thalamocortical loops.
SYNAPTIC INTERACTIONS IN THE THALAMOCORTICAL SYSTEM DURING SENSORY PROCESSING
Alexander Groh
TU München

The cerebral cortex is arguably the ‘cognitive’ headquarter of the brain thought to accommodate distinct cortical circuits for decision making, conscious perception and other cognitive functions. But how does the cortex communicate with the rest of the brain to fulfill these functions? Unlike the cortex, subcortical structures like the thalamus are located deep in the brain and are thus inaccessible with cellular imaging techniques, rendering the study of cortico-subcortical interactions a major challenge in neuroscience. I will first present anatomical data showing a comprehensive subcortical target map of cortical output pathways from the mouse barrel cortex. We will then focus on the long range interactions between the cortex and the thalamus studied with deep brain electrophysiology techniques in combination with optogenetics in the rodent somatosensory system. A substantial fraction of the synaptic input to the thalamus comes from the cortex. By measuring synaptic signals directly using patch clamp we found that some areas in the thalamus – the higher order thalamus – are dominated by cortical activity through sparse yet strong excitatory synaptic inputs. In contrast, we also found transiently inhibitory and weak sustained excitatory synaptic interactions between the cortex and the thalamus which impose an adaptive sensory filter onto touch signals sampled by the mouse’ whiskers. These examples demonstrate that sensory processing is dynamically controlled by long range synaptic interactions between the cortex and subcortical structures and provide a mechanistic basis to address more complex behavior related interactions between the cortex and the rest of the brain.
Symposium

SY05.
Social decision making in animals
NEURAL CORRELATES OF HELPING BEHAVIOUR IN RATS
Inbal Ben-Ami Bartal, Dacher Keltner, Daniela Kaufer
University of California, Berkeley, U.S.A

Objectives: The participants will be familiarized with a novel animal paradigm for helping behaviour, and learn about methods used to do whole-brain imaging in rats.

Purpose: to describe the neural mechanisms that underlay the decision to help a conspecific in rats.

Methods: rats were exposed to a behavioural paradigm testing for pro-social motivation. The social context for the test was modulated between conditions to dissociate empathic motivation. Following testing, brains were imaged with immunohistochemistry for c-fos early gene expression, an index for neuronal activation. Using microscopy, activation levels were quantified. Oxytocin receptor numbers were similarly assessed.

Results: rats are motivated to help conspecifics by releasing them from a restrainer. Rats learn this behaviour in the lack of any external motivation other than the liberation of the trapped rat. Rats are selective in their pro-social motivation, helping only rats of their own group. Rats do not help rats of an unfamiliar strain unless they have social experience with the other strain. Pharmacological interruption of distress in the observer with a benzodiazepine interferes with helping.

Conclusions: Rats experience pro-social motivation towards same-sex conspecifics. This behaviour is goal-directed and socially selective. Rats are motivated to help by the distress of the trapped rat. A specific neural network is activated in rats who participate in the helping behaviour test. The possible biological mechanisms will be discussed.

Literature Reference
MESOTOCIN AS A HORMONAL MECHANISM OF SOCIAL BONDING IN PINYON JAYS
Juan F. Duque, Anna Rodriguez, Jeffrey R. Stevens
University of Nebraska-Lincoln, Lincoln, Nebraska, USA

Objectives: The audience will be introduced to an avian model for social bonding and the function of mesocotin, the avian homologue of human oxytocin. The short- and long term effects of the hormone will be discussed.

Purpose: Though the effect of the neuropeptide oxytocin on mammalian social bonding is becoming clear, we do not know whether the function of the avian homologue mesotocin is evolutionarily conserved across birds. This project aimed to investigate how mesotocin regulates social bonding in pinyon jays, a member of the crow family.

Methods: We formed three groups of four individually housed birds, with two groups being all males and one group being all females. In the first, ‘dyadic bonding’ phase of the experiment, we placed dyads of birds from within the groups together in a cage for 45 minutes. Prior to entering the cage, we intranasally administered one of three hormone solutions to both members of the dyad: mesotocin, oxytocin antagonist, or saline. Dyads received 10 sessions with administration of the same hormone. In the first five sessions, no food was present, whereas in the second five sessions, food was introduced to the cage 30 minutes into the session. In the second, ‘social network’ phase of the experiment, all four members of the group were placed together in a large cage for 30 minutes. No hormones were administered during this phase. For both phases, we measured the physical distance between birds as our proxy for social bonding.

Results: In the dyadic bonding phase with no food present, dyads receiving mesotocin exhibited closer distances than dyads with oxytocin antagonist or saline. Oxytocin antagonist and saline dyads did not differ in distance. In the dyadic bonding phase with food present, dyads receiving mesotocin had closer distances than dyads with oxytocin antagonist but not those with saline. Oxytocin antagonist and saline dyads did not differ in distance. Males tended to have closer distances than females across hormonal treatments. In the social network phase, there were no differences in distance across the three hormone treatments or between the sexes, but distances increased across sessions.

Conclusions: Our results suggest that mesotocin administration increases social bonding in pinyon jays as measured by physical distance between dyad members. These effects, however, are short lasting and do not carry over to larger group contexts when mesotocin is no longer administered. Therefore, mesotocin produces short-term dyadic bonds but not strong, long-term bonds. These findings indicate that some aspects of the social bonding function of oxytocin-like neuropeptides are evolutionarily conserved across birds and mammals.
WHEN TO COOPERATE? THE INFLUENCE OF FOOD TOLERANCE LEVELS ON THE DECISION TO COOPERATE WITH A PARTNER
Rachel Dale, Sarah Marshall-Pescini, Friederike Range
Wolf Science Center, Messerli Research Institute, University of Veterinary Medicine Vienna, Medical University of Vienna, University of Vienna

Objectives: The audience will be introduced to a canine model for cooperation and its relation to tolerance in food access tests.
Purpose: Cooperation is an important aspect of group living for many species. However, little is currently known about the factors that influence whether or not animals will cooperate with specific partners. This project aimed to assess how food tolerance may influence an animal’s, specifically wolves and dogs, decision about whether to cooperate with a partner.
Methods: Animals at the Wolf Science Center, Austria were tested for their cooperative tendencies in dyads using the loose string paradigm, whereby both partners needed to pull a rope in order to gain access to a food reward. Various dyadic combinations within the pack members were tested. These results were then related to food sharing tendencies with the same partners in simple food sharing tests. In these tests both animals were released onto a food source at the same time and behaviours such as sharing and aggression were measured.
Results: Although typically wolves showed overall greater food tolerance and less despotic interactions around food than dogs, the social relationship (rank and friendship) with a partner influenced the level of tolerance in both species. In a cooperation task, wolves showed more success than dogs both spontaneously and, for those which failed the spontaneous test, after individual training. The dogs rarely succeeded to coordinate their string pulling actions at all. In the successful wolves, this cooperation was also affected by the social relationship. The links between cooperation and tolerance will be presented.
Conclusions: The results so far suggest that wolves are more tolerant around food and better able to coordinate actions with a conspecific partner than similarly raised dogs. Tolerance levels are further mediated by the social relationship with the partner and these tolerance levels seem to further influence their success in cooperative interactions.
THE NEURAL BASIS OF SOCIAL CHOICE IN RATS
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Objectives: The participants will be familiarized with paradigms for social choice in rats, and the influence of ultrasonic vocalizations on social decision making. The neural networks involved in social decision making in rats will be discussed.

Purpose: to describe the neural mechanisms governing social decision making and the processing of ultrasonic vocalisations in rats.

Methods: rats were exposed to the rodent pro-social choice task (Hernandez-Lallement et al., 2015) to index pro-social preferences. Pro-social choice could rely on feedback by the partner through ultrasonic vocalisations. In a variant of the task, rats were able to choose between recordings of different types of ultrasonic vocalisations, associated with appetitive or aversive situations, respectively. Neural activity from the ventral tegmental area was recorded while animals chose to approach these stimuli.

Results: rats exhibit pro-social preferences in the aggregate, while showing substantial inter-individual differences. Similarly, animals choose to be exposed to certain types of appetitive ultrasonic vocalisations. Neural activity recorded in single cells in the ventral tegmental area discriminated between vocalisation types for a subset of recorded cells

Conclusions: Rats exhibit pro-social preferences towards conspecifics. These preferences could rely on the processing of ultrasonic feedback from the partner. Hearing appetitive vocalisations indeed activated neurons in the VTA, linking ultrasonic vocalisations to social motivation.

Literature Reference
Symposium

SY06.
What do major neuromodulatory systems do for behavior? Insight from comparative approaches
NEUROCHEMICAL INFLUENCES OVER WAITING, ACTING AND CHOOSING
Mark E Walton
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Objectives: We are interested in understanding how fast fluctuations in dopamine transmission influence different facets of a decision, from choosing whether to act, what to do, how fast to do it, and whether to repeat the choice.

Purpose: This work seeks to uncover the role of dopamine in action initiation and action selection, and to compare this with the influence of serotonin transmission.

Methods: We use fast-scan cyclic voltammetry to measure sub-second dopamine release in behaving rodents and pharmacological agents to manipulate different aspects of neurotransmission.

Results: Dopamine release in the nucleus accumbens scales with predicted future reward. However, these signals do not straightforwardly map onto animals’ current preferences and are strongly influenced by whether or not a new action is initiated. Stimulation of D1 receptors, which are acted upon by phasic dopamine transients, not only causes a rapid, reward-dependent reduction in the ability to withhold responses, but also impairs choice accuracy, with animals selecting their preferred actions even if they were inappropriate to the context. A similar increase in impulsive actions is also observed following serotonin manipulations. However, unlike the dopamine stimulation, these serotonin effects are characterised by a gradual increase in the likelihood of moving as time elapsed, and were accompanied by improvements in choice accuracy.

Conclusions:
This implies that phasic dopamine release, acting through D1-type receptors, may play little role in decisions about what to choose. Instead, its role in decision making may be to preferentially bias animals to initiate actions towards “default” options at the expense of alternatives in the environment. By contrast, serotonin neurotransmission can shape instrumental drive and response precision.
NORADRENALINE AND DOPAMINE IN THE EFFORT-REWARD TRADE-OFF
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Objectives: Catecholaminergic neuromodulation is critical for numerous aspects of behaviour. Both dopamine and noradrenaline are directly involved in various functions including attention, motivation, decision-making, learning and memory. But as we extend the range of cognitive functions in which they are involved, the boundaries between the specific contribution of dopamine and noradrenaline become increasingly tenuous.

Purpose: We aim at clarifying the functional complementarity between noradrenaline and dopamine using neurophysiology and pharmacology in monkeys performing tasks that manipulate the ratio between costs and benefits.

Methods: We first compared single-unit activity from substantia nigra pars compacta dopaminergic neurons and from locus coeruleus noradrenergic neurons, in monkeys performing an effort/reward task. In another experiment, we examined the influence of clonidine (2.5-7.5 ug/kg, an alpha2 noradrenergic agonist that decreases NA release) on motivation and decision making.

Results: Even though they share numerous features, the activity of dopaminergic and noradrenergic neurons differs markedly. On the one hand, the firing of dopaminergic neurons is more closely associated with the incentive influence of rewards on behaviour. On the other hand, the firing of noradrenergic neurons is closely related to the arousing property of the cue and the amount of force produced to obtain the reward. Using pharmacology, we confirm the specific causal role of noradrenaline on force production and choice variability, clarifying the role of the noradrenergic system in decision-making.

Conclusions: Altogether, this work is compatible with the idea that even though noradrenaline and dopamine share several features and both contribute to motivation, the nature of their contribution differs. Whereas dopamine mediates the incentive influence of potential rewards on behaviour, noradrenaline seems to mediate the mobilization of effort to face difficulties.
ACTIVATION OF DORSAL RAPHE SEROTONERGIC NEURONS DELAYS LEAVING IN A PROBABILISTIC FORAGING TASK

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Objectives: The central neuromodulator serotonin (5-HT) has been implicated in impulse control, yet the mechanisms by which it affects behavior remain mostly unresolved.

Purpose: To address this issue we contrast two competing hypotheses: (1) that 5-HT mediated promotion of patient behavior reflects a direct motor suppression; and (2) that the increased patience results from a modulation of decision-making processes in ways that delay the implementation of active responses.

Methods: To distinguish between these alternatives we developed a probabilistic foraging task for mice. In the task, mice experienced uncertainty about when to leave, but unlike many waiting tasks, they were required to actively nose poke to check reward status, thus "waiting" was active rather than passive. We also used optogenetics to directly excite dorsal raphe nucleus (DRN) 5-HT releasing neurons at different time points within the task and measured the effects of this manipulation on mouse behavior.

Results: We found that optogenetic activation of DRN 5-HT neurons during foraging-like behavior promotes further exploitation of the same location, at the expanse of reduced frequency of switching locations. In contrast, the microstructure of behavior was relatively unaffected by the stimulation. Additionally, photostimulation during movement between reward sites had no effect on this behavior.

Conclusions: Our results are consistent with a model in which 5-HT affects the decision-making processes leading up to (potentially impulsive) actions, rather than on lower level motor functions. Thus 5-HT does not inhibit behavior, but biases decision-making to exploitation over exploration. These findings extend and clarify previous research on the role of serotonin in behavioral inhibition with potential clinical implications.
ACCUMBENS ACETYLCHOLINE-DOPAMINE INTERACTIONS REGULATE CUE-MOTIVATED BEHAVIOR
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Objectives: To present evidence that that nucleus accumbens core (NAc) acetylcholine signaling gates the expression of cue-motivated behavior via terminal modulation of cue-evoked phasic dopamine signaling.

Purpose: To expose the interacting functions of the NAc dopamine and acetylcholine neuromodulatory systems in cue-motivated behaviour.

Methods: To assess cue-motivated behaviour, we use a Pavlovian-to-instrumetal transfer task designed to assess the motivating influence of a reward-predictive cue over an independently-trained instrumental action. We couple this behavioural task with voltammetry for neurochemical monitoring and pharmacological, chemogenetic, and optogenetic manipulations of NAc dopaminergic and cholinergic signalling.

Results: Our data demonstrate that NAc cue-evoked dopamine release correlates with and mediates cue-motivated behaviour and that such signalling is sensitive to need state, one critical variable that determines the current adaptive utility of cue-motivated behaviour. We have also found that NAc cholinergic interneuron activity functions to suppress cue-motivated behaviour, via action at nicotinic acetylcholine receptors, which we demonstrate regulate cue-evoked dopamine release.

Conclusions: Combined, the data suggest that NAc acetylcholine signaling gates the expression of cue-motivated behavior via terminal modulation of cue-evoked phasic dopamine signaling, perhaps providing a mechanism through which the motivating influence of cues is regulated according to their current adaptive value. This motivational influence can become excessive and/or disproportionate with need, and this is thought to contribute to overeating and maladaptive drug seeking. These results therefore have implications for the understanding and treatment of compulsive overeating, addiction, and other disorders marked by maladaptive motivation.

Literature Reference
Symposium

SY07.
Mechanisms of Remote Memories: Insight from human and animal studies
THE MEDIAL PREFRONTAL CONTRIBUTION TO LONG-TERM MEMORY
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Objectives: What enables us to acquire and use our knowledge? The classical declarative memory system with the hippocampus at its core appears not sufficient to explain knowledge acquisition and retrieval satisfactorily. Recent evidence suggests an extension of this classical model by assigning the medial prefrontal cortex a particular, yet not fully defined role in long-term memory. Here I will integrate recent evidence providing the basis for an extended declarative memory system that includes the medial prefrontal cortex.

Purpose: Review of recent evidence for a central role of medial prefrontal cortex in human memory.

Methods: We probed in a series of functional neuroimaging studies the role of the medial prefrontal cortex in memory encoding, consolidation and retrieval.

Results: Initial experiments provided evidence for an extension of the classical systems-level consolidation model by adding the medial prefrontal cortex. This brain area appears to be specifically involved in remote memory retrieval and it may have taken over a hippocampal binding function integrating representations in posterior brain regions. Such a model with two memory systems with distinct time constants, a fast hippocampally-centered and a slow neocortically-centered memory system, has been fine-tuned based on studies manipulating the relationship between new memories and already pre-existing knowledge. Retrieval of information congruent with pre-existing knowledge, as opposed to incongruent information leads to stronger medial prefrontal activity and connectivity with posterior representational areas. While congruent memory retrieval appears associated with medial prefrontal computations, formation of such memories appears also processed preferably in this brain region. However, the representation of underlying knowledge might not be stored in the medial prefrontal cortex, but in connected posterior brain areas like the angular gyrus that combine underlying perceptual features with a mental structure of those features into one conceptual representation.

Conclusions: I propose that the evidence linking the medial prefrontal cortex to memory warrants an extension of the declarative memory system. There is a medial prefrontal – hippocampal interaction, critical for memory formation, consolidation and retrieval. Medial prefrontal involvement appears enabled by or most needed for when there is overlap between new information to be encoded or consolidated with already existing knowledge, enabling integration in existing mental schemas and generalization across specific episodes. The memory dependent on the medial prefrontal cortex appears associative in nature, but rather less episodic or vivid. Thus, it does not fall easily on one side of the semantic-episodic divide. In sum, the medial prefrontal cortex, interacting with the medial temporal lobe, posterior representational areas and specific subcortical structures, may help obtain, integrate and apply our knowledge for long-term usage.
GLOBAL CHANGES IN ACTIVITY AND INTERACTIVITY OF BRAIN REGIONS SUPPORTING CONTEXTUAL FEAR MEMORY OVER TIME IN MICE
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Objectives: 1) Differentiate global patterns of brain region activity and interactivity in the mouse during fear memory recall and depict how they change over time 2) Describe how graph theory metrics of centrality can be used to identify hubs in remote memory networks with unbiased predictive value.

Purpose: To use global mapping approaches to identify networks of brain regions that are activated and co-activated following recall of recent and remote contextual fear memory in mice.

Methods: Mice were conditioned to associate a series of mild footshocks with a context and then tested either 1 or 36 days later. Following testing Fos expression was quantified across 84 brain regions using immunohistochemistry. Global activity and interactivity of brain regions associated with memory expression were assessed using partial least squares (PLS) and interactivity networks were assessed with graph theoretical methods.

Results: Activity analysis revealed that remote memory engages a broad collection of cortical and subcortical regions in comparison to recent memory expression. Interactivity analyses revealed that functional connectivity associated with fear memories depends on memory age and that remote long-term fear memory engages a network that has a distinct thalamic-hippocampal-cortical signature. Graph theory centrality metrics identify hub regions most likely to play critical roles in memory expression.

Conclusions: These results identify and describe functional activity and interactivity of brain regions underlying recent and remote fear memory expression and provide strong evidence for reorganization and distribution of the functional organization of memories over time. Ablation studies have subsequently demonstrated that centrality measures have predictive value for identifying regions that play a critical role in functional memory networks. Brain wide mapping of regional interactivity in the mouse may be a powerful approach for assessing brain networks engaged during behaviour.
DIFFERENT NEURAL MECHANISMS ENCODE REMOTE APPETITIVE AND FEARFUL MEMORIES IN THE AUDITORY CORTEX

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Objectives: Strong emotional memories are quickly learned and lifelong remembered; at the conclusion of this presentation, the participants should be able to value the crucial importance of higher order sensory areas in the storage and retrieval of remote emotional memories.

Purpose: Here, our aim is to reveal the neural mechanisms underlying the secondary auditory cortex, Te2, activity in response to the recall of positive or negative well-stored memories.

Methods: For this purpose, we used cellular compartment analysis of temporal activity by fluorescent in situ hybridization, catFISH, and immunohistochemical analysis of immediate early genes expression in Te2 in rats retrieving remote fear and appetitive memories. In order to detect functional activity and connectivity of Te2 we made use of electrophysiological techniques – local field potential and multi-unit activity recording – during the recall of emotional memories.

Results: We have observed that, in rats, Te2 supports the storage and retrieval of memories that have acquired a behavioral negative or positive valence with the experience. Appetitive and aversive memories activate different sub-regions in the auditory secondary sensory cortex, Te2, suggesting different neural circuits in the processing of positive and negative auditory stimuli. Moreover, within the Te2 there is a fraction of neurons responding exclusively to aversive or incentive associated stimuli, signaling its valence rather than its salience. Indeed, the blockade of only one of these neural populations produces specific amnesia, while leaving the other emotional memory intact. Furthermore, during the recall of remote, but not recent, auditory threatening memories, the activity of the Te2 drives BLA within the theta frequency range and predicts the animals' ability to recognize aversive auditory stimuli.

Conclusions: Our findings support the idea that memory information is processed in a distributed network in which higher order sensory areas play a crucial role for both the retention and the assignment of the affective value. This new knowledge could have a great impact for ameliorating the clinical approaches of emotional disorders.

ASTROCYTES IN THE TRANSITION FROM RECENT TO REMOTE MEMORY

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Memory stands at the basis of cognitive function, and thus attracts major interest in the neuroscience community. Memory disruption is relatively easy to induce, but memory enhancement is a more complicated task that had challenged scientists for many years. We chose to target astrocytic activity as a way to generate synaptic potentiation and enhance memory performance.

Whereas the supportive roles of astrocytes, such as glucose metabolism maintenance, glutamate levels monitoring and neurotrophic factors secretion are well recognized, their direct effects on neuronal activity remain elusive. Pioneering studies had shown that astrocytes directly affect neuronal activity as part of a "tripartite synapse", in which the astrocytes do not merely encapsulate and insulate synapses, but actively modify their activity. In order to directly and specifically modulate astrocytic activity and explore their effect on neuronal activity and memory performance, we have employed a chemogenetic approach: We expressed the Gq-coupled designer receptor hM3Dq in astrocytes, which allowed their time-restricted activation by the application of the designer drug clozapine-N-oxide (CNO). We found that astrocytic activation dramatically modulates neuronal activity and improves memory:

Astrocytic Gq activation resulted in increased frequency of presynaptic miniature events, accompanied by elevated post-synaptic current amplitude. Furthermore, we found that astrocytes are sufficient to induce potentiation of evoked EPSCs to a Schaffer collaterals electrical stimulus when no potentiation protocol is administered to the neurons. These effects were accompanied by a remarkable functional consequence: Astrocytic activation during FC training resulted in improved contextual memory tested one day later, when CNO is no longer present, specifically in the hippocampal-dependent contextual memory task, but not in auditory-cued memory. Remote recall tested 28 days later was not enhanced, but astrocytic Gq activation during recall if at the remote time period had improved recall.
Symposium

SY08.

Role of the Locus Coeruleus in cellular and systems consolidation
NEUROMODULATORS, and in particular, noradrenaline (NA), play a role in many cognitive processes and are important players in all stages of memory from encoding to consolidation and retrieval. The literature is extensive and convincing. Nevertheless, to fully understand how the tiny pontine nucleus Locus Coeruleus (LC), the sole source of NA to the forebrain, influences such a wide range of memory processes, we need to know at what precise point these cells are engaged during and after behavioral experiences. Only when the cognitive (behavioral) contexts driving LC activity are established can gain or loss of function experiments with a temporally valid protocol be envisaged. Recording the activity from neurons of this nucleus in behaving rats can be challenging because of its very small size and its location deep in the brain stem.

Over the past decades we have been recording from LC during a wide variety of behavioral tasks and during rest and sleep periods following active behavior. LC neurons fire to novelty with rapid habituation, and to any change in the predictive value of a stimulus (stimulus-reinforcement contingency), requiring behavioural adjustment to changes in response-reinforcement contingency. These results reinforce the notion that LC/NA system is involved in executive function, maintaining adaptive behavior during ongoing changes in environmental contingencies. Off-line, LC re-engages during sleep and rest periods after learning and is temporally related to ongoing brain oscillations. Its impact on memory consolidation thus occurs at all stages of the memory process beginning with the encoding phase, through consolidation, retrieval and reconsolidation. Current experiments are aimed at driving LC neurons optogenetically during a set-shifting task in which LC has demonstrated task-related activity.
NORADRENERGIC CONTROL OF HIPPOCAMPAL FUNCTION: THE β-ADRENERGIC RECEPTOR AS A DETERMINANT OF THE CONTENT AND PERSISTENCY OF SYNAPTIC INFORMATION STORAGE AND MEMORY

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Objectives: Noradrenaline, a key neurotransmitter in the brain released from the locus coeruleus after novelty or arousal, modulates hippocampal synaptic plasticity.

Purpose: The aim of the project is to depict how the locus coeruleus activation via β-adrenoreceptors influences the persistency and content of synaptic long-term plasticity and memory.

Methods: The locus coeruleus was electrically stimulated with 100 Hz and field excitatory postsynaptic potentials and population spike amplitudes were conducted after test pulse stimulation in the dentate gyrus and CA1 region to measure synaptic plasticity in freely-moving rats.

Results: Noradrenaline is released in hippocampal subfields such as the CA1 and dentate gyrus after the locus coeruleus is activated (Lemon et al., 2009). Activation of the locus coeruleus facilitates long-term depression (LTD) in the dentate gyrus and the CA1 region (Lemon et al., 2009). Furthermore, novel spatial memory is promoted by LC activation, and depends on the activation of β-adrenoreceptors (Lemon et al., 2009). Thus, noradrenaline determines whether new spatial experiences result in persistent synaptic long-term plasticity. Synaptic long-term plasticity as exhibited in long-term potentiation (LTP) and LTD as major mechanisms of memory storage is modulated by the activation of β-adrenoreceptors in rodents. LTP and LTD are differently modulated in hippocampal subfields by activating β-adrenoreceptors in rodents (Hagena et al., 2016; Lemon et al., 2009), implying that these subregions play unique roles in processing information within the hippocampus and in consecutive memory storage.

Conclusions: Noradrenaline release in the hippocampal subfields modulates the persistency and content of synaptic long-term plasticity for further memory storage via the β-adrenoreceptor. This seems to indicate that noradrenaline plays a pivotal role in controlling hippocampus-based memory.

Literature Reference:
DISTINCT NORADRENALINE CELL POPULATIONS COORDINATE EMOTIONAL AND FLEXIBLE LEARNING STATES

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Aversive experiences produce powerful emotional memories which trigger stereotyped defensive responses. However, these emotional responses need to be extinguished when they are no longer appropriate to enable normal, flexible behavior. Noradrenaline is important for both fear and extinction learning and an important drug target for the treatment of anxiety and mood disorders. Traditional views of noradrenaline function suggest that it modulates global brain states and diverse behaviors through what is believed to be a homogeneous cell population in the brainstem locus coeruleus (LC). However, it is unclear how the LC coordinates disparate behavioral functions. In direct contrast to traditional models of LC function, we’ve found that distinct populations of LC-noradrenaline neurons projecting to the amygdala or medial prefrontal cortex (mPFC) differentially regulate fear or extinction learning, respectively. Brain-wide efferent mapping of these cell populations revealed unique and specific connectivity with amygdala and mPFC targets. Coupled with this functional and anatomical modularity, LC neurons multiplex distinct signals during fear and extinction learning. In response to strong aversive stimuli occurring during fear learning most LC neurons are strongly activated. By contrast, distinct populations of LC neurons are selectively and mildly engaged in response to fear or safety cues. This is reflected as a shift in the balance of activity across amygdala and mPFC projecting cell modules during early and late extinction. These results suggest a revised view of LC-noradrenaline function in which a mosaic of projection- and behavior-specific modules is coupled with combinatorial activation modes to enable the adaptive tuning of emotional responding and behavioral flexibility.
LOCUS COERULEUS CONTROLS HIPPOCAMPAL MEMORY CONSOLIDATION THROUGH NON-CANONICAL RELEASE OF DOPAMINE

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Dopamine receptor-dependent memory stabilization mechanisms are activated in the hippocampus during novel experiences, acting as a gating mechanism that promotes the retention of episodic memories. It has long been assumed that this novelty signal originates from dopamine neurons in the ventral tegmental area (VTA) (Lisman and Grace, 2005), but recent evidence implicates the locus coeruleus (LC) as another potential source of hippocampal dopamine (Smith and Greene, 2012).

We have developed a realistic model of everyday memory for mice and confirmed that unrelated novel experiences can facilitate the persistence of spatial memory in a hippocampal dopamine D1/D5 receptor dependent manner. We then characterised the relative contributions of LC and VTA neurons to this novelty-associated enhancement of memory persistence, using tyrosine hydroxylase (TH)-Cre mice to selectively target catecholamine neurons. We found that (1) TH-expressing (TH+) neurons in LC are more strongly activated by novelty than VTA-TH+ neurons, (2) hippocampal LC-TH+ projections are much denser than VTA-TH+ projections, (3) optogenetic activation of LC-TH+ neurons mimics the effect of novelty on memory persistence and (4) ex vivo optogenetic activation of hippocampal-projecting LC-TH+ axons enhances hippocampal long-term potentiation at CA3-CA1 synapses. Surprisingly, the effects of optogenetic LC-TH+ activation on memory and hippocampal plasticity were blocked by D1/D5 receptor antagonists but not by β-adrenoceptor antagonists.

Thus, our results indicate that cellular memory consolidation in the hippocampus is mediated by LC and could be associated with non-canonical release of dopamine from hippocampal-projecting LC axons (Smith and Greene, 2012; Takeuchi et al, 2016; Kempadoo et al, 2016).

Symposium

SY09.

Neural mechanisms of reinforcement-guided behavior under uncertainty: a cross-species perspective
SPECIALIZED REPRESENTATIONS OF VALUE IN ORBITAL AND VENTROLATERAL PREFRONTAL CORTEX: DESIRABILITY VERSUS CERTAINTY OF OUTCOMES
Peter H. Rudebeck
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Objectives: To determine the distinct roles of the orbitofrontal (OFC) and ventrolateral prefrontal cortex (VLPFC) in choices guided by desirability or certainty.

Purpose: Although the economic basis of choices based on desirability and certainty are reasonably well understood at the behavioral level, less is known about the brain areas necessary for processing these two aspects of valuation.

Methods: Here we trained macaques with bilateral excitotoxic lesions of OFC, VLPFC, and unoperated controls on two tasks; the first assessed how monkeys used information about outcome availability to guide choices, whereas the second assessed how monkeys used information about outcome desirability to guide choices.

Results: We found that VLPFC, but not OFC, was critical for choices based on the certainty of receiving an outcome. By contrast, OFC, but not VLPFC, was critical for choices based on outcome desirability. The deficit following VLPFC lesions affected both contingent and noncontingent learning about the certainty of receiving an outcome, but only under conditions of dynamic, stochastic stimulus–outcome associations. When the association between stimuli and outcomes was static or deterministic, or when there was one clearly good option, monkeys with VLPFC lesions were able to learn at the same rate as unoperated control and monkeys with OFC lesions.

Conclusions: Our data indicate that separate parts of ventral prefrontal cortex in primates represent the desirability and certainty of receiving different potential outcomes, both of which are critical for deciding advantageously.
Basolateral amygdala (BLA) and orbitofrontal cortex (OFC) participate in outcome valuation but their specific roles in this process are frequently difficult to dissociate. The neural mechanisms of outcome uncertainty monitoring, in particular, have been predominantly investigated using primate behavioral paradigms. To systematically study the causal neural mechanisms of value updating in uncertain reinforcement conditions, we developed a novel task in rodents in which outcome values are determined by normally-distributed delays to reward receipt. To probe sensitivity to different types of uncertainty, we presented rats with two options identical in average rate of reward (1 sucrose pellet/10s), different only in the variance, e.g., *uncertainty*, of wait times for the outcome (High Variability, HV, $\sigma_{HV}=4s$ versus Low Variability, LV, $\sigma_{LV}=1s$). Following the establishment of stable choices, rats experienced upshifts (reduced wait times) and downshifts (longer wait times) on each option independently, followed by a return to baseline. Response selection using this paradigm can be affected by different sources of uncertainty ranging from dramatic shifts in value distributions (i.e., *volatility*) to random fluctuations within a value distribution (i.e., *risk*).

Using a combination of molecular, lesion, pharmacologic, and computational approaches we found evidence that rats, like primates, can distinguish volatility and risk. We also demonstrate that BLA is required for facilitation of learning in response to volatility, whereas medial OFC is necessary for the representation of risk to stabilize expected value and maintain stable choice preferences. These results challenge the canonical role for OFC in inhibitory control over action, and add to growing evidence for a role of medial OFC in economic choices in rats. These results also support a special role for BLA in early learning, when reinforcement conditions are most uncertain. Current experiments are aimed at determining the microcircuit mechanisms and direction of the complementary contributions of BLA and OFC.
TOP DOWN CONTROL OF UNCERTAINTY IN NEURAL MODELS
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Objectives: Most studies of learning in experimental environments focus on how internal models are updated due to externally imposed surprising events. However, arguably the level of flexibility of neural models should also be controlled internally – for example learning rate could be enhanced during active exploration. What is the neural basis of this top-down control?

Purpose: We investigated how internal models of the environment are modified by top-down signals from the anterior cingulate cortex during exploration.

Methods: We used functional MRI in human subjects. To decode the neural model of the experimental environment on a trial-by-trial basis we identified characteristic patterns of activity associated with different possible actions, and modelled multivariate activity on each trial as a mixture of these characteristic patterns. We then identified how and when bulk activity in anterior cingulate cortex predicted changes in these neural models – specifically increases in model entropy (uncertainty).

Results: Anterior cingulate activity predicts increased entropy in neural models at the initiation of exploration. This effect is over and above what would be expected simply due to a response switch.

Conclusions: Anterior cingulate cortex plays a top-down role in initiating new learning by injecting entropy into internal models of the environment stored elsewhere in cortex.
PROCESSING OF REWARD VARIANCE RISK BY AMYGDALA NEURONS IN DECISION-MAKING

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Objectives: To understand the role of primate amygdala neurons in the computation of reward risk for economic decision-making.

Purpose: We tested whether amygdala neurons extract information about two principal reward parameters—probability and magnitude—from sequential visual cues, and integrate this information into economic decision parameters, including expected value and risk.

Methods: We recorded the activity of 483 amygdala neurons while two monkeys viewed sequential stimuli that signaled separately the probability and magnitude of upcoming liquid rewards. Sequential, non-overlapping cue presentation separated the influence of probability and magnitude information on neuronal responses and allowed us to test their flexible integration over the timecourse of single trials.

Results: Behavioral data confirmed accurate reward expectation based on probability and magnitude cues and choice sensitivity to expected value and risk. During sequential presentation of probability and magnitude cues, individual neurons often processed both probability and magnitude dynamically over time, consistent with potential integration of these reward parameters. As soon as probability and magnitude cues had been shown, a substantial number of neurons encoded either expected value or risk of the upcoming reward outcome. Crucially, these parameters were not explicitly cued but required internal computation from cued probability and magnitude. Some neurons reflected this computation through dynamic coding transitions that linked initial probability and magnitude signals with subsequent expected value or risk signals.

Conclusions: These data suggest that amygdala neurons dynamically integrate basic reward parameters into decision variables, including risk. Our findings support the emerging view that primate amygdala neurons participate in economic decision-making.

Literature Reference
Symposium

SY10.
Addiction: tightening the link between animal and human models
OBJECTIVES: Habitual behaviour is thought to rely on stimulus-response learning, however, there is little data to address how stimulus influences may change across extended training as habit strength is thought to increase.

PURPOSE: The aim of this project was to examine any changes in the magnitude of stimulus influences on instrumental responding across extended alcohol self-administration.

METHODS: Rats self-administered alcohol or sucrose for 2 or 8 weeks, training regimens shown elsewhere to produce goal-directed and habitual control of responding, respectively. Rats then received Pavlovian training where discrete stimuli signalled alcohol delivery in the absence of the instrumental response. Finally, the impact of the Pavlovian stimuli on responding was assessed in a Pavlovian instrumental transfer (PIT) test where the instrumental response was available throughout and the stimuli were periodically presented.

RESULTS: PIT was observed following both 2 and 8 weeks of self-administration but the magnitude of the PIT effect was greater following 8 weeks of training. Similar results were observed for rats trained to administer sucrose or alcohol. The specificity of the PIT effect appeared unchanged by the amount of training.

CONCLUSIONS: These data indicate that stimulus influences on responding increase with extended training. This finding provides insight into the factors that control responding after extended training and/or drug exposure, with stimuli playing an increasingly important role in initiating and maintaining reward-seeking behaviour. Understanding and targeting drug-predictive stimuli will be important for developing effective methods for controlling and reducing drug-seeking following long-term drug use.
PAVLOVIAN-INSTRUMENTAL TRANSFER IN ALCOHOL-DEPENDENT PATIENTS
Garbusow M1, Sommer C2, Nebe S2, Sebold M1,3, Kuitunen-Paul S2, Wittchen H-U2, Smolka MN2, Rapp MA3, Huys QJM4, Schlagenhauf S1,5, Heinz A1
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Objectives: At the conclusion of this presentation, the participants should be able to recognize Pavlovian-instrumental transfer (PIT) as one mechanism relevant for the development and maintenance of alcohol dependence and the involved brain areas for relapse prediction.

Purpose: Contextual cues have impact on the motivation to conduct a behaviour (PIT effect, for review see Cartoni et al. 2016) with implications for substance use relapse, therefore I will present accumulating evidence for behavioural and neural PIT effects in social drinkers and alcohol dependent patients.

Methods: We investigated three samples: 1) n=201 18-year old social drinker, 2) n=109 alcohol dependent patients during and after detoxification treatment regarding relapse status, as well as 3) n=93 controls matched for patients sociodemographics. Subjects completed i) instrumental training, learning to collect or not collect certain stimuli by probabilistic monetary feedback; ii) Pavlovian conditioning, using deterministic monetary reward; iii) a transfer part combining Pavlovian conditioned stimuli in the background and the instrumental task in the foreground and iv) query trials to verify Pavlovian conditioning. Subjects conducted the transfer part during an fMRI scan.

Results: We observed stronger behavioural PIT effects (i.e. higher number of button presses in the presence of higher valued background stimuli) both in high risk social drinkers compared to low risk social drinkers, and in alcohol dependent patients compared to matched controls. Behavioral PIT effects were associated with a stronger activation in amygdala and nucleus accumbens, with the latter being predictive for relapse in alcohol dependent patients.

Conclusions: Our results of enhanced PIT effects in high risk drinkers and alcohol dependent patients shed light on behavioural and mesolimbic dopaminergic mechanisms regarding problematic alcohol consumption and relapse behaviour. Associated neural activations are in line with the incentive salience theory of addiction (Robinson & Berridge 2001). Therefore, our data underline the importance of contextual cues in influencing behaviour and may stimulate therapeutical applications for relapse prevention.

Literature Reference
EFFECTS OF COCAINE SELF-ADMINISTRATION ON BEHAVIORAL AND NEURAL CORRELATES OF CACHED VERSUS INFERRED VALUE DURING SENSORY PRECONDITIONING
Geoffrey Schoenbaum
NIDA-IRP

Objectives: This talk will review behavioural and neural correlates of inferred versus cached value and how they are altered by prior experience self-administering cocaine.

Purpose: The purpose of this talk is to discuss behavioural and neural correlates of value in the OFC and VTA and how they are affected by prior cocaine use in rats.

Methods: Rats were trained in a sensory preconditioning task in which they learned to associate auditory cues (A->B, C->D), after which they learned that one cue predicted reward (B->US), before being presented with each cue in an unrewarded probe test. Some rats had self-administered either sucrose or cocaine for 2 weeks approximately a month earlier. Some rats had electrode arrays implanted in the OFC or VTA to record single unit activity during training.

Results: Drug-naïve rats showed the expected increased responding to both the inferred (A) and the cached (B) value cues in the probe test. These changes were associated with signalling of reward prediction errors at the time of cue presentation in VTA dopamine neurons and with signalling of associative predictions in the OFC, both before and after reward pairing. Rats with cocaine experience continued to respond normally to the cached value cue in the probe test but no longer showed any responding to the inferred value cue. Changes in neural activity in OFC and VTA in these rats will be discussed.

Conclusions: The data will show 1) that OFC and VTA dopamine neurons represent complimentary information about reward-predictive cues – with the former signalling predictions and the latter signalling prediction errors – for both cached and inferred value cues, and 2) that OFC also represents associative information independent of value, and 3) that inference is selectively disrupted by cocaine use, raising implications for long-term defining features of addiction such as relapse.
DOPAMINERGIC PHARMACOLOGY OF CUE-INDUCED RESPONDING IN HUMANS

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Objectives: Many models of addiction suggest that it is a form of pathological reward processing. One marker of addiction is increased responding to drug-associated stimuli (cue reactivity), which has been implicated in the development and maintenance of drug addiction. This project investigates the role of the dopamine system in human cue reactivity.

Purpose: While data from animal studies suggest that the dopamine system is involved in cue reactivity, its role in humans is less clear. Moreover, it is unclear how specific or general this effect is, that is whether dopaminergic drugs elevate responding to cues associated with specific rewards or lead to general increases in responding to reward related cues. We therefore also investigate how blocking dopamine receptors influences cue-induced responding to general reward cues as opposed to outcome-specific reward cues.

Methods: In two randomized, double-blind, between-subject designs we administered the selective dopamine D2/D3 receptor antagonist amisulpride (400 mg, study 1 n=41, study 2 n=18) or placebo (study 1 n=40, study 2 n=20) to healthy humans and measured cue-induced responding with a Pavlovian-instrumental transfer (PIT) task. While study 1 did not distinguish between outcome general and outcome specific forms of PIT, study 2 did.

Results: Compared to placebo, amisulpride significantly suppressed cue-induced responding to unspecific reward related cues in both studies. In contrast, responding to outcome specific cues was largely preserved under dopamine blockade in study 2.

Conclusions: Our results demonstrate that a selective blockade of dopamine D2/D3 receptors reduces general PIT, while it does not affect outcome-specific PIT, compatible with a role of dopamine in enhancing general motivation to cues associated with positive outcomes.
Symposium

SY11.
Brain programming by early-life stress; focus on environmental factors, epigenetics and inheritance
NUTRITIONAL FACTORS AND NEURO-IMMUNOLOGICAL MODULATORS INVOLVED IN PROGRAMMING THE LASTING EFFECTS OF EARLY-LIFE STRESS ON THE BRAIN
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Early-life stress (ES) leads to increased vulnerability to develop psychopathologies and cognitive decline. Which environmental elements and biological underpinnings underlie the ES-induced programming of the brain is not fully understood. Considerable attention has been given to stress hormones and sensory stimuli, however nutritional and immunological factors have been largely ignored in this context. These factors act simultaneously and are highly interrelated, thus the ES-induced effects are likely mediated by the synergistic rather than an independent action of these factors. We investigated if ES affects 1) central nutritional availability and composition; 2) neuro-immunological profile; 3) whether these factors contribute to the ES-induced phenotype and 4) if and how nutrition based peripheral interventions can protect the brain against the deleterious effects of ES.

To study these questions, we subjected mice to a chronic ES paradigm, consisting of limiting nesting and bedding material from postnatal day (P)2 to P9, that elicits chronic stress in the dams, and lasting effects on cognitive performance and brain structure in the adult offspring. We found that ES altered the levels and availability of different macro- (essential fatty acids) and micronutrients (essential methyl donors) in the offspring. In addition, ES altered microglial activation and cytokine mRNA expression both early in life and in adulthood. We tested two different nutritional interventions based on either enriched methyl donors or enriched fatty acid composition. Early-life dietary supplementation with these diets was able to prevent partly (methyl donor-based) or fully (fatty acid-based) the cognitive impairments after ES. The involvement of neuronal plasticity, neuroinflammation and stress hormones in the beneficial effects of these diets is currently being investigated.

Better understanding of the interplay of these various factors in concert will help us to understand the biological underpinnings of the ES-induced phenotype, and can open new avenues to design peripheral (e.g. nutrition based) interventions.
MINERALOCORTICOID RECEPTOR SEX-DEPENDENTLY MODULATES BEHAVIORAL AND NEUROENDOCRINE STRESS RESILIENCE AFTER EARLY LIFE STRESS IN MICE

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Adverse environmental factors (i.e. early life stress), in interplay with genetic predisposition, are considered major risk factors for developing psychopathology. Prevailing clinical and rodent studies shown that high function of the brain mineralocorticoid receptor (MR) sex-dependently confers resilience to stress. Yet, the mechanism underlying behavioral, neural and endocrine responses are still poorly understood.

Here we examined i) the effect of early life stress (ELS; limited nesting/bedding model P2-9) on neuroendocrine, physiological and behavioral parameters relevant for mood disorders. ii) Whether this is exacerbated in the forebrain-specific MR knockout (MRKO) mouse and iii) if females and males are differently affected.

Developmental trajectories of various behavioural domains were assessed by a behavioral battery from 4 weeks of age onwards in control or MRKO mice subjected to control or ELS condition. In males, anxiety-related behavior was increased after ELS and in MRKO control animals while females seemed unaffected. Other behavioral domains (ie social and cognition) are currently being analyzed. Preliminary data suggests that the effects of ELS and/or MRKO are domain- and sex-specific.

Next, basal and stress-induced HPA axis activity (restraint stress, 10 min) were assessed. No differences circadian corticosterone levels or body weight was found. Restraint stress effectively evoked an acute stress response in all groups which did not differ significantly between the male groups. In the females however, ELS and MRKO resulted in blunted stress peak levels which was further exacerbated in the MRKO ELS group. The difference in corticosterone release could be explained by reduced pituitary ACTH output as POMC content was significantly lower in these groups. Brains and pituitaries are now studied for markers of the stress system and glucocorticoid target genes.

Our findings support that adverse early life conditions affect the brain and stress system sex-specifically and that MR may be an important moderator of stress resilience.
TRANSGENERATIONAL ACCUMULATION OF IMPAIRMENTS IN MATERNAL BEHAVIOUR FOLLOWING POSTNATAL SOCIAL STRESS

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Early environment such as maternal care can have long-term physiological and behavioral effects on offspring and future generations. Exposure to chronic social stress (CSS), an ethologically model of postpartum depression and anxiety, during lactation impairs maternal care and exerts similar effects on the F1 dam offspring of the stressed F0 dams. These changes associate with increased corticosterone and neuroendocrine alterations. CSS F2 offspring further display decreased social behavior as juveniles and adults and decreased basal levels of corticosterone.

We investigated the transgenerational inheritance of alterations in maternal behavior in F2 CSS dams together with neuroendocrine and immune markers to explore whether aspects of maternal behavior are transgenerationally inherited through immune and neuroendocrine mechanisms.

We found that maternal care behavior in the F2 dams is more severely impaired than in the F0 and F1 dams and the expression of maternal anxiety is expanded in F2 dams. This occurred together with reduced basal cortisol (in contrast to an increase in F1 dams), a lack of changes in neuroendocrine gene expression, and reduced serum ICAM-1 (intercellular adhesion molecule-1) levels - a marker for inflammation and blood-brain barrier integrity.

The results support the hypothesis that the effects of chronic social stress can accumulate across three generations to depress maternal care, increase maternal anxiety, and alter basal functioning of the immune system and hypothalamic pituitary adrenal axis.
Symposium

SY12.

Cortico-hippocampal circuits and episodic memory: revisiting the whatwhere distinction
THE EVIDENCE FOR DEDICATED SPATIAL AND NON SPATIAL SUBNETWORKS SEGREGATED ALONG THE PROXIMO-DISTAL AXIS OF THE HIPPOCAMPUS

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A well-accepted model of episodic memory includes the processing of spatial and non-spatial information by segregated cortical pathways and their association within the hippocampus (the ‘Two stream hypothesis’). However, the end points of these pathways, namely the lateral entorhinal and the medial entorhinal cortices, project to distinct proximodistal levels of the hippocampus, which appears to be inconsistent with this standard view. Here, we will present the evidence that led us to formulate a completely new concept according to which subnetworks segregated along the proximodistal axis of the hippocampus would preferentially process spatial or non-spatial information and discuss the extent to which this ‘segregated’ view of information processing and the ‘standard’ model are reconcilable (Nakamura et al, Journal of Neuroscience, 2013; Beer et al, submitted; Flasbeck et al, submitted)
The importance of the entorhinal cortex (EC) in the processing of spatial and non-spatial information, two components of episodic-like memory is now widely acknowledged. However it is striking that in contrast with the hippocampus, our knowledge of the contribution of the EC to the processing of spatial allothetic (environmental) information is quite superficial. Previous studies have indicated that the processing of distal and proximal environmental landmarks are dissociated in the brain and would be mediated by different circuits involving the EC (distal), the associative parietal cortex (proximal) and the hippocampus (distal and proximal). To clarify the role of the medial entorhinal cortex (MEC) and lateral entorhinal cortex (LEC) in these processes lesioned rats were trained in two water maze navigation tasks with distal or proximal landmark conditions. The results show that the MEC is crucial for navigation when animals have to rely on distal but not proximal landmarks. In contrast the LEC is not necessary for both landmark conditions. These results are in line with the widely-accepted view that the MEC is specifically involved in the processing of space. In contrast the LEC is hypothesized to be involved in the processing of non-spatial information. Recently, we have found that decreasing the complexity of the environment in terms of number and diversity of landmarks allowed to restore the abilities of MEC- and LEC-lesioned rats to process spatial and non-spatial information. Overall, the data suggest that the MEC and LEC play different roles allowing the animals to use different spatial frameworks to navigate. The processing of distal landmarks requires the MEC (and the hippocampus) whereas the processing of proximal landmarks requires extra-entorhinal circuits. In addition, as hypothesized, both MEC and LEC contribute to the processing of spatial and non-spatial information but the involvement of these sub-regions can be modulated by environmental factors.
LATERAL ENTORHINAL CORTEX AND ASSOCIATIVE RECOGNITION MEMORY
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Episodic memory and navigation rely on neural mechanisms within the hippocampal-entorhinal circuitry. Models of this network suggest that item or object information from lateral entorhinal cortex (LEC) is combined with spatial information from medial entorhinal cortex (MEC) to form representations of events and locations within the hippocampus. Support for this model comes from studies showing numerous types of spatial representation in MEC including grid cells, head directions cells, border/boundary vector cells and speed cells. The function of LEC, however, is less well understood. LEC does not process spatial information in the simple environments used in standard place cell experiments. However, there are populations of LEC neurons that produce spatial responses when objects are introduced and moved within familiar environments. My recent work has examined the hypothesis that LEC is needed to integrate object information into a spatial and contextual local framework. I will present data showing that activation levels in LEC increase when rodents demonstrate a memory for objects within a specific context. I will go on to show that LEC is not needed for recognition of individual features of an environment but is needed to associate multiple features together. I will present a possible mechanism for this by showing that CA1 place cells receiving LEC input are much more responsive to objects manipulations than those receiving MEC input. These data suggest that the LEC input is preferentially involved in processing how local features of an environment are integrated. Finally I will present data using new genetic and molecular tools that allow us to dissect the functional properties of the pathway from LEC to hippocampus in more detail.
NEURAL PROCESSING FOR METRIC SPACE AND TOPOLOGICAL SPACE
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Recent research from our group has explored brain regions involved in coding metric space (distance between locations) and topological space (connections between streets). We have used virtual simulations and functional magnetic resonance imaging (fMRI) with humans to explore how these two types of “where” information may be encoded by the hippocampus. We find the anterior hippocampus (homologue of the rodent ventral hippocampus) is associated with coding the Euclidean distance and the global topology in the street network, whereas the posterior hippocampus (homologue of the posterior hippocampus) is associated with coding the path distance to the goal and the local connectivity of the street network. These results help advance theories of how the hippocampus contributes to spatial processing during navigation.
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AMYGDALA RESPONSES TO SUBLIMINAL SPATIAL-FILTERED FACES IN ADULTS WITH HIGH-FUNCTIONING AUTISM SPECTRUM DISORDER: A MEG STUDY
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Objectives: Autism spectrum disorder (ASD) is a set of heterogeneous neurodevelopmental conditions characterized by early-onset difficulties in social communication and unusually restricted, repetitive behavior and interests. Magnetoencephalography (MEG) is used in ASD research for its noninvasive nature of recordings and for its excellent temporal and spatial resolution.

Purpose: The aim of this study was to investigate the amygdala responses to subliminal spatial-filtered fearful faces in adults with high-functioning ASD. We hypothesized that the responses in ASD were weaker than those in healthy adults without ASD (HC) because ASD was characterized by deficit of understanding emotional meanings of human faces.

Methods: Eighteen adults with ASD and 18 HC were participated in this study. At first they were checked their intelligence quotient (IQ). MEG experiment: Stimuli were fearful or neutral faces and objects which image resolutions were filtered by broad, low or high spatial frequency. Stimuli were randomly presented 17 or 300 ms duration with 1~1.2 s inter-stimulus intervals. Subjects were instructed click the mouse as soon as the target stimulus (a picture of train) was presented on the monitor. Magnetic brain responses were recorded by 306-ch whole head MEG machine. Each subject’s structural brain image was taken by a 3T MRI equipment. MEG data were analyzed by adaptive beamformer method.

Results: All subjects carried out the experiment. FIQ of all subjects was over 80 and there was no statistical difference of FIQ between the ASD and HC groups. As our expectation, MEG responses to the subliminal faces at the amygdala in ASD were weaker than those in HC. However, MEG responses to the supra liminal faces and objects at the amygdala in ASD were not.

Conclusions: The amygdala weak responses to the subliminal face in adults with ASD may be responsible for lack of ability to insight other’s face emotion.
MATERNAL SEPARATION: BEHAVIORAL EFFECTS IN ADOLESCENCE AND EARLY ADULTHOOD IN TWO RAT MODELS

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Objectives: Maternal separation (MS) is an extensively used early life stress model. There is some variability in the MS lengths used, which leads to different emotional and behavioral alterations. It would be helpful to compare in adolescence and adulthood the effects of two lengths of early MS over a range of behaviors.

Purpose: We assessed in adolescent and adult male wistar rats the effects of two lengths of early MS over anxiety, recognition and associative memory.

Methods: Two length models were used: from postnatal day 1 until day 10 (MS10) and from postnatal day 1 until day 21 (MS21). Litters were separated from dams for 4 hours per day in both groups. Controls were reared under animal facility rearing (AFR) conditions. Six groups were included in the experiment, two control groups or AFR (n = 20) and two experimental groups: MS10 (n = 20) and MS21 (n = 20). Ten animals per group were tested at each age: between PND 26 and PND 34 (adolescent results) and between PND 86 and 94 (adult results). Behavioral tests used were object recognition, zero maze, and passive avoidance.

Results: The results showed that separated groups, MS10 and MS21, could not discriminate between a previously encountered object and a novel object in adolescence. In adulthood, results showed that only MS10 and AFR groups could discriminate whereas MS21 did not. Regarding anxiety score on the zero maze, adolescent and adult MS21 groups were more anxious than MS10 and AFR. In passive avoidance, adolescent MS10 group enters to the dark chamber on the recall phase in half of the time spent by the other two groups. During adulthood, no differences were found between groups in passive avoidance behavior.

Conclusions: We found that the longer model leads to anxious behavior and impairs recognition in adolescence and adulthood whereas the shorter one deteriorates associative/emotional learning only in adolescence. In our opinion, these results can be explained by the fact that different lengths lead to different profiles: the longer one is an anxious profile, whereas the shorter one is not. These two models could partially represent the complex human early stress scenario.
The relation between background input-output characteristics and CA3-CA1 LTP performance induced by high frequency stimulation (HFS, 100 Hz, 1 s,) was determined in the hippocampal slices of one month Wistar rats subjected to early proinflammatory stress (lipopolysaccharide injected at PND 3 and PND 5, LPS, 50mg/kg). We found that after neonatal inflammation LTP induction may be failed in result of low synaptic activation during HFS. In females the most of slices did not demonstrate even early potentiation, this effect was only sometimes observed in the male hippocampus. When the part of slices with early potentiation was taken into consideration LTP maintenance was similar to control in both males and females. LTP deficit in female slices of LPS group may be prevented by bicuculine. The shape of input-output curves evidences about decreased synaptic efficacy in LPS group compared to control, especially in females. We proposed that the problem with LTP induction after neonatal inflammation may be related to the deficit of synaptic depolarization producing too low underthreshold Ca2+ signal in response to HFS. Significant positive correlation between LTP performance and amplitude of CA3-CA1 responses at stimulus intensity used for HFS confirms that LTP deficit is associated with initial synaptic depression in the slices of LPS male rats. Though we can not reveal such correlation in the slices of LPS female rats, it does not argue against our hypothesis since slices were initially depressed. In addition after neonatal inflammation short-term postsynaptic depression significantly increased proportionally to background synaptic inflow in female, but not male hippocampus, while LTP in male hippocampus initiated multiple spikes (epileptiform-like discharges). We hypothesized that LTP deficit may be related to compensatory metaplasticity rather than disturbed mechanisms of long-term plasticity, that is less effective in male hippocampus.

This work was supported by the Russian Science Foundation (grant #14-25-00136).
STUDY OF THE NORADRENERGIC SYSTEM IN RECONsolidATION OF MEMORY: INVOLVEMENT IN A MOUSE MODEL OF POST-TRAUMATIC STRESS DISORDER

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Objectives: A previously consolidated memory can enter a new active state when reactivated, requiring a new stabilization process named memory reconsolidation. Interfering with this process allows to delete memory, opening the way for new therapeutic approaches to treat diseases involving maladaptive memory, such as post-traumatic stress disorder (PTSD).

Purpose: Study the role of propranolol, a β-adrenergic antagonist, for reconsolidation blockade-based PTSD treatment.

Methods: Combining behavioral and physiological approaches in mice, this study proposes to investigate the mechanisms underlying memory reconsolidation and the propranolol mode of action on traumatic memory reconsolidation.

Results: Results showed that, in a new behavioral test developed as PTSD model, control mice strongly avoided compartments containing cues associated with the electric shocks. Injection of propranolol after reactivation greatly reduced the memory of the traumatic event and produced a decrease of heart rate during this long term memory test.

Conclusions:
- Our results suggest that our new behavioural paradigm is well adapted to PTSD study in mice.
- Propranolol reduce fear memory but the effect depends on the reactivation protocol.
- This is relevant to the use of propranolol to block memory reconsolidation in individuals with PTSD.
- These data are important for short-term improvement of the therapeutic protocol in trauma patients.
ABSENCE OF MATERNAL PINEAL MELATONIN DURING PREGNANCY AND LACTATION IMPACTS PHYSICAL GROWTH, NEURODEVELOPMENT, AND BEHAVIOR OF OFFSPRING


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Chronic exposure to light at night, as in shift work, alters biological clocks, negatively impacting pregnancy outcome in humans. It also leads to suppression of nocturnal melatonin pineal synthesis. Maternal melatonin regulates the timing of offspring internal rhythms by providing circadian photoperiodic information. Maternal melatonin deprivation during gestation and lactation has negative health consequences for the offspring that continue into adulthood (e.g. altered energy metabolism). As there is few data examining the effects of maternal melatonin deprivation during pregnancy and gestation (MDDGL) on neurodevelopmental outcomes of offspring, this was the aim of present study. Female Wistar rats were submitted to pinealectomy (PINX) or SHAM surgery (CTL). The PINX rats were divided into two groups and received either melatonin (PINX+MEL) or vehicle (PINX). After 4 weeks, the rats were allowed to mate and received the treatment until lactation’s end. Somatic, physical and reflex development offspring were determined. In addition, we evaluated the effects of MDDGL on male adult offspring's spatial memory outcomes and hippocampal neurogenesis by mRNA expression and immunohistochemistry of Ki-67, BDNF and DCX. Our findings show that MDDGL significantly delayed the male offspring’s onset of fur development, pinna detachment, eyes opening, eruption of superior incisor teeth, testis descent and the time maturation of palmar grasp, righting reflex, free-fall righting and walking. On the other hand, female offspring were not affected. MDDGL disrupts both spatial reference and working memory in MWM; whereas theses deficits do not correlate with changes in mRNA expression of genes related to hippocampal neurogenesis. The immunohistochemistry analysis is ongoing. Importantly, these impairments were reversed by maternal melatonin replacement. In summary, we demonstrate that MDDGL delays the appearance of physical features and the pointing to a putative public health implications for night working mothers.
BEHAVIOURAL CHARACTERIZATION OF TWO MOUSE MODELS OF MATERNAL IMMUNE ACTIVATION
Sara Anna Bonini, Andrea Mastinu, Marika Premoli, Giuseppina Maccarinelli, Maurizio Memo
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Objectives: The aim of the study was to characterize behavioural deficits in two mouse models of Maternal Immune Activation (MIA): a genetic mouse, with a deletion of the gene coding for p50 NF-κB subunit, and a mouse in which NF-κB is activated by a strong immune system stimulus (LPS).

Purpose: Aberrant immune activity during vulnerable and critical periods of neurodevelopment could participate in the generation of neurological dysfunction characteristic of several neurodevelopmental disorders (NDDs). NDDs are characterized by structural and functional alterations in the brain and in behavioural deficits. We studied the effect of MIA on social and repetitive behaviours.

Methods: We used two MIA mouse models: mice lacking the p50 NF-κB subunit (p50 KO) and mice prenatally exposed to LPS (LPS-mice). We compared the two groups to wild type (WT) mice. We performed the following behavioural tests: reciprocal social interaction test, and social approach test with the three-chambered apparatus to analyse social behaviour; open field test, stereotypies analysis and marble burying to analyse repetitive behaviour.

Results: We found that both p50 KO and LPS-mice present increased locomotor and exploratory activity compared to WT mice. Furthermore, we found that both p50 KO and LPS-mice present reduced social interaction compared to WT mice.

Conclusions: These data provide new insight on the possible link between altered immune function, NF-κB pathway and pathogenesis of NDDs. In particular, it emerged that maternal immune system activation during pregnancy cause lifelong changes in brain function and behaviour of offspring. Indeed we found dramatic impairments in both social and repetitive behaviours in both the MIA models used for the study.

Literature Reference
ANALYSIS OF ULTRASONIC COMMUNICATION IN A MOUSE MODEL OF NEURODEVELOPMENTAL DISORDERS
Marika Premoli, Sara Anna Bonini, Andrea Mastinu, Giuseppina Maccarinelli, Maurizio Memo
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Objectives: To analyze ultrasonic communication in mice lacking the NF-kB p50 subunit (p50 KO) and wild-type (WT) mice during mother-separation test.

Purpose: Mice emit ultrasonic vocalizations (USVs) under different social conditions: pups separated from the nest and the mother, juveniles play and adult’s courtship, mating and/or social investigation. The USVs measurement has become an important instrument for behavioral phenotyping in neurodevelopmental disorders, especially for disorders characterized by communication impairment, e.g. autism spectrum disorders (ASD). In this study, we analyzed USVs in a mouse model of neurodevelopmental disorders.

Methods: Ultrasonic vocalizations were recorded using an ultrasound sensitive microphone and quantitatively analyzed by Avisoft software. Each syllable was categorized manually based on spectral features as frequency modulation and duration.

Results: We previously demonstrated that p50 KO mice present ASD-like cortical and behavioral alterations and represent a valid animal model for neurodevelopmental disorders. By means of the USVs analysis we found that KO pups emit significantly more and longer vocalizations compared to WT pups. A complete USVs classification in WT and p50 KO mice has been also reported.

Conclusions: USVs analysis revealed alterations in social communication in p50 KO compared to WT mice. This analysis strengthens the use of p50 KO mice as valid animal model of ASD.
CNTN4, A CANDIDATE GENE FOR AUTISM SPECTRUM DISORDERS, AFFECTS FEAR CONDITIONING, HIPPOCAMPAL NEURONAL MORPHOLOGY AND FUNCTION
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Objectives: Autism spectrum disorders (ASD) are neurodevelopmental disorders that are clinically detected by impairments in social interaction and restricted, repetitive behavior. Learning and memory behavior is one of the endophenotypes that can be studied to simplify the huge variety in ASD. Contactin4 (CNTN4), an Ig cell adhesion molecule (IgCAM) gene, is associated with ASD. We target the functional analysis of CNTN4 and how it changes hippocampal brain functions.

Purpose: The goal of this study is to understand how CNTN4 loss-of-function impacts brain development and behaviour. To this end we used a Cntn4-knockout (KO) mouse model and determined hippocampal neuronal morphology, subjected mice to fear conditioning and hippocampal long-term potentiation.

Methods: Nissl and Golgi staining of hippocampal neurons were analyzed for morphological analysis and reconstruction of dendritic arbors by manual tracing (Neuro Lucida software). We also assessed memory related behaviours in Cntn4 KO, heterozygous and wild type mice. Field Excitatory Postsynaptic Potentials (fEPSPs) in the CA1 hippocampus were recorded before and after high/low frequency stimulation.

Results: Golgi analyses showed abnormal dendritic arborisation of hippocampal CA1 neurons and an increased hippocampal volume. Furthermore, it was also investigated whether these changes correlated with deficits in learning and memory behavior. For that purpose, short- and long-term recognition memory, spatial memory and fear conditioning responses were assessed. These behavioural studies showed increased contextual fear conditioning in heterozygous and homozygous KO mice, quantified by a gene-dose dependent increase in freezing response. In comparison to wild-type mice, Cntn4-deficient animals froze significantly less and groomed more, indicative of an increased stress responsiveness under the test conditions. In addition, we tested if Cntn4 gene expression affects CA1 synaptic transmission and the ability to induce LTP in hippocampal slices. Stimulation in CA1 stratum radiatum with 900 pulses at 10 Hz decreased significant synaptic potentiation in Cntn4 KO mice.

Conclusions: Our neuro-anatomical behavioural and electrophysiological results in Cntn4 KO mice suggest that CNTN4 has important functions for fear memory through the neuronal morphological and synaptic plasticity changes in hippocampus CA1.
ONTOGENY OF OBJECT-PLACE RECOGNITION MEMORY CONSOLIDATION IN RATS

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Objectives: This study examined: i) the age range when the consolidation of the Where component of the episodic memory emerges and, ii) the contribution of prior learning experience to this memory emergence.

Purpose: To investigate the ontogeny of the Where component of the episodic memory.

Methods: In order to assess memory emergence we performed the object-place recognition (OPR) task in different groups of rats on different postnatal days (PD); PD15, PD18, PD25, PD31, PD38, PD48, PD70. Retrieval was performed 3 hours after the sampling phase, in order to specifically test for the presence of a consolidated memory. During this interval, rats were left undisturbed to ensure regular morning sleep. To evaluate how performance change with previous learning, each group was subjected to 3 further OPR tests (with an interval of 48 hours) using each time a novel pair of objects.

Results: The emergence tests showed that rats at PD18 have a preference for the object that remained stationary (familiar preference). Later on, rats at PD38 expressed a significant preference toward the displaced object (novelty preference). However, results from the prior learning tests showed that rats from the PD25 group after experiencing 3 OPR tests, expressed significant preference for the displaced object (novelty preference) at PD31.

Conclusions: The Where component of the episodic memory can be consolidated at PD18. Against to our expectation, the memory was expressed as a preference for the stationary object (familiar preference). This pattern changes at PD38 and the memory is expressed as a preference for novelty, like in adult rats. Regarding to the prior learning contribution to the memory emergence, our results suggest that memory emergence expressed as preference for novelty can be accelerated until PD31. These results suggest that the Where component of episodic memory can be differently expressed through lifespan, which should be considered in studies of episodic memory during development.
DIET SUPPLEMENTATION WITH MILK FAT GLOBULE MEMBRANE-PHOSPHOLIPIDS AND KRILL OIL PHOSPHOLIPIDS IMPAIRS CONTEXTUAL FEAR CONDITIONING IN OLD RATS AND INHIBITS TPH1 EXPRESSION IN THE HIPPOCAMPUS

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Phospho- and sphingolipids are critical components for brain development as well as in learning and memory processes. The milk fat globule membrane (MFGM) is rich in phosphatidylserine (PS) and sphingomyelin (SM), while krill oil is rich in PLs containing very long-chain fatty acids EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid). Here, we investigated the cognitive effects of a chronic (3 months) supplementation with bioactive phospholipids (PLs) from milk and krill oil in 18-month old rats. Animals were orally administered with either MFGM-PLs (PS 8 mg/d + SM 17 mg/d) or krill oil PLs (15 mg EPA+DHA) or both.

Results showed that PLs-supplementation impairs contextual fear conditioning in old rats without affecting tone-cued fear conditioning. In addition, the expression of genes in the hippocampus of the different experimental groups was investigated. Over 22900 genes were screened with Affymetrix Clariom S Assays. 38 differently expressed genes (adjusted p-value <0.05 was considered as statistically significant) were found for krill oil (11 upregulated and 27 downregulated), 58 for MFGM (2 upregulated and 56 downregulated), and 72 for MFGM +Krill oil (11 upregulated and 61 downregulated). We found that both, MFGM-PLs or krill oil-PLs, when administered separately inhibited hippocampal expression of tryptophan hydroxylase 1 (tph1), an important rate-limiting enzyme in serotonin synthesis tph1. However, concomitant administration of MFGM-PLs and krill oil-PLs, affected neither tph1 expression in the hippocampus nor impaired contextual fear conditioning. Our results suggest a possible mechanism of action of MFGM-PLs and krill oil-PLs on impairing contextual fear conditioning and points to a complex interaction of both treatments on the regulation of tph1 hippocampal expression.
LIPID PROFILE IN PARKINSON’S DISEASE: THE POSSIBLE ROLE OF BRAIN-DERIVED NEUROTROPHIC FACTOR
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Objective: Parkinson’s disease (PD) is a neurodegenerative disorder that affects many body systems, including cardiometabolic function. Brain-derived neutrophic factor (BDNF) is altered in PD and has also been implicated in cardiometabolic function. However, few studies examined the effect altered BDNF on lipid profile among PD.

Purpose: Therefore, the current study examined the relationship of BDNF with lipid profile in PD.

Methods: Serum BDNF and lipid profile were determined in 28 PD and 28 age/gender matching control.

Results: The comparisons show that BDNF and lipid profile are altered (p>0.05) in PD as compared to the control. Additionally, simple linear regression in the patients only, showed that BDNF predicted 11.9% of total cholesterol (p=0.05), 3.0% of HDL (p=0.003), 27.3% of LDL (p=0.006), 16.6% of triglyceride (p=0.04), 15.8% of total cholesterol/HDL (p=0.06), 22.1% of total cholesterol/LDL (p=0.01), and 35.1% of triglyceride/HDL (p=0.001). However, after including these variables in a stepwise regression, BDNF predicted only 50.0% triglyceride (p=0.0001) and 35.1% of triglyceride/HDL (p=0.001).

Conclusions: The results indicate that BDNF is related to "desired" lipid profile, especially triglyceride and triglyceride/HDL in PD. Therefore, strategies aiming at improving BDNF levels are warranted.
EFFECTS OF ABDOMINAL VAGOTOMY IN RATS ON BEHAVIORAL DESPAIR

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Objectives: Clinical studies investigating vagus nerve stimulation (VNS) have shown promising results in treating major depressive disorder (MDD), although its neural mechanism has not been fully understood.

Purpose: The present study aimed to explore the effects of abdominal vagotomy on depressogenic and anxiogenic treatments in rats.

Methods: Adult female Wistar rats (n=20) kept on a 12h light:12h dark lighting schedule (lights on at 07:00 AM) underwent abdominal surgery (n=11 vagotomised, n=9 sham) that cut the anterior gastric left vagus nerve (3mm).

Fifteen days later animals were administered two forced swim test (FSTs) on two consecutive days for 15 min and 5 min, respectively, to induce behavioral despair. Subsequently, they were administered an open field test (OFT) to assess locomotor activity and anxiety.

Thirty days later, rats underwent another FST for 5 min, followed approximately 90 min later by perfusion and tissue harvesting for subsequent immunohistochemical analysis (to be reported later).

Results: The vagotomised and sham rats did not differ in their initial FST immobility scores or in their OFT performance. However, when tested one month later, the vagotomy group (n=11, M=73.8, SEM= 5.4) displayed greater immobility in FST compared with shams (n=9, M=40, SEM=8.4).

Conclusions: Our results suggest that the vagus nerve may be involved in depression-like behavior in an animal model and may provide the basis for further investigation of vagus nerve and its interaction with depression.
IMPACTS OF INTRAUTERINE EXPOSURE TO THE RADIOFREQUENCY ELECTROMAGNETIC FIELD ON SEROTONERGIC DEVELOPMENT IN FETAL RAT
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Objectives: Verification the potential health effects of radiofrequency electromagnetic field (RF-EMF) on neurodevelopment in fetal rat

Purpose: We investigated that the effects of intrauterine exposure to RF-EMF on maternal serotonin, placental tryptophan hydroxylase 1 (TPH1) and its impact in fetal brain.

Methods: Eighteen pregnant Sprague-Dawley (SD) 12-week-old rats were divided into three groups of 6 rats: cage- control group, sham exposure group, and EMF exposure group. The dams were exposed to RF-EMF signal (915 MHz radiofrequency identification) at a whole-body specific absorption rate of 4 W/kg for 8 h per day from Gestational Day 1 to 19. The placental TPH1 level, fetal forebrain serotonin, hindbrain serotonin, and maternal blood serotonin were measured by ELISA analysis.

Results: Increased in levels of maternal blood serotonin and placental TPH1 were observed in EMF exposure group. Besides, increased in levels of serotonin in the fetal forebrain and hindbrain were observed in EMF exposure group.

Conclusions: Collectively, our findings indicate that exposure to RF-EMF at during early stage of serotonergic development might disrupt not only maternal environment such as synthesis of placental serotonin and delivery of maternal serotonin to fetal forebrain, but also fetal environment such as synthesis of fetal serotonin in hindbrain.
Neural Excitability, Synapses and Glia: Cellular Mechanisms
THE MECHANISMS OF PLASTICITY IN MESOLIMBIC DOPAMINE FUNCTION UNDERLYING BEHAVIORAL AND NEUROCHEMICAL SENSITISATION

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Objectives: Behavioral sensitization, measured as the progressive, long lasting increase in locomotor activity, occurs with repeated administration of psych stimulant drugs such as nicotine and amphetamine.

Purpose: An important question to address is whether the intermittent administration of nicotine or amphetamine causes long-term sensitisation and/or cross-sensitisation.

Methods: To investigate this question, we examined the behavioral sensitisation in response to nicotine or amphetamine administration. And we investigate the expression of early response genes (IEG) c-fos and activity-regulated cytoskeleton-associated protein (Arc), that have been implicated in synaptic plasticity, in the nucleus accumbens (NAc), shell and core sub regions using immunohistochemistry. Firstly, male Lister-hooded rats received five daily injection (i.p.) of either nicotine (0.6mg/kg), amphetamine (1mg/kg.) or saline (1ml/kg) and locomotor activity (distance travelled mm) was recorded immediately after drug injection, for 60 min. Ten days later, rats were challenged (i.p.) with nicotine (0.6mg/kg), amphetamine (1mg/kg) or saline (1ml/kg) and their locomotor activity was measured. Secondly, two hours later, rats were euthanized, fixed by transcardiac formaldehyde perfusion and NAc sections (30µm) were cut and immunolabeled for c-fos or Arc.

Results: Rats pre-treated with nicotine or amphetamine exhibited increased locomotor activity, through the repeated daily drug treatment and when challenged ten days later with nicotine or amphetamine. Accompanying this behavioral sensitization, there was an increase in Arc protein expression in NAc core in nicotine sensitised rats and in NAc shell in amphetamine sensitised rats, but no significant changes in c-fos in either nicotine or amphetamine treated animals. In addition, we observed no evidence of behavioral cross-sensitisation between the two drugs, nor of cross-sensitisation changes of immunohistochemical markers.

Conclusions: Behavioral sensitization to repeated nicotine or amphetamine injection was accompanied by increases in Arc expression in NAc suggesting that nicotine and amphetamine sensitization may be linked to increase neurons plasticity within different sub regions of NAc.
The aim of this study was to investigate whether novel prolin-containing dipeptide Noopept (NP) influences synaptic transmission in central neurons. NP was synthesized as peptide analog of piracetam (Giurgea, 1972; Winblad, 2005). NP is similar to piracetam in its chemical structure and memory-enhancing ability but displays the effect in much lower concentration. In addition to nootropic activity NP also displays an anxiolitic effect (Ostrovskaya et al, 2006). We examined the effect of NP on spontaneous and evoked IPSCs in CA1 pyramidal cells in rat hippocampal slices using patch-clamp technique in whole-cell configuration. It was found that NP(1µM) increased spike-dependent release of GABA from terminals of inhibitory interneurons on CA1 pyramidal cells. The effect manifested itself in the increase of amplitude and frequency of spontaneous TTX-sensitive sIPSCs whereas TTX-non sensitive mIPSCs remained unchanged. We also found that IPSCs evoked by Shaffer collaterals stimulation, either short-latency (feed-forward), or long-latency (feed-back) ones increased after NP application. We hypothesized that NP directly excited inhibitory interneurons which terminate on CA1 pyramidal cells. To check this hypothesis we performed current clamp registration of several (n=5) interneurons residing in stratum radiatum (SR). In all cases NP induced a 2-3 fold increase of spiking rate. In the experiments with direct measurement of neuronal [Ca2+]i in hippocampal organotypic slices we revealed that NP selectively increased [Ca2+]i activity in SR interneurons without significantly changing it in stratum pyramidal neurons. Taken together these data clarify that the target of NP action is inhibitory interneurons located in SR of hippocampus. Supported by the Russian Science Foundation (Grant 16-15-00235).
RATS WITH CRONIC HYPERAMMONEMIA REPRODUCE THE ALTERATIONS IN THE MISMATCH NEGATIVITY (MMN) FOUND IN PATIENTS WITH MINIMAL HEPATIC ENCEPHALOPHATY (MHE)

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Objectives and purpose:
Between 30-40% of cirrhotic patients who do not present hepatic encephalopathy, present MHE with mild cognitive impairment which reduces quality of life and lifespan. Patients with MHE show alterations in the auditory event-related potential MMN, which reflects attentional trigger, correlating with reduced performance in attention tests. Development of a procedure to measure MMN in rats with MHE would allow to investigate the pathophysiological mechanisms by which this potential is altered in patients with MHE and look for treatments to reverse this alteration and cognitive alterations.

Methods:
To measure the evoked potential MMN, the electrodes were inserted stereotaxically in the inferior colliculus, primary auditory cortex, hippocampal CA1 and prelimbic cortical in rats with MHE (rats made hyperammonemic by feeding a diet rich in ammonium acetate). MMN was evoked using appropriate sounds while recording the electroencephalographic (EEG) signals, which were processed to measure the variables of interest.

Results:
Rats with hyperammonemia and MHE show a decrease in both the area under the curve and the maximum peak of the MMN wave compared to the control rats in CA1 of hippocampus. The MMN response in the remaining areas analysed does not appear to be affected by hyperammonemia.

Conclusions:
Hyperammonemic rats reproduce in CA1 the decrease of the area under the curve of the MMN wave reported in patients with MHE. This indicates activation of a smaller number of neurons and during a shorter time during the MMN response. The reduced amplitude of the maximum peak in CA1 would indicate a decrease in the response of the neurons. These results are consistent with the results obtained in patients and thus validate the hyperammonemic rats as a model to study the alterations in the evoked potential MMN in MHE.
THE EFFECT OF MEMBRANE POTENTIAL DYNAMICS ON ACETYLCHOLINE RELATED STDP MECHANISMS
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The synaptic plasticity observed in the CA1 area of hippocampus can be induced by the process of learning and memory or behaviour. It is known that the synaptic changes are produced during spike timing-dependent plasticity (STDP) protocol injection. Meanwhile, the neuromodulator acetylcholine (ACh) is involved in attentional process, and can increase the magnitude of STDP. However, its mechanism is unclear. In this study, the dynamics of membrane potential during the STDP stimulation was focused on to clarify the ACh related STDP mechanisms.

The patch clamp recordings were made in the soma of CA1 pyramidal neurons using rat hippocampal slices under interneuron-blocked network. A train of stimuli at 5 Hz was delivered to the Schaffer collaterals for 16 s, with each pulse paired with postsynaptic action potential. Eserine, a cholinesterase inhibitor, was applied to induce an ACh-treated condition. The LTD induced by the application of STDP protocol was switched to LTP if ACh was applied. Thus, the membrane potential during STDP protocol was evaluated, and the elevation was observed in the presence of ACh. According to these results, membrane potential may be one of the factors to induce STDP enhancement. Next, the role of muscarinic ACh receptor (mAChR) and nicotinic ACh receptor (nAChR) respectively for membrane potential was investigated, and the activation of mAChR was more responsible than the nAChR for elevating potentials.

We demonstrated the significant membrane potential elevation by the activation of mAChRs on pyramidal neurons. These results suggest that the dynamics of membrane potential contribute to an ACh related STDP inducing mechanism.
Alzheimer and Parkinson are the main neurodegenerative diseases in the elderly. Together with these pathologies, cancer and cardiovascular diseases constitute the major challenge in our society. Although causes of Alzheimer and Parkinson diseases are unknown, excitotoxicity and oxidative stress seem to be involved. However, a good nutrition and the intake of several nutrients have showed beneficial effects and they can reduce the probability of developing these pathologies, or slow down its progression. Moderate consume of alcoholic drinks, like wine or beer, have benefit effects in cancer or cardiovascular diseases. However, there are few studies about beer consume and neurological diseases. Benefits of beer can be due to the wide kind of compounds present in this beverage as antioxidants, polyphenols or flavonoids. Previous results of our group have shown altered levels of receptors implicated in memory and neuromodulation, as metabotropic glutamate (mGluRs) or adenosine receptors (AdoRs). In Alzheimer disease, mGluRs are decreased with the illness progression while AdoRs are increased since early stages which are asymptomatic. For this reason, these receptors and other related metabolites have been studied in two cellular models, C6 glioma and SH-SY5Y neuroblastoma cells which have been subjected to different insults related to AD (oxidative stress, excitotoxicity...) and the effect of beer (extract of beer, hop and polyphenols) was studied. Viability results show cell death due to these insults and a recovery of life cells after beer exposure. On the other hand, gene expression of receptors which are altered in AD was modified in cells after treatment with beer. These results demonstrate a protective effect of beer in these cell cultures and the ability of beer to modulate the expression of these GPCRs, suggesting that a moderate consume of beer could be protective versus oxidative stress and other factors associated to neurodegeneration.
PHENYTOIN PROMOTES REMYELINATION OF THE CORPUS CALLOSUM IN THE ADULT MOUSE BRAIN
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Objectives: Oligodendrocytes loss and myelin sheet destruction are one of the main events that characterize Multiple Sclerosis, a chronic neurodegenerative disease. Endogenous neural precursors in the adult brain may be good candidates to help restore the oligodendroglial population. Phenytoin promotes cell proliferation of neural precursor cells (NPCs) in the postnatal brain. Hence, the pharmacological stimulation of NPCs with phenytoin may represent a viable alternative to promote white matter regeneration.

Purpose: To evaluate whether phenytoin promotes remyelination in the corpus callosum of adult mice intoxicated with cuprizone.

Methods: 24 CD1 male mice were exposed to 0.2% cuprizone mixed with food chow for 8 weeks; then we assembled two groups: phenytoin-treated group and the untreated control group. The treated group received oral phenytoin (10 mg/kg) for 4 weeks upon cuprizone removal. The control group only received vehicle solution. To evaluate remyelination, we quantified the number of oligodendrocyte precursor cells (OPC) and mature oligodendrocytes that expressed Olig2/Brdu, NG2/Brdu, RIP/Brdu cell markers, and the expression level of myelin basic protein (MBP), as well as and the muscle strength and motor coordination.

Results: The number of OPC and oligodendrocytes significantly increases after the phenytoin administration as compared to untreated group. Densitometric analysis also show an increase in the expression of MBP in the corpus callosum. Functional test show a significant improvement in the score rates obtained with horizontal bars test in the phenytoin group.

Conclusions: Phenytoin stimulates OPC proliferation that contributes to re-establish the oligodendroglial population and promotes remyelination of the corpus callosum. These cellular effects are associated with functional recovery in motor coordination and strength.

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INDUCED MEMORY TRACE INSTABILITY IN RAT HIPPOCAMPUS

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Mental representations demonstrate nonlinear attractor-like dynamics, allowing memories with similar content to be kept as separate items. We aim to understand the process of memory trace association in neural networks, namely in hippocampus.

**Methods:** Rats were trained to develop two uncorrelated spatial representations of distinct environments with identical geometry but different lighting configuration. This arrangement allowed their sudden change (‘teleportation’) known to induce rapid switch between respective representations often followed by their temporary flickering (Jezek et al., 2011). We hypothesized that teleportation and flickering might facilitate fusion of orthogonal representations as activity patterns are brought into temporal proximity of single theta cycle level. Teleportation protocol was used in rats with implanted electrode assemblies into hippocampal CA3 and CA1 and we measured correlations between population vectors from two hippocampal representations during sessions before and after the teleportation experiment.

**Results:** The teleportation experience led to correlation increase between respective CA3 representations \( r=0.08\pm0.25 \) to \( r=0.20\pm0.30, \ p<0.0001 \). To test whether this effect might come from internal network kinetics, we decomposed post-teleportation recordings into theta cycle-based population vectors and correlated them with the activity templates from pre-teleportation sessions. We found that post-teleportation recordings yielded higher network state instability as the number of spontaneous concurrent representation occurrences (flickers) increased \( (0.002\pm0.001\% \) to \( 0.004\pm0.002\%, \ p<0.05 \). Subsequent flicker omission almost abolished the correlation increase. Similar effect was observed in CA1 \( (r=0.18\pm0.23 \) to \( r=0.33\pm0.28, \ p<0.0001 \), including the increased flickering effect (Posani et al., in press).

**Conclusions:** While memory states retain their orthogonality even after a repetitive conflicting sensory experience, it promotes long term instability of memory states in the network lasting at least tens of minutes. Such destabilization might be a unique tool in measuring attractor stability in brain neural networks and provide an insight into mechanisms of human neuropathologies as schizophrenia or various forms of dementia.

**Literature Reference:**

Resveratrol (RSV) is a polyphenol produced by plants under stressful conditions in the environment. This compound seems to exhibit some protective roles in several diseases ranging from cancer, metabolic and immune disorders, cardiovascular and neurodegenerative diseases, among others. However, the molecular mechanism by which is acting remain still unclear. Focusing on the Central Nervous System, it has been reported that this polyphenol is able to modulate the neurotransmitters release, suggesting a role through their respective receptors which most of them belong to the G-protein coupled receptor (GPCR) family. Adenosine, dopamine and group I metabotropic glutamate receptors have been found to be altered in neurodegenerative diseases such as Alzheimer’s and Parkinson’s disease. The aim of this study was to determine whether RSV intake was able to modulate the gene expression of these three GPCR receptor types by using SAMP8 mice which have been considered as Alzheimer disease model. Our results clearly show some significant differences on the gene expression modulation after RSV supplementation in 5 months old mice when compared to untreated mice. In the adenosinergic system, while A1R and A2AR were decreased, a significant increase on A3R mRNA levels was detected without changes on the A2BR gene expression. In the glutamatergic system, group I metabotropic glutamate receptors were analyzed, showing a significant increase only on mGluR5 gene expression. In the case of dopaminergic system, no changes were detected on D2R mRNA levels. Therefore, we conclude that RSV differentially modulates these three neurotransmission systems, which may suggest that protective role of this polyphenol could be related to GPCR-mediated signaling modulation.
EVALUATION OF NEUROPROTECTIVE EFFECTS OF ETHANOLIC EXTRACT OF CALIPHRURIA SUBEDENTATA AND DRUG GALANTHAMINE ON UNDIFFERENTIATED SH-SY5Y CELLS EXPOSURE TO AMYLOID BETA PEPTIDE (1-42)

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Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by the presence of neuritic plaques (NPs), and neurofibrillary tangles (NFTs). β-Amyloid peptide1-42 (Aβ1-42) is the principal component of NPs and it has been strongly associated to oxidative stress, as well as dysfunction of cholinergic neurotransmission system and cell death. The current therapeutics approaches for AD improve the symptoms temporarily; and despite intensive efforts, none of the treatments available today alters the course of the disease. One of the most promising approaches for treating this disease is to enhance the acetylcholine (ACh) level in brain using acetylcholinesterase inhibitors (AChEi); and among vegetable agents with therapeutic potential are the plants of the Amaryllidaceae family. The growing demand for galanthamine has prompted searches for new sources of this compound, as well as other bioactives with AChEi activity. This way, species of Amaryllidaceae family as C subedentata, genus endemic to Colombia and threatened by extinction, in previous phytochemical studies by classical methods were isolated different alkaloids which exert AChEi and antioxidant activity. This fact has motivated the screening of other alkaloids as possible modulators of the disease in addition to AChEi activity. In this context, the purpose of this study was to investigate whether C. subedentata extract and galanthamine modulate Aβ1-42-induced neurotoxicity in the undifferentiated SH-SY5Y cell line. In our work, galanthamine and C. subedentata extract were tested following Aβ1-42 treatments in SH-SY5Y cells used as a model system, mimicking a similar condition observed in neurological disorders as AD. To understand the mechanisms of neuroprotection, a set of biomarkers such as AChE inhibitory activity, clonogenic, cytokinesis block micronucleus cytome (CBMNcyt) and comet assays, beside transmission electron microscope and Docking molecular in silico analysis were realized. The results showed that C. subedentata extract and galanthamine were capable to reduce the Aβ1-42-induced cytotoxicity and genotoxicity, however, post-treatments with C. subedentata extract lead to a significantly recovery of cell survival and the different events Aβ1-42-induced neurotoxic. The 3D model of Docking molecular in silico indicated that alkaloids from C subedentata interacted with the recombinant human AChE enzyme (rhAChE)-binding sites and several of them present major affinity than galanthamine for the enzyme. Taken together, these findings indicate an additional mechanism resulted of the synergistic interaction of constituents present in the total extracts of Caliphruria subedentata higher than isolated metabolite. As far as we know, this is the first report to demonstrate antigenotoxic capacity exerted by members belong Amaryllidaceae family again AD. This hypothesis might be attractive in terms of efficiency of the neuroprotective compound toward preventing or delaying neuronal death in patients with neurodegenerative diseases.
EFFECT OF TOLUENE ON CORTICAL EXCITABILITY, NEUROPLASTICITY, AND COGNITIVE FUNCTIONS IN HEALTHY HUMANS

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Objectives: Numerous chemical substances in everyday life have a potential effect on brain functions, including brain physiology, and cognitive processes. This is caused by their impact on neuronal membranes, ion channels and receptors. Toluene, a widely used and commonly abused organic solvent, is a component of many colours, glue, and other materials and a lot of people are exposed to it in occupational settings on daily basis. Considering its common use, knowledge about acute neurophysiological effects of toluene on cortical excitability and plasticity, and its impact on motor and cognitive functions is required, however limited.

Purpose: In this study, we assess how neuroplasticity and cortical excitability are affected by acute exposure to 200 ppm toluene, and whether these effects are associated with motor performance decline.

Methods: Seven healthy right-handed subjects (26.3±3 years old) participated in two sessions, one with real and one with sham toluene exposure. Changes in corticospinal excitability were measured via motor evoked potentials (MEP) elicited by single-pulse TMS (transcranial magnetic stimulation, Magstim200) and resting motor threshold (RMT). Cortical inhibitory and facilitatory circuits were evaluated by short-interval intracortical inhibition (SICI), short-latency afferent inhibition, and intracortical facilitation (ICF) TMS protocols. tDCS (transcranial direct current stimulation, Soterix Medical, 1×1 tDCS Device) was employed to induce neuroplasticity in the motor cortex (Nitsche & Paulus, 2000) and motor performance was explored by a motor learning protocol, the serial reaction time task (SRTT).

Results: Toluene exposure resulted in reduced neuroplasticity (shown by abolished excitability enhancement induced via anodal tDCS, F(1,96)=18.91, p<0.01), reduced cortical facilitation (revealed by decreased facilitation in ICF, F(1,26)=9.12, p<0.01), and correspondingly diminished cognitive performance (shown by asymptotic slower increase of reaction time in SRTT in the presence of toluene). No significant changes were observed in RMT and cortical inhibition (evaluated by SICI).

Conclusions: Considering the cellular basis of toluene effects on central nervous system functions, which include perturbations of different neurotransmitter systems, e.g. increase in dopaminergic and GABAergic activity (Maclver, 2009) and decrease in glutamatergic and nicotinic receptor activity (Lo, Wu, Sue, & Chen, 2009), we expected that toluene exposure results in reduced neuroplasticity, enhanced cortical inhibition, reduced facilitation, and impaired cognitive performance. Our findings are consistent with these expectations. The results of this study might be helpful to guarantee safe acute exposure of people to this substance in their working environment.

Literature Reference
Disorders of the Nervous Systems
EFFECT OF IMMUNOTOXIN 192IgG-SAPORIN: BEHAVIORAL IMPAIRMENTS AND ALTERATION OF EXPRESSION OF MICROGLIA AND ENDOTHELIAL-SPECIFIC GENES

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Objectives: It is known that degeneration of cholinergic neurons is one of key events during development of Alzheimer’s disease.

Purpose: Here, we studied effect of intracerebroventricular injection of toxin saporin conjugated with antibody to receptor p75 on the learning performance of rats.

Methods: In three weeks after the injection we started behavioral testing after which we performed RNAseq and analyzed expression of genes in the hippocampus.

Results: Administration of the immunotoxin led to a significant increase in the total distance moved and higher velocity in the Morris Water Maze test (p<0.05) and slight impairment in passive avoidance learning. We found that during probe trial, when the platform was removed from the maze, saporin-treated rats spent significantly less time in a quadrant, where the platform was during training, and swam shorter distance in it, as compared to the control animals. In contrast, locomotor and exploratory activity in the open field task did not change as compared to the control. Analysis of rat behavior in T-maze did not reveal any significant differences in the number of errors compared to the control. Analysis of differentially expressed genes in the hippocampus using RNAseq showed that the expression of majority of microglia-specific genes was elevated whereas expression of majority of endothelium-specific genes decreased.

Conclusions: These data suggest that degeneration of cholinergic neurons leads not only to some disturbances in memory but also to alterations in functioning of microglia and vascular endothelium.

The work was supported by Grant of Russian Science Foundation No 16-15-10403.
HIPPOCAMPAL MEMBRANE EXPRESSION OF AMPA RECEPTORS, TNFα LEVELS, AND SPATIAL REFERENCE MEMORY ARE RESTORED BY IN VIVO ADMINISTRATION OF EXTRACELLULAR cGMP IN HYPERAMMONEMIC RATS
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Hepatic encephalopathy (HE) is a complex neuropsychiatric syndrome which appears in patients with liver failure. In these patients, the synergic effect of hyperammonemia and neuroinflammation is the main factor contributing to motor and cognitive impairments, which include working and spatial memory deficits. Rats with hepatic encephalopathy also show spatial learning impairment as well as deficits in learning a conditioned discrimination task in the Y-maze. It has been demonstrated that extracellular cGMP restore learning in the Y-maze in rats with hyperammonemia.

The aim of this work was to assess if extracellular cGMP restore spatial learning in rats with hyperammonemia as well as to unveil the mechanisms implicated. With that purpose, it has been studied if cGMP reduce neuroinflammation and modulate membrane expression of AMPA and NMDA ionotropic glutamate receptors in the hippocampus of these rats.

In hyperammonemic and control male Wistar rats, extracellular cGMP was administrated in vivo during 28 days through intracranial perfusion with osmotic minipumps. During this period, Morris water maze and radial maze were the chosen tasks to study spatial reference and working memory in the animals. After the sacrifice, neuroinflammation was assessed by immunohistochemistry and western blot, while membrane expression of receptors was studied using a crosslinking protocol.

Chronic hyperammonemia impairs reference memory, activates microglia, increases TNFα expression and alters membrane expression of AMPA receptors in the hippocampus, and all these effects are reversed by extracellular cGMP. Nevertheless, it has no effect in other alterations induced by hyperammonemia, such as working memory impairment, astrocytes activation, increased IL-1β levels and alterations in the membrane expression of NMDA receptors in the hippocampus.

These results show that there is more than one mechanism implicated in the effect of neuroinflammation in cognitive impairment leaded by hyperammonemia. One of them, which include microglia activation, TNFα expression, alterations in surface expression of AMPA receptors and reference memory impairment is modulated by cGMP and can be reversed by its in vivo administration to hyperammonemic rats.
HIGH DOSES OF PALIPERIDONE PALMITATE IN PATIENTS WITH SEVERE RESISTANT SCHIZOPHRENIA: EFFECTIVENESS AND TOLERABILITY

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Objectives/Purpose
Tolerability of antipsychotics is important to increase treatment compliance, and consequently to reach rehabilitation goals in people with severe schizophrenia. The aim of this study was to evaluate effectiveness and tolerability of doses of paliperidone palmitate (PP) of 175 mg-eq. and over/28 day in people with severe schizophrenia (CGI-S of 5 and over) and their retention in treatment.

Methods
36-month prospective, observational study of patients with severe schizophrenia who were treated with 175 mg and over every 28 days of PP in order to get clinical stabilization (N=30). Assessment included: CGI-S, WHO-DAS, Camberwell Assessment of Need (CAN) and Medication Adherence Report Scale (MARS). Laboratory tests, weight, side effects, reasons for discharge and hospital admissions were measured.

Results
The average dose of PP was 228.7 (11.9) mg-eq/28 days. There was one discharge due to side effects. Weight and prolactin levels decrease. After three years, CGI-S (p<0.01), CAN (p<0.01) and WHO-DAS in the four areas (p<0.05) decreased. The MARS increased (p<0.001). There were less hospital admissions (p<0.001). Retention in treatment after 36 months was 90%.

Conclusions
Tolerability of 175 mg-eq/28 days and over of paliperidone palmitate was very good, being useful in improving treatment adherence in severely ill patients, and helping in this way to get clinical stabilization and better social functioning. These patients were clozapine candidates, so high doses of PP could be an alternative for them.
THE LABORATORY MODEL OF CHRONIC BEHAVIORAL PATHOLOGY - KRUSHINSKY-MOLDKINA (KM) RAT STRAIN WITH AUDIOGENIC EPILEPSY
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The Krushinsky-Molodkina rat strain is the important member of audiogenic prone rat strains group. The strain selection started in 1947 on the basis of local Wistar population. Now KM is the inbred strain with the history of more than 40 generations of close brother-sister matings. The 100% of KM rats develop the prompt generalized clonic-tonic seizures after 5-9 sec of loud sound exposure (bell sound, 120dB). The clonic-tonic seizures of KM rats are preceded by the typical wild-run stage, which is typical for audiogenic epilepsy, which is also known as “clonic run”. At the same time after the end of seizure fit the intense postictal catalepsy develops in KM rats (the specific state of body muscle tone). The repetitive daily sound exposure results in the emergence (after 12-18 daily sessions) of different type of seizures of another category - myoclonic seizures. The single but prolonged sound exposure – 15 minutes of repetitive loud and weak 10 s sounds resulted in paresis and palsy symptoms and sometimes of animal death, which are the consequences of brain circulation disorders. The valuable data were obtained on the numerous anticonvulsant drugs although laboratory model needs now the new group of comparison as Wistar and KM rats were bred separately for a long time. Aiming to create it the new rat strain was selected for the “absence of audiogenic fit” (strain “0”), which was initiated on the basis of KM x Wistar (with two backcrosses on KM strain). The parallel audiogenic seizure prone strain (strain “4”) was selected as well, and this triade was already tested in pharmacological experiments with chronic fluoxetine treatment as the example. It was demonstrated that no comorbidity of anxiety, depression and audiogenic seizures were detected when several rat genotypes were investigated. Supported by RFBR, grant N 15-04-01732 a. State registration theme: “Neurobiology of animal behavior” N NIOKTR AAAA-A16-116021660055-1.
ACTIVITY CHANGES IN THE STRIATUM-CORTICO-LIMBIC CIRCUITRY AFTER MPFC AND CEREBELLAR DEACTIVATIONS. AN INHIBITORY PATHWAY TO REGULATE RESPONSES TRIGGERED BY COCAINE-RELATED CUES

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Objectives: In the present investigation, we wonder whether impairment of prefronto-cerebellar networks might change the activity patterns in functional related regions of the striatum-cortico-limbic circuitry.

Purpose: We evaluated effects of deactivations in different areas of mPFC and cerebellar cortex in rats undergoing conditioning training in order to acquire preference towards an olfactory stimulus paired with cocaine.

Methods: Six experimental groups and their sham controls were training in cocaine-induced preference conditioning. Two groups of rats were subjected ten minutes before every conditioning trial to a temporary prelimbic or infralimbic inactivation by lidocaine. Another two groups were lesioned in either the ventral or dorsal region of the posterior cerebellar vermis with quinolinic acid before training. Finally, we trained two groups of rats under simultaneous deactivation of infralimbic/dorsal regions or prelimbic/ventral regions. All animals received eight cocaine paired sessions on alternate days (16 days). Preference was evaluated 48h after the last cocaine administration in a 30min drug-free test. Immunohistochemistry was performed on free-floating sections. Tissue was incubated for 48h with a polyclonal primary antibody, rabbit anti-cFos.

Results: Our results indicate higher cFos levels in specific regions of infralimbic, nucleus accumbens, amygdala and thalamus after the dorsal cerebellar lesion. After infralimbic deactivations, we observed higher cFos levels in the dorsal cerebellar region. This increased neuronal activity was associated with a facilitation effect on the acquisition of cocaine-induced preference conditioning. A simultaneous inactivation of both sites prevented those effects.

Conclusions: These findings suggest that the infralimbic cortex and dorsal posterior vermis interact within the larger circuitry that enables the inhibitory regulation of those behavioural responses triggered by drug-related memories.
STOPPING NATURAL DESIRES: DEFINING THE HYPERSEXUALITY NETWORK IN IMPULSE CONTROL DISORDERS

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Objectives: Humans are prone to approach natural stimuli with positive connotation such as food or sex. Impulse control disorders (ICD) is a side-effect of dopamine agonist medication to treat motor symptoms in Parkinson’s disease (PD) whereby desire towards natural rewards increases and uncontrolled actions occur as a result.

Purpose: We investigated the behavioral and neural basis responsible for hypersexual ICD using an erotic stop-signal task inside an MRI scanner.

Methods: Male ICD (n=13; age= 64.3), PD patients (n=15; age= 65.1) performed the task while on and off medicated and compared to healthy male controls (n=12; age=58.9). The erotic stop-signal task presented participants either an erotic or non-erotic image (1s), followed by a go signal sometimes replaced with a stop signal (33%).

Results: Behaviorally, ICD patients were slower to inhibit actions that followed an erotic image as compared to PD patients and controls. Erotic stimuli produced a BOLD increment in ICD as compared to PD group (on medication) over globus pallidum (main effect; z = 3.32, p < .01). When stopping was successful in the erotic condition, PD and controls activated anterior putamen and caudate while ICD patients activate the posterior putamen section (z = 3.12, p < .01). However, in unsuccessful stop, an enlarged activity over supplementary motor area and globus pallidus external was detected in ICD patients (z=2.42, p < .01).

Conclusions: These findings provide an aberrant cortico-subcortical interaction during stopping sexual desire in hypersexual ICD patients. The study thus represents the initial step towards defining optimal targets for neuromodulation approaches in ICD treatment.
CHOLINE TREATMENT IMPROVES BEHAVIORAL ASPECTS ASSOCIATED WITH AUTISM IN A MOUSE MODEL

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Objectives: Autism Spectrum Disorders present with stereotyped-behaviors, anxiety and memory difficulties. In humans and mice, Methyltetrahydrofolate-reductase (MTHFR) deficiency is a risk-factor for autistic behavior. Choline is a nutrient essential for neurotransmitter synthesis, cell-membrane signaling, lipid transport and methyl-group metabolism. We investigated whether choline treatment alleviates behaviors related to autistic phenotype in MTHFR-deficient mice.

Purpose: Investigate whether choline-treatment in young-adult mice improves autism-associated behavioral aspects.

Methods: 2-2.5 months-old MTHFR+/+ (wildtype) and MTHFR-heterozygote knockout (MTHFR+-) mice were administered either 0.003% choline-supplemented or ordinary drinking-water for two weeks pre and during post-choline round of testing. Behavior was evaluated in autism-related tests.

Results: In the open field test, monitoring general and anxiety-like behavior, mice moved a similar distance regardless of choline-treatment but choline significantly decreased the duration the MTHFR+/- group spent in the center of the arena (p= 0.0004), and their frequency moving to the margins (p=0.005) and to the center (p=0.002).

Memory was tested in the object-recognition test. Wildtype mice spent 80% of the exploration-time with the novel object; MTHFR+/- mice had no preference (58%). Choline rescued the preference of the MTHFR+/- group for the novel object (wildtype: 73%, MTHFR+/: 74%, p= 0.96).

Nesting behavior was quantified by processing of the nesting material as an index of repetitive behavior. The MTHFR+/- group processed their nests 63% compared to 33% demonstrated by the wildtype group (p=0.05), a difference eradicated by choline.

Repetitive behavior was also assayed by marble-burying test. MTHFR+/- mice buried 10.8 vs. 7.0 marbles (averages) by the wildtype group (p=0.02). Choline abolished this difference (MTHFR+/- and wildtype groups buried 7 marbles, p=0.93).

Conclusions: Choline-treatment is beneficial in decreasing anxiety- and repetitive-behavior and enhancing memory-skills. Rescue of behavioral-impairment at young-adulthood suggests that a critical intervention-window is still open even after the end of the developmental period.
THE EVIDENCE FOR ALTERED BRAIN EXPRESSION OF BRAIN-DERIVED NEUROTROPHIC FACTOR IN SOCIALLY ISOLATED RATS

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Objectives: Research suggests that disrupted signaling via brain-derived neurotrophic factor (BDNF) may be involved in mediating the negative effects of stress on the brain. Social isolation widely used in rats to elicit chronic stress and model symptoms of major mental illness, such as schizophrenia and depression. The objective of our research was to comprehensively review the findings on the expression of BDNF and its receptor TrkB in the brain of rats reared or housed in social isolation.

Purpose: To assess the consensus on the role and the determinants of BDNF/TrkB expression in a commonly used experimental rat model of stress-related psychiatric disorders and highlight future research priorities.

Methods: We searched Medline PubMed, Scopus and Web of Science databases for papers written in English (published until February 2017). Two researchers independently screened all titles and abstracts for inclusion. Only original research reports were considered. Data were extracted from full-text reports.

Results: The search yielded 478 citations (after removing duplicates). After the assessment of titles/abstracts, 35 were retained. After the assessment of full-texts, 21 were considered as relevant and were included into the analysis. Across all age groups (postweaning, adolescent, adult rats), majority of the identified studies (16/21) reported a decreased expression of BDNF in the hippocampus. There are far less published data on BDNF expression in other brain regions. Studies on the expression of TrkB receptors are lacking. Data are also scarce to assess the behavioral changes as a function of BDNF expression, but the downregulation of BDNF seems to be associated with increased anxiety-like symptoms.

Conclusions: The reviewed data generally support the putative involvement of BDNF in the pathogenesis of stress-related mental illness. However, the mechanisms linking chronic social isolation, BDNF expression and the elicited behavioral alterations are currently unknown and should be addressed by future studies.

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OLIGOMERS-INDUCED NEURODEGENERATION: RELEVANCE TO PARKINSON’S AND ALZHEIMER’S DISEASES
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Objectives: To assess the effects of misfolded protein oligomers as new in vitro and in vivo model of neurodegenerative diseases

Purpose: The purpose of this project is to develop and validate new rodent models of Parkinson’s and Alzheimer’s diseases using oligomers

Methods: We developed a highly-defined process to produce stable oligomers of Aβ, human tau and α-synuclein (αSO) without chemical modification or helper proteins. We investigated the oligomer-induced neurodegeneration in vitro in rodent primary neurons and in human neurons derived from iPS cells, as well as the release of pro-inflammatory cytokines from primary astrocytes. Behavioural effects of the oligomers injected intracerebrally were also investigated

Results: In-vitro, oligomer preparations induce dose- and time-dependent neurodegeneration in rodent primary neurons and human neurons derived from iPS cells, as well as the release of pro-inflammatory cytokines from primary astrocytes. Cognitive analysis of mice injected intracerebrally with the small amounts of the oligomers revealed deficits reminiscent of the early phases of the corresponding diseases. In addition, mice injected with αSO and challenged with amphetamine displayed an anticlockwise circling behaviour, typical of dopaminergic deficit and relevant to Parkinson’s disease. In mice, intracerebral injection of oligomers induced an increase in inflammatory markers, whilst decreasing synaptic ones.

Conclusions: This work strongly supports the hypothesis that small soluble misfolded protein aggregates, the so-called oligomers, are the toxic species responsible for disease progression and targets counteracting their effects are thought to give rise to novel therapeutic intervention for neurodegenerative diseases.
EFFECTS OF VOLUNTARY WHEEL RUNNING AND CHRONIC ADMINISTRATION OF 8-OH-DPAT ON ADULT NEUROGENESIS IN MICE WITH AN OVEREXPRESSION OF THE POSTSYNAPTIC SEROTONIN$_{1A}$ RECEPTOR

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Objectives: The exact pathological mechanisms of major depression are still unknown. In the present study, we want to elucidate the correlation between major depression, adult neurogenesis and the postsynaptic serotonin$_{1A}$ receptor (5-HT$_{1A}$R).

Purpose: The purpose of our study is to specify the role of the postsynaptic 5-HT$_{1A}$R in pharmacological and exercise-induced adult hippocampal neurogenesis.

Methods: Experiments were carried out in mice with a permanent overexpression of postsynaptic 5-HT$_{1A}$Rs (OE mice). Young adult OE and wildtype (WT) mice were treated 15 days with the 5-HT$_{1A}$R agonist 8-OH-DPAT or vehicle. For investigating the effects on exercise-induced adult hippocampal neurogenesis, mice had free access to a running wheel over the same period (controls without wheels). Newborn cells were labelled by bromodeoxyuridine (BrdU), which was injected on the last three days of treatment or access to the running wheel, respectively. One day (proliferation) or three weeks (survival) after the last BrdU injection, mice were sacrificed and brains were immunohistochemically stained for counting of BrdU-reactive cells in the dentate gyrus (DG) of the hippocampus.

Results: Chronic pharmacological 5-HT$_{1A}$R stimulation did not alter adult neurogenesis in OE mice and WT controls compared to vehicle treated mice. Voluntary wheel running significantly increased the number of newly born cells in both groups without significant differences between the genotypes.

Conclusions: The previously found increased adult neurogenesis in naïve OE mice (Noto et al., 2016), was not detected in the present study. This may have been caused by chronic injection stress or compensatory down-regulation of the 5-HT$_{1A}$R. A proneurogenic effect of voluntary wheel running could be confirmed in our study. However, the postsynaptic 5-HT$_{1A}$R seems not to play a major role in this process. Behavioural studies concerning depressive-like behaviour and hippocampus-dependent learning are under the way to gain more information about major depression and the postsynaptic 5-HT$_{1A}$R.

Literature Reference
COCAINE-INDUCED REGULATION OF PERINEURONAL NETS IN THE INFRALIMBIC-CEREBELLUM PATHWAY
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Objectives. A Perineuronal net (PNN) is an aggregation of extracellular matrix molecules in a net-like manner that envelopes the perikaryon and proximal neurites of special subsets of neurons. In the adult brain, PNNs create restrictive conditions for synaptic plasticity, so they have been proposed as a candidate mechanism for learning and memory. The present research aimed to assess PNN expression in the infralimbic cortex and dorsal cerebellum after a repeated experience with cocaine.

Purpose. We evaluated deactivation effects of either the infralimbic cortex or lobule VIII of the vermis on cocaine-induced preference conditioning and PNN expression in rats.

Methods. Six experimental groups were trained to acquired cocaine-induced odor preference conditioning. One group was subjected to a deactivation of the infralimbic cortex by lidocaine before every conditioning trial. Another one was lesioned in the dorsal region of the posterior cerebellar vermis with quinolinic acid before training. The other four were their corresponding sham and pseudo-conditioning groups. All groups received eight cocaine-paired sessions on alternate days (16 days). Preference was evaluated in a 30min drug-free test. PNNs were detected using Lectin from Wisteria Floribunda Agglutinin (WFA) immunolabelling.

Results. We found that either the deactivation of the infralimbic cortex or a lesion in the dorsal cerebellum promote preference towards cocaine-associated and regulates the expression of PNNs in the distal structure, but in a different manner. The deactivation of the infralimbic cortex increases the intensity of PNNs in the dorsal cerebellum, producing stronger PNNs. However, a lesion of the dorsal cerebellum enhances the number of cells expressing a PNN in the infralimbic cortex.

Conclusions. Both structures seem to be part of a functional and structural network which would work on producing an inhibitory effect on the acquisition of drug-dependent memories. PNNs in this network might be an important mechanism for storage of drug-induced conditioned memories.
PRENATAL VALPROATE INDUCES AUTISTIC-LIKE BEHAVIOR ASSOCIATED TO DECREASED LONG 3’UTR-BDNF TRANSCRIPTS LEVEL AND INCREASED MGLUR1a-IR IN SPECIFIC AREAS OF JUVENILE RAT HIPPOCAMPUS

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Autism is a neurodevelopmental disorder characterized by a deep deficit in communication and social interaction, accompanied by stereotyped/repetitive behavior. A defect in the synaptic pruning-dependent maturation of neural circuits has been indicated as the main neurobiological alteration in autistic syndromes. Also, synaptic mRNA translation activated by mGluR5 signaling, has been suggested as a convergent physiopathological pathway. However, the role of the other member of class I mGluRs, as mGluR1a, and the levels of dendritically targeted mRNAs have been poorly studied.

Objective: Explore new molecular targets to treat autism, studying mGluR1a immunoreactivity (mGluR1a-IR) and the levels of prototypic dendritic transcripts: panBDNF (total transcripts), \(L-bdnf\) (the pruning-related long-3’UTR BDNF transcript), CamKII and Arc in an animal model of autism.

Purpose: We have studied the effect of prenatal exposition to valproate, a well validated model of induced autism, in the hippocampal mGluR1a-IR; and panBDNF, \(L-bdnf\), CamKII and Arc levels.

Methods: Pregnant Sprague-Dawley rats were treated with 450 mg/Kg of sodium valproate in embryonic day 12.5. Behavior was evaluated at PN30 and, 24 h later, brain was processed for mGluR1a-IR analysis by immunohistochemistry and \textit{in situ} hybridization analyses of transcripts.

Results: Experimental rats exhibited autistic-like profile, characterized by reduced sociability, anxiety and repetitive behavior. Valproate treated rats also showed increased mGluR1a-IR in hilar and CA1 oriens/alveus interneurons. PanBDNF, CamKII and Arc transcripts showed no changes or slightly reduction in specific regions. In contrast, \(L-BDNF\) showed extended reduction involving dentate gyrus and CA3 subfields.

Conclusion: Prenatal valproate increased mGluR1a-IR in hippocampal areas implicated in inhibitory feed-back loops, while decreased \(L-bdnf\) in dentate gyrus-CA3 pathway. Knowing the role of mGluR1a and \(L-bdnf\) in synaptic pruning, these data may be relevant to understand the pruning deficit in autism and may enlighten new therapeutic targets.
PHARMACOLOGICAL APPROACHES IN A NEW MOUSE MODEL OF NEURODEVELOPMENTAL DISORDERS
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Objectives: To test the effect of different drugs able to improve behavioural deficits in a new mouse model of neurodevelopmental disorders (NDDs).

Purpose: NDDs are a group of disorders in which the development of the central nervous system is altered. Recently, we demonstrated that a deletion of the NFKB1 gene that encodes for the p50 NF-κB pathway subunit produces a mouse with neurodevelopmental alterations. In particular, p50 KO mice displayed abnormal columnar organization in the somatosensory cortex, altered neurite orientation, hyperactivity and impairment in social behaviours, with a reduction in social interaction. In order to act on hyperactivity of p50 KO mice, initially, in this work we treated the mice with risperidone. After, we evaluated effect on social interaction of a melanocortin 4 receptor agonist associated to oxytocin production.

Methods: Risperidone (0.03, 0.06, 0.125, 0.5, 1 mg/kg in a 10 mL/kg volume) or THIQ (N-[(1R)-1-[(4-Chlorophenyl)methyl]-2-[4-cyclohexyl-4-(1H-1,2,4-triazol-1-ylmethyl)-1-piperidinyl]-2-oxoethyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxamide, 0.5, 1, 2 mg/kg in a 10 mL/kg volume) were administered via intraperitoneal injection 30 min before testing for the open field and social approach tests. Subsequently, mice were sacrificed and brain areas were isolated for molecular analysis. We measured in cortex DRD2 and HTR2A mRNA expression; in hypothalamus oxytocin pathway expression by PCR-real time and radioimmunoassay.

Results: Risperidone treatment improves only hyperactivity but not social interaction in p50 KO mice. Moreover we found that DRD2 mRNA level was significantly higher in the cortex of p50 KO compared to WT and risperidone treatment did not cause any significant change. Regarding THIQ treatment, p50 KO mice present lower oxytocin and oxytocin receptor mRNA expression levels in the hypothalamus compared to WT mice. Also, THIQ treatment significantly increased social interaction both in WT and p50 KO mice acting on endogenous oxytocin production.

Conclusions: Our data confirmed that the risperidone is effective in reducing aggressive behaviour and hyperactivity. More interesting, the involvement of the melanocortin 4 receptor agonism in social behaviour oxytocin-mediated will lay the foundations for future therapeutic strategies in NDDs.
GLUN3A KNOCKOUT MICE EXHIBIT REDUCED ANXIETY AND FACILITATED ASSOCIATIVE LEARNING

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Anxiety and stress-related disorders are characterized by a persistent or disproportionately enhanced vigilance that interferes with normal life. Despite their prevalence, molecular and cellular basis is unknown. One important clue to identify the molecular substrate of anxiety is the comorbidity among different psychiatric disorders. For example, the circuits involved in substance abuse and addiction largely overlap with the ones thought to underlie anxiety. Of interest in this context are the non-conventional GluN3A subunits of NMDA-type glutamate receptors (NMDARS) which are highly expressed in the brain just before and throughout the critical period of postnatal development. GluN3A subunits are principal modulators of network rewiring by early experience. Early neuronal circuit rewiring has a long-lasting impact and shapes adult emotional and affective behavior, and mutations in GRIN3A (the gene encoding GluN3A) have been linked to nicotine, alcohol and cocaine addiction in adult individuals a,b.

To address whether altered GluN3A expression modulates anxiety responses, we applied a battery of behavioral tasks to test anxiety and stress in knockout mice lacking GluN3A (GluN3A KO) and transgenic mice that express GluN3A beyond its physiological time window (GFP-GluN3A dt). Our analysis revealed a robust anxiolytic-like phenotype on juvenile and adult mice that lack GluN3A expression (GluN3A KO). By contrast, GFP-GluN3A dt exhibit anxiogenic features. We further explored the consequences of altered GluN3A expression on the emotional responses to sub-chronic repeated stress and found that GluN3A KO mice are remarkably resilient to sub-chronic stress. We finally found that, GluN3A KO mice showed improved associative fear-learning in the Conditioned Taste Aversion Test. Our results reveal putative new molecular targets to treat neurological disorders associated to stress and anxiety. Further work is attempting to define the molecular pathway affected in different brain areas associated to stress, anxiety and fear learning, with a focus of pathways affecting di novo protein translation.


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EFFECT OF TRIIODOTHYRONINE ON BRAIN MYELINATION AND ASTROGLIOSIS AFTER CUPRIZONE-INDUCED DEMYELINATION IN MICE
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Purpose: Chronic demyelination and plaque formation in multiple sclerosis is accompanied by persisting astrogliosis, negatively influencing central nervous system recovery and remyelination. Triiodothyronin (T3) is thought to enhance remyelination in the adult brain by the induction of oligodendrocyte maturation. We investigated additional astrocyte-mediated mechanisms by which T3 might promote remyelination in chronically demyelinated lesions using the cuprizone mouse model.

Method: C57BL/6 mice were fed cuprizone for 12 weeks to induce lesions with an impaired remyelination capacity. While the expression of oligodenrocyte progenitor markers, i.e., platelet derived growth factor-α receptor was not affected by T3 administration, myelination status, myelin protein expression as well as total and adult oligodendrocyte numbers were markedly increased compared to cuprizone treated controls. In addition to these effects on oligodendrocyte numbers and function, astrogliosis but not microgliosis was ameliorated by T3 administration. Intermediate filament proteins vimentin and nestin as well as the extracellular matrix component tenascin C were significantly reduced after T3 exposure, indicating additional effects of T3 on astrocytes and astrogliosis.

Conclusion: Our data clearly indicate that T3 promotes remyelination in chronic lesions by both enhancing oligodendrocyte maturation and attenuating astrogliosis.

Keywords: Cuprizone Demyelination Astrogliosis Multiple sclerosis Triiodothyronine
Neuropathological Changes in the Transgenic Mouse Model of Alzheimer’s Disease

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Purpose: Alzheimer’s disease (AD) is a uniquely human disorder. Although the pathogenesis of AD is not fully understood, growing evidence indicates that the deposition of beta-amyloid (Aβ) and the local reactions of various cell types to this protein play major roles in the development of the disease.

Methods: In the present study transgenic mice expressing mutant amyloid precursor protein (APP) has been used. These mice exhibit selective neuronal death in the brain regions that are most affected in AD, suggesting that amyloid plaque formation is directly involved in AD neurons loss. Brains from 12 transgenic animals and 12 age-matched non transgenic littermate controls (1 and 2 years old) were examined histopathologically.

Results: One year old transgenic animals (n=6) exhibit deposits of human Aβ in the hippocampus, corpus callosum and cerebral cortex. By 2 years of age, a great number of diffuse and mature plaques were present in the cortex and hippocampus, and subcortical regions like thalamus and striatum. Another major finding was reduction of cholinergic cells in the medial septum, striatum and diagonal band of Broca.

Conclusion: The present data are consistent with the hypothesis that the neuropathology begins in the cerebral cortex and hippocampus before spreading in a retrograde fashion to subcortical regions.
THE MYELIN MUTANT RAT TAIEP SHOWED AN ALTERATION ON THE SPEED OF WALKING IN THE CATWALK SYSTEM
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Taiep rat is a myelin mutant with progressive motor syndrome characterized by: tremor, ataxia, immobility, epilepsy and paralysis. The mutant had an initial hypomyelination followed by progressive demyelination in the central nervous system. The alteration is due an accumulation of microtubules in the cytoplasm and its processes in the oligodendrocytes.

**Objective:** The aim of this study was to analyze stepping pattern and coordination during locomotion in *taiep* and control Sprague-Dawley (SD) rats.

**Methods:** The rats were maintained in standard conditions with 12/12 light-dark cycle (lights on at 0700). Rats had free access to rodent pellets and purified water. Rats were trained to walk along runway by 3 days and then recorded gait analysis one time per month using CatWalk system (Noldus, Netherlands) between 1 to 6 months of age in both groups of rats.

**Results:** Our results showed the speed of walking had a significantly decrease in *taiep* respect to SD rats from 1 to 6 months of age (P<0.01), with lower stride length cadency, but these differences are not due to allometric factor. The stance and swing phase of gait analysis showed a decrease in *taiep* rats respect to SD rats at all ages (P<0.01). Additionally, *taiep* rats had a significant increase in the large and width of the support base along the period of analysis (P<0.01). These results showed that demyelination induced change in the support base probable to counter ataxia and tremor in this myelin mutant.

**Conclusions:** Taiep rats is an adequate model for myelination diseases, particularly multiple sclerosis, and for testing new treatments to improve locomotion.

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A BEHAVIORAL DISSECTION OF COGNITIVE COMPETENCES OF Fmr1 KO MICE IN CONTINGENCY LEARNING AND REVERSAL

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Intellectual disability, albeit in variable degree, is the most common and prominent behavioral phenotype in human Fragile-X syndrome (FXS). Cognitive impairments in affected people are known to be inversely correlated to the availability of the FMR protein. Surprisingly, learning impairments in mice carrying the constitutive, complete deletion of Fmr1 gene (Fmr1 ko) are relatively subtle, and difficult to replicate, as witnessed by the largely contradictory reports of the literature.

**Purpose:** the unequivocal identification of a compromised cognitive competence is of paramount importance for the use of this mouse model to develop therapeutic strategies to the human syndrome.

**Methods:** In the quest for a more robust and consistent cognitive phenotype, we tested Fmr1 ko mice of the C57BL/6J and FVB/N strains in a series of learning paradigms differing to each other in the contribution of the spatial information that could be used to solve these tasks.

**Results:** Trace fear conditioning, place learning in a Morris water maze, and food-rewarded place learning in a small arena and in a T-maze, requiring a win-stay strategy, were not impaired in Fmr1-ko mice. However, a slower acquisition of a place/reward contingency reversal appeared in the more simplified arenas. In visual discrimination tasks performed in a small box, a clear and consistent deficit appeared upon reward contingency reversal; these deficits appeared even for the acquisition of the first associative rule, and especially so for FVB/N mice, when spatial information came into conflict with the cue–contingency rule.

**Conclusions:** Cognitive impairments of Fmr- ko mice seem better detectable in simplified settings. Cognitive tasks involving hippocampal as well as medial frontal cortical regions are relatively spared in Fmr1 ko mice, which instead show consistent impairments in the contingency reversal steps of simple visual – yet not spatial – discrimination tasks, suggesting orbitofrontal regions as mostly affected in the mouse model of FXS.
ELECTROACUPUNCTURE PROMOTES THE DIFFERENTIATION OF GRAFTED TRKB GENE-MODIFIED MESENCHYMAL STEM CELLS AS WELL AS FUNCTIONAL RECOVERY IN ISCHEMIC STROKE  
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Objectives: Transplantation with mesenchymal stem cells (MSCs) has been used to improve functional outcomes in a rodent model of ischemic stroke. This study attempted to graft TrkB receptor gene modified MSCs (TrkB-MSCs) into the peri-infarct region of the lesioned brain and investigate whether therapeutic electroacupuncture (EA) stimulation could promote the survival and differentiation of grafted TrkB-MSCs.

Purpose: In this study, we show the evidence that EA stimulation can increase mature brain-derived neurotrophic factor (BDNF) and neurotrophin-4/5 (NT4) levels of damaged brain and promote the survival and differentiation of TrkB-MSCs into neuron-like cells as well as further functional improvement after ischemic stroke.

Methods: EA stimulation with 2 Hz was applied at two acupoints to Baihui (GV20) and Dazhui (GV14) in middle cerebral artery occlusion (MCAO) mice. CM-DiI labeled MSCs, which were isolated and purified from mouse bone marrow, were transplanted into the damaged brain at 5 days after MCAO. We performed behaviour tests at 15, 27, and 30 days after MCAO using corner, cylinder, rotarod, wire grip, and passive avoidance test. To confirm the survival and differentiation of MSCs with secretion of growth factors, we performed immunohistochemistry using the specific markers.

Results: The results showed that TrkB-MSCs graft combined with EA stimulation (TrkB-MSCs+EA group) significantly improved the motor function by wire grip test as compared to MSCs+EA group. The largest number of transplanted DiI-labeled MSCs were detected in TrkB-MSCs+EA group at 30 days after MCAO. Some of the differentiation into immature neuroblasts (Dcx⁺), astrocytes (GFAP⁺), or OPCs (PDGFRα⁺) was detected, however there was no significant differences between groups. TrkB-MSCs+EA treatment could increase the secretion of mature BDNF or NT4 compared to MSCs+EA. To confirm the specific effects of TrkB, we showed that treatment of T-MSCs+EA animals following MCAO with a selective TrkB antagonist, ANA-12, produced losses of DiI-labeled MSCs and motor functions that were ameliorated by EA stimulation. Furthermore, at 60 days following MCAO, we observed that TrkB-MSCs+EA group was more differentiated into neuron-like cells than MSCs+EA group.

Conclusions: The present results have shown that TrkB-MSC transplantation combined with EA stimulation can more promote mature BDNF and NT4 expression in the lesion site, and further enhance the grafted TrkB-MSCs to differentiate into neuron-like cells, and improve behavioural function after ischemic stroke. Our results indicate TrkB-MSC transplantation combined with EA stimulation may be a new strategy for treatment of cerebral ischemic stroke.
EFFECT OF ANTIEPILEPTIC DRUGS IN A NEW MODEL OF ABSENCE SEIZURES: THE TAIQP RAT
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Absence seizure epilepsy is characterized by generalized spike-wave discharges (SWD) with loss of consciousness affecting about 10% of all pediatric patients with epilepsy, among them 30% are drug-resistant. The pathways responsible of generalized seizures are the thalamo-cortical and reticulo-cortical pathways through a reduction of gabaergic activity in the somatosensory cortex and a concomitant increase on the inhibition in the thalamus-cortical circuit.

The taeip rat exhibits an initial hypomyelination followed by a progressive demyelination of the central nervous system. In electroencephalographic (EEG) 24 h recordings taeip rats have cortical (SWD) with a peak frequency at 6.5 Hz theta band, and occurs spontaneously along 24 h. Absence seizure in taeip rat have a pharmacological profile similar to other rat models of absence seizures, being diminished by ethosuximide and lamotrigine.

Objective: The aim of the present study was to analyze the effect of gabapentin and pregabalin in a rat model of absence seizures.

Purpose: To evaluate the absence seizure in adult male taeip rats.

Methods: We analyzed the effects of oral administration of gabapentin (50, 100, 400 mg/Kg) y pregabalin (25, 50, 100 mg/Kg) on absence seizures and evaluate them during continuous electrographic recordings along circadian cycle. The rats were maintained in standard conditions with a 12/12 light-dark cycle (lights on at 0700). Rats were free access to rodent pellets and purified water. Rats were anesthetized by i.p. injection of ketamine-xylazine mixture and under stereotactic surgery, implanted electrodes for EEG recordings.

Results: The mean durations of absence seizures decreased around 30% in the first 2 h after the administration of 100 mg/Kg (2.72 ± 0.13s), 200 mg/Kg (2.94 ± 0.16s) and 400 mg/Kg (2.84 ± 0.12s) of gabapentin during 2 h after and up to 41% with 25 mg/Kg (2.66 ± 0.11s), 50 mg/Kg (2.42 ± 0.09s) and 100 mg/Kg (2.16 ± 0.15s) of pregabalin respect to control groups (4.04 ± 0.2s and 3.96 ± 14s, respectively). However the frequencies did not differ between treatments.

Conclusions: Pregabalin is more potent drug that modify the duration of absence seizures in myelin mutan taeip rat and could be consider by pediatricians.

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COMBINATION THERAPY OF TREADMILL TRAINING AND ELECTROACUPUNCTURE PRODUCE RECOVERY OF MOTOR FUNCTION FROM NEONATAL HYPOXIA-ISCHEMIA VIA ENHANCING OLIGODENDROGENESIS

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Objectives: Cerebral white matter injury, occurring through loss of oligodendrocytes, is the leading cause of cerebral palsy in prematurely-born children. We investigated whether combined treatment with treadmill training (TM) and electroacupuncture (EA) have synergic effect in motor function recovery via oligodendrogenesis in neonatal hypoxia-ischemia rat.

Purpose: In a cerebral palsy-like rat model, we show the evidence that combination therapy of TM and EA (TMEA) enhances motor function recovery and restores white matter via stimulation of oligodendrogenesis.

Methods: On postnatal day 7, Sprague-Dawley rat pups were subjected to left common carotid artery ligation followed by 2.5 h of hypoxia (8% O₂). After 14 days, TM training and EA treatment (2 Hz, 1 mA) performed five and three times per week for 3 weeks, respectively. For proliferative cell labelling, 5-bromo-2'-deoxyuridine solution (30 mg/kg) was intraperitoneally injected for a week. The motor dysfunction was evaluated by behaviour tests such as cylinder and rotarod test. Immunofluorescence staining and western blot analysis were performed to assess beneficial effects of TMEA on oligodendrogenesis.

Results: TMEA treatment significantly improved motor function by cylinder and rotarod tests compared to vehicle. EATM treatment showed an increase of thickness and expression of myelin basic protein (MBP) in the corpus callosum (CC) compared to vehicle. Proliferation of neuronal/glial antigen 2 (NG2) and 2',3'-cyclic-nucleotide 3'-phosphodiesterase (CNPase)-positive cells was significantly increased and phosphorylated cAMP-response element binding protein (pCREB)/NG2 or CNPase-double positive cells were also increased in the CC compare to group treated with TM or EA only. Furthermore, the mature BDNF-positive neuron was increased in the contralateral cortex of hemisphere. We confirmed that TMEA treatment increased the expression of MBP, NG2, CNPase, pCREB, and mature BDNF compared to other groups by western blot.

Conclusions: These data indicated that combination therapy of TM training and EA have synergic effect to enhance motor function via stimulation of oligodendrogenesis in neonatal hypoxia-ischemia, due to increase of BDNF and subsequent activation of CREB. Combination therapy of TM training and EA offers another treatment option for motor function recovery in cerebral palsy.
THREE-DIMENSIONAL TRANSPLANTATION OF ADULT NEURAL STEM CELLS IN AN ACUTE BRAIN INJURY MODEL
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Purpose: Brain injury is the leading cause of death and disability in the most active population. There is no definite clinical treatment for repair of damaged brain tissue. Application of nanoscaffolds supporting stem cells can be helpful.

Methods: The present study examined the effects of autologous adult neural stem/progenitor cells (NS/PCs) seeded in PuraMatrix in acute brain injury. The right brain subventricular zone of adult wistar rats was stereotactically harvested. Then, NS/PCs were cultured using neurosphere assay. At day 45, brain injury was performed in left side of brain and PBS, PuraMatrix, NS/PCs or PuraMatrix+NS/PCs was injected into the created cavity. The neurological status was evaluated for 4 weeks. Then, morphological and immunohistochemical studies were done.

Results: The neurologic status improved after treatment of brain injury with PuraMatrix, NS/PCs or PuraMatrix+NS/PCs. The lesion volume was decreased in PuraMatrix+NS/PCs. By 3D transplantation of NS/PCs, not only the rate of inflammation was reduced but also the survival rate in the site of injury was increased. In addition, the transplanted cells expressed the differentiation markers after 4 weeks.

Conclusion: Transplantation of adult NS/PCs in PuraMatrix may be a feasible method for reduction of tissue damage following brain injury.

Keywords: Brain Injury, Neural Stem Cells, Autologous Transplantation, Nanoscaffold, Neural Tissue Engineering.
LEPTIN IN THE NUCLEUS ACCUMBENS DIFFERENTIALLY REGULATES COCAINE-INDUCED LOCOMOTOR ACTIVITY
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Objectives: Leptin receptors exist in the nucleus accumbens (NAcc), a site important for mediating the motivated behaviors and locomotor activating properties of psychostimulant drugs. Besides controlling feeding behavior, we may be able to identify a new role for leptin in this site in modulating rewarding effects of psychomotor stimulants.
Purpose: In this study, we examined the effect of leptin in the NAcc on acute or chronic cocaine-induced locomotor activity in the rat.
Methods: First, leptin (0.1, 0.5 or 2.5 µg/side) was bilaterally microinjected into the NAcc, immediately followed by saline or acute cocaine (15 mg/kg, IP) injection, and rat’s locomotor activity was measured for 2 hours. Next, we further examined the effect of leptin microinjection on the expression of cocaine-induced behavioral sensitization. Rats were either saline or cocaine (15 mg/kg, IP) pre-exposed (once daily for 7 days), and after 2 weeks of withdrawal, their locomotor activity were measured with a systemic cocaine challenge following microinjection into the NAcc of either saline or leptin (0.1 or 2.5 µg/side).
Results: In the first experiment, leptin inhibits the increase of acute cocaine-induced locomotor activity in a dose-dependent manner, while leptin alone produces no significant change in basal locomotor activity. In the second experiment, microinjection into the NAcc of leptin dose-dependently enhances the increase of locomotor activity produced by cocaine challenge in cocaine pre-exposed group.
Conclusions: These findings indicate that leptin, an appetite-suppressing hormone, may have a bidirectional role in the NAcc to regulate locomotor activity following acute or chronic cocaine injections and further suggest that leptin may have a functional role in mediating psychostimulant-induced motivated behaviors.
STIMULATION OF THE BRAIN SEROTONIN RECEPTOR 7 RESCUES SENSORY-MOTOR GATING IMPAIRMENTS, EMOTIONAL MEMORY DEFICITS AND BRAIN MITOCHONDRIAL DYSFUNCTION IN A MOUSE MODEL OF RETT SYNDROME

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Objectives Rett syndrome (RTT) is a rare neurodevelopmental disorder, characterized by severe behavioral and physiological symptoms. Mutations in the methyl CpG binding protein 2 gene (MECP2) cause more than 95% of classic cases, and currently there is no cure for this disorder. Recently, we have demonstrated that neurobehavioral and brain molecular alterations can be rescued in a RTT mouse model, by pharmacological stimulation of the brain serotonin receptor 7 (5-HT7R). The 5-HT7R is crucially involved in the regulation of brain structural plasticity and cognitive processes and can be stimulated by systemic repeated treatment with LP-211, a brain-penetrant selective agonist.

Purpose: The present study verified whether repeated systemic treatment with LP-211 affects emotional memory and sensorymotor gating in RTT female mice. We also explored whether mitochondrial dysfunction can be rescued targeting the brain serotonin receptor 7 in RTT mouse brain.

Methods: MeCP2-308 female mice and wild type littersmates were daily ip injected with either LP-211 (0.25 mg/kg, once per day for 7 days) or vehicle. After the treatment, mice were tested in the Prepulse Inhibition (PPI) task and the cued Fear conditioning test (CFC). The brains were subsequently collected to investigate mitochondria functionality in RTT mouse brain and LP-211 effects thereon.

Results: The LP-211 treatment rescued sensory-motor gating impairments (PPI) and emotional memory-associative learning deficits (CFC) in RTT female mice. Moreover, LP-211 treatment rescued mitochondrial respiratory chain impairment and the reduced energy status in the brain of RTT female mice.

Conclusions: The present study demonstrates that the LP-211 treatment provides a widespread beneficial effect on the neurobehavioural phenotype of a RTT mouse model and provides the first evidence that RTT brain mitochondrial dysfunction can be rescued targeting the brain serotonin receptor 7.
**A₂A- and A₂C-adrenoceptor subtypes expression in postmortem prefrontal cortex of subjects with schizophrenia**

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α₂A- and α₂C-adrenoceptor subtypes are present in the human prefrontal cortex (PFC) and could play a role in schizophrenia. Moreover, α₂-adrenoceptors are targets for different antipsychotic drugs. In this context, the density of both α₂-adrenoceptor subtypes and their pre/postsynaptic expression has not been deeply evaluated in the PFC of schizophrenic subjects.

α₂A- and α₂C-adrenoceptor protein expression was determined by Western Blot in postmortem PFC of 24 subjects with an antemortem diagnosis of schizophrenia, and 24 controls. Both groups were matched by age, gender, and postmortem delay. Twelve of the schizophrenic subjects were taking antipsychotics at death (based on positive blood toxicological analysis), while the other 12 were antipsychotic-free (negative toxicology). α₂A- and α₂C-adrenoceptor expression was measured both in a preparation of synaptosomes and in postsynaptic membrane fractions, and was normalized for actin immunoreactivity as loading control.

α₂A-adrenoceptor protein expression in synaptosomes showed a non-significant trend to increase (+37%, p=0.114) in schizophrenia subjects compared with controls. When subjects were divided regarding antipsychotic treatment, there was a significant increase in α₂A-adrenoceptor expression in antipsychotic-treated (+78%, p=0.025) but not in antipsychotic-free subjects compared with controls. α₂A-adrenoceptor expression in postsynaptic fraction was significantly increased in schizophrenia subjects vs controls (+71%, p=0.026). Again, the increase was significant in antipsychotic-treated subjects (+131%, p=0.014) but not in antipsychotic-free subjects. α₂C-adrenoceptor protein expression was not significantly different between schizophrenia subjects and controls in synaptosomes and postsynaptic fraction, neither in antipsychotic-treated or antipsychotic-free subjects.

In conclusion, α₂A-adrenoceptor protein expression was increased in PFC of schizophrenia subjects receiving antipsychotic treatment. This increase was stronger in the postsynaptic fraction compared to synaptosomes (which include both pre- and postsynaptic membranes). These results might be a consequence of the α₂A-adrenoceptor antagonistic properties of some antipsychotic drugs.

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ACUTE AND SUBCHRONIC ADMINISTRATION OF ANTIDEPRESSANT DRUGS LEADS TO DOWNREGULATION OF mGlu5 RECEPTORS
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Objectives:
The late onset of therapeutic effects, unsatisfactory relapse rates and side effects of classical antidepressants illustrates the need for improved therapeutics. Recently, mGluR5 has been proposed as an attractive target for novel therapeutic approaches to depression. The main purpose of this project was to study changes in metabotropic glutamate receptor 5 (mGluR5) signaling pathway after antidepressant treatment to find a promising target for antidepressant and anxiolytic drug development.

Purpose:
The goal of this study was to determine early effects of antidepressant treatment on brain mGluR5 levels.

Methods:
In this study, three antidepressant drugs with various mechanisms of action (reboxetine, imipramine, escitalopram) and R-citalopram and haloperidol (negative controls) were used for acute or subchronic (7 days) treatment of rats. Protein levels in rat hippocampus and cortex of mGlu5 receptors were measured (Western blot analysis).

Results:
Our study revealed lower levels of regional mGluR5 in both cortex and hippocampus after reboxetine, imipramine and escitalopram. Dysregulation was observed after both acute and subchronic treatment. R-citalopram and haloperidol did not cause a statistically significant changes.

Conclusions:
Our results confirms that mGluR5 is engaged in the mechanism underlying antidepressant action. Most effective treatment options for depression are based on the monoamine hypothesis, and aim to increase the availability of monoamines in the synaptic cleft. We were able to show that mGluR5 signalling pathway can be modulated by serotonin and norepinephrine reuptake inhibitor class of drugs, but not by antipsychotic like haloperidol. This results may indicate that further modulation of metabotropic glutamate receptor may be a new way to create new combined therapies for depression. Unfortunately, the exact molecular mechanisms that mediate mGluR5 potential therapeutic effects are not yet fully understood. Our future studies will be focused on correlations between antidepressant treatment and levels of proteins involved in mGluR5 signal transduction.
SELECTIVE 5-HT1A BIASED AGONISTS (F13714 AND F15599) AS A NEW PHARMACOLOGICAL TOOLS IN THE DEVELOPMENT OF TREATMENT OF NEURODEGENERATIVE AND PSYCHIATRIC DISORDERS

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Objectives: Robert J. Lefkowitz, said that “biased agonists may represent an entirely novel form of therapeutic agent”. The functional selectivity of drugs at G protein-coupled receptors is the ability to activate specific signaling pathways preferentially. In neurodegenerative and psychiatric disorders serotonin 5-HT1A receptors are attractive targets. These receptor are expressed both as pre-synaptic located on 5-HT cell bodies in the raphe nuclei and as post-synaptic in brain areas associated with mood, cognition and pain [1]. The compounds, F13714 and F15599, are the first brain-region selective biased agonists at 5-HT1A receptors (5-HT1A). The F15599 preferentially targets post-synaptic cortical serotonin receptor, while F13714 targets pre-synaptic 5-HT1A autoreceptors [2]. The brain-region selectivity of these compounds corresponds with biochemical mechanisms which may determine their unique pharmacological profiles.

Methods: The compounds with high affinity for the serotonin receptor on four cell signaling pathways were tested: ERK phosphorylation (pERK), adenyl cyclase (cAMP) inhibition, calcium mobilization and β-arrestin recruitment assay. In in vivo studies we used mouse model of corticosterone-induced depression. As behavioral endpoint we used forced swim test (antidepressant-like activity). We also investigated the influence on locomotor activity of mice.

Results: Functional assays show F15599 significantly prefers pERK signaling pathways and is a partial agonist at Ca2+ mobilization. In contrast, F13714 does not discriminate between pERK, cAMP and β-arrestin but significantly less potently stimulates Ca2+ mobilization (although being a full agonist). It is noticed, serotonin shows no discrimination between all four signaling pathways. Studies in vivo show that single administration of F15599 but not F13714 decreased immobility the forced swim test in mice with corticosterone-induced model of depression. None of the compounds affected locomotor activity.

Conclusions: Both tested compounds activated different cell signaling pathway (pERK, Ca2+, cAMP and β-arrestin). Only F15599 showed antidepressant-like activity after acute administration in mouse model of corticosterone-induced depression.

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Literature Reference:
HEVIN, A MATRICELLULAR PROTEIN INVOLVED IN INDIVIDUAL VULNERABILITY TO MOOD-RELATED DISORDERS
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Psychiatric disorders such as drug addiction or major depression are characterized by alterations in neuronal activity of the brain’s limbic circuitry. The underlying cellular mechanisms involve, at least in part, alterations in synaptic plasticity and morphology. Synapses are highly dynamic structures and increasing evidence suggests that matricellular proteins are essential regulators of synaptic function and architecture. However, their potential role in adult neuroplasticity and more specifically in the pathophysiology of mood-related disorders is just beginning to be explored.

My research project focuses on the role of hevin, a matricellular protein, as a novel molecular mechanism underlying the individual vulnerability to stress and drugs of abuse. The two prototypical matricellular proteins SPARC and hevin have been implicated in depression-like behaviors, antidepressant response and resilience to stress. I found that hevin is induced by chronic social stress in the nucleus accumbens (NAc), a key brain reward region, only in resilient individuals. Importantly, its overexpression in susceptible mice could reverse social avoidance. This key observation, along with other evidence supporting a role for hevin in synaptogenesis and its presence at excitatory synapses, suggests that hevin is involved in the neuroplasticity underlying positive affect and motivation. My main objective is to define the role of hevin in the adaptation to stress and drugs of abuse. To test this hypothesis we first determined hevin cellular expression in the striatum using mRNA colocalization experiments. This allowed us to develop adeno-associated virus to specifically target hevin in those cells. We tested the behavioral and functional consequences of hevin alteration in those cells after exposure to cocaine. Our results showed that hevin is modulated by cocaine and seems to play a role in cocaine response.
ANXIOLYTIC-LIKE AND ANTICONVULSANT ACTIVITY OF NEW AROXYALKYL- OR AROXYETHOXYETHYL DERIVATIVES OF PIPERAZINE
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Objectives: Central nervous system disorders such as depression and anxiety, as well as epilepsy are important health and social challenges, and they are sometimes comorbid. Coexistence and common etiology of these disorders include factors such as trauma, intoxication, or neurodegeneration. 20-50% of epilepsy patients suffer from depression. Since serotonergic system plays pivotal role in major depressive disorder, but also has some role in anxiety and epilepsy, we decided to search for compounds with antidepressant-like, anxiolytic-like, and anticonvulsant properties among newly synthesized serotonergic receptors ligands.

Purpose: The aim of our study was to find a novel compound with antidepressant-like, anxiolytic-like, and anticonvulsant activity among newly synthesized 22 serotonin receptor ligands (5-HT₁A, 5-HT₂A, 5-HT₆, 5-HT₇).

Methods: The compounds were tested in radioligand binding assays for various serotonergic receptors (5-HT₁A, 5-HT₂A, 5-HT₆, 5-HT₇). The compounds with high affinity for the above serotonin receptors were then tested in the functional assays (AequoScreen method, Perkin Elmer). The most promising compounds were selected for in vivo tests i.e. forced swim test, four-plate test, and maximal electroshock seizure test (MES) in mice.

Results: Most studied compounds showed high affinity for 5-HT₁A receptor, and much lower towards the rest of serotonin receptors, and turned out to be weak 5-HT₁A antagonists. For in vivo studies, we chose 3 most promising compounds (compound 5, 17 and 20). None of the compounds showed antidepressant-like activity, but compounds 17 and 20 displayed anxiolytic-like properties. In MES test only compounds 5 and 20 were active and protected animals against MES seizures and death.

Conclusions: The most promising compound was compound 20, which not only showed anticonvulsant, but also anxiolytic-like properties in mice. In conclusion, there are premises for potential new active compounds among aroxyalkyl- or aroxyethoxyethyl derivatives of piperazine. The research was financed by the National Science Centre, Poland, grant no. DEC-2013/11/B/NZ7/04834
SINGLE ADMINISTRATION OF HBK-15 – A TRIPLE 5-HT1A, 5-HT7 AND 5-HT3 ANTAGONIST – REVERSED DEPRESSIVE-LIKE BEHAVIOR IN CHRONICALLY STRESSED MICE
Karolina Pytka, Monika Głuch-Lutwin, Elżbieta Żmudzka, Magdalena Kotańska, Klaudia Lustyk, Magdalena Jakubczyk, Anna Waszkielewicz  
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Objectives: Depression is a prevalent, highly debilitating mental disorder, which exact neurobiological mechanisms remain unknown. Antidepressants, even those recently discovered, are effective in only half of the patients. Moreover, the clinical response occurs following weeks to months of treatment. Thus, scientists still search for new, fast-acting antidepressants. 1-[(2-chloro-6-methylphenoxy)ethoxyethyl]-4-(2-methoxyphenyl)piperazine hydrochloride (HBK-15) – a triple 5-HT1A, 5-HT7 and 5-HT3 antagonist – showed significant antidepressant-like, anxiolytic-like, and memory-enhancing properties in behavioral tests in rodents.

Purpose: In this study, we aimed to investigate its antidepressant potential after acute administration in mouse model of unpredictable chronic mild stress.

Methods: We used mouse model of unpredictable chronic mild stress. As behavioural endpoints, we chose sucrose preference test and forced swim test to determine anhedonic- and antidepressant-like activity, respectively. We also evaluated the influence of HBK-15 on BDNF and p-CREB levels in the hippocampus.

Results: We observed a significant increase in immobility and reduced preference for sucrose solution in chronically stressed mice receiving saline compared with non-stressed controls. Single administration of HBK-15 reversed an increase in immobility and reduced preference for sucrose in the stressed mice. HBK-15 regulated the decreased levels of BDNF and p-CREB in the hippocampus in the stressed mice.

Conclusions: We found that a single administration of HBK-15 – a triple 5-HT1A, 5-HT7 and 5-HT3 antagonist – reversed depression-like behavior and regulated decreased BDNF and p-CREB levels in the hippocampus in mice under unpredictable chronic mild stress. Our results suggest that the blockade of serotonergic 5-HT1A, 5-HT7 and 5-HT3 receptors might be beneficial in the treatment of depressive disorders. This study was supported by Jagiellonian University grant number K/DSC/001955.
NOVEL NON-IMIDAZOLE H3 RECEPTOR ANTAGONIST REDUCES SCOPOLAMINE-INDUCED MEMORY IMPAIRMENT IN VARIOUS MICE MODELS

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Objectives: Research into histamine H3 antagonists/inverse agonists have found that these compounds have the potential to improve cognitive performance and thereby, they can become valuable therapeutic option in the treatment of different types of dementia including Alzheimer’s disease. We decided to assess the procognitive properties of the compound DL76, which is the new non-imidazole H3R antagonist showing high affinity towards the H3R (hK1 1/4 22 ± 3 nM). Moreover, pharmacokinetic studies showed that the compound crossed the blood–brain barrier and the brain exposure to DL76 was almost 30-fold higher than serum.

Purpose: The main purpose of our study was to determine whether the compound DL76 would reduce amnestic effect of scopolamine and what is the role of histamine, acetylcholine and histamine H1R and H2R in the mechanism of action.

Methods: We investigated the influence of DL76 on memory processes in various paradigms, including Passive Avoidance, Novel Object Recognition and Morris Water Maze in which scopolamine was used to induce a cholinergic deficit, and subsequent memory and learning impairment. We compared all results with the effect of the reference H3R antagonist Pitolisant. Moreover, we assessed the interaction of DL76 and Pitolisant with H1R and H2R antagonists. Finally, we measured the concentration of brain histamine and acetylcholine after acute treatment with DL76 or Pitolisant.

Results: After administration of histamine H3Rs antagonists we observed the significant improvement of scopolamine-induced memory deficits in all paradigms. Interestingly, the procognitive effects of DL76 were significantly attenuated by H2R antagonist but not by H1R antagonist. Moreover, administration of DL76 increased the levels of histamine and acetylcholine in the hippocampus but not in the prefrontal cortex or striatum.

Conclusions: These results confirm that the blockade of histamine H3Rs might have therapeutic utility for the treatment of memory deficits and learning disorders. We showed that, secondary to H3R blockade, the release of histamine and subsequent activation of H2R-dependent pathways might have crucial role in the procognitive mechanism of action of H3R antagonists.

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DEFICIT IN ISOLATION-INDUCED ULTRASONIC VOCALIZATION IN \textit{FMR1} KO MOUSE PUPS IS NOT MEDIATED BY POSTNATAL MATERNAL CARE

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Fragile X syndrome (FXS) is a neurodevelopmental disorder caused by the silencing of the fragile X mental retardation 1 gene (\textit{FMR1}). It is the most common heritable cause of intellectual disability and the largest monogenic cause of autism with which it shares a number of symptoms including cognitive inflexibility and social anxiety. The \textit{fmr1} knock-out (KO) mouse recapitulates numerous symptoms of the condition including learning deficit, abnormal sociability and sensory hyperreactivity. Isolation-induced ultrasonic vocalization (USV) is a reliable measure of social communication in neonatal mice, and our lab has found that both male and female \textit{fmr1} deficient pups exhibit reduced USVs during the first postnatal week relative to wild type (WT) pups. Abnormal pup vocalizations have been observed in a number of mouse models of neurodevelopmental disorders and, in human, reduced and delayed onset of infant vocalization has been linked with subsequent diagnoses of autism. However, reduced isolation-induced USVs were accompanied by altered maternal care as measured by increased pup retrieval latency and duration, maternal behaviors which could influence pup vocalization patterns. We therefore performed a cross-fostering experiment to ascertain whether reduced pup USVs were mediated by deficits in maternal care or if they may be an early behavioral marker of neurodevelopmental abnormalities. Although the crossfostering procedure increased the overall vocalization baseline across all pup sex and age groups, KO pups reared by WT dams continued to show reduced USVs during the first postnatal week relative to WT pups reared by WT dams, while WT pups reared by KO dams produced comparable vocalization patterns to this control group. This data suggests that reduced social communication in the \textit{fmr1} deficient neonate is not a maternal care-induced behavior, but rather a marker of neurodevelopment associated with an abnormal adult sociability phenotype.
DRUG REWARDS MODULATE SYNAPTIC PLASTICITY DIFFERENTIALLY IN THE DORSAL STRIATUM AND HIPPOCAMPUS: IMPLICATIONS FOR DRUG ADDICTION

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The multiple memory systems hypothesis posits that different neural circuits function in parallel and may compete for information processing and storage. Instrumental conditioning depends on the striatum, whereas spatial memory is processed by a circuit centered on the hippocampus. Emotional content of events greatly influence functional interactions between these systems. Strikingly, little is known about how drug rewards may influence these interactions. We have implemented an experimental set-up to investigate consequences of drug-induced activation of the reward system on different forms of memory and synaptic plasticity. C57BL/6J mice were implanted with a stimulation electrode into the basolateral nucleus of the amygdala (BLA), and a recording electrode into either the dorsal CA1 or the dentate gyrus (DG) of the hippocampus, and the dorsal striatum (DS). Following surgery, we compared the acquisition of a cued learning task in mice rewarded with either palatable food (crisps) or ventral tegmental area drug (morphine) injections. Mice were then switched on a spatial learning protocol to assess cognitive flexibility. During training, we recorded BLA-evoked field potential in the CA1 and DS in freely-moving mice 15 min before, and 1, 15 and 60 min after completion of sessions 1, 5 and 10 of the task. Mice learned the cued Y-maze arm discrimination task similarly whether they were drug- or food-rewarded. Both groups exhibited a strong increase in response amplitude in the DS, but this increase was greater in drug- than in food-rewarded subjects. Conversely, a decrease in response amplitude was observed in the dorsal CA1 of morphine-rewarded mice, which did not return to the baseline between sessions, and exhibited a learning deficit when switched on a spatial protocol. In contrast, food-rewarded mice remained able to switch to a spatial learning strategy. Importantly, these forms of synaptic plasticity were not observed in mice receiving non-contingent morphine injections. We conclude that drug-induced activation of the VTA configures memory systems interactions to promote the control of behavior through S-R learning processes. This drug-induced cognitive bias could play a critical role in the instatement of addictive behaviors.
HIPPOCAMPAL GLIAL GLUTAMATE TRANSPORTERS LINK METABOLIC DISORDERS TO DEPRESSION: USING RILUZOLE AS A THERAPEUTIC REAGENT
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Objectives: Epidemiological studies indicate an association between metabolic disorders and depression. An over-activated hippocampal glutamatergic output projecting from the hippocampus to the nucleus accumbens is known to cause depression. Here, we attempt to investigate whether the dysregulation of the hippocampal glutamatergic transmission is involved in the development of metabolic disorder-associated depression.

Purpose: Characterizing the roles of hippocampal glial glutamate transporters in the pathogenesis of metabolic disorder-associated depression and examining the therapeutic effect of riluzole, a glutamatergic transmission normalizer.

Materials and methods: Eight-week-old male B6 mice were divided into Chow and high-fat diet (HFD) groups which were respectively fed with normal diet and HFD for 12 weeks. Forced swimming test and sucrose preference test were used to assay the depression-like behaviors. The hippocampal expression of glial glutamatergic transmission-related proteins was measured. In testing the therapeutic effect of riluzole on depression, the mice were daily injected with riluzole (4 mg/kg body weight, i.p.) for 21 days starting from the 10th week of the 12-week feeding period.

Results: HFD induced obesity and systemic insulin resistance in mice. HFD also induced depression-like behaviors, but not hippocampus-related memory deficits and anxiety-like behaviors in mice. Moreover, HFD repressed the process arbor complexity of astrocytes and decreased the expression of glial glutamate transporters, i.e. GLAST and GLT-1, in the hippocampus. Viral knockdowning the hippocampal expression of GLAST and GLT-1 induced depression-like phenotype in naïve mice. A 21-day riluzole treatment restored the hippocampal expression of GLAST and GLT-1, and rescued the HFD-induced depression-like behaviors.

Conclusion: Our results suggest that the decrements of the hippocampal GLAST and GLT-1 contribute to the development of depression-like phenotype in mice with metabolic disorders. Riluzole restores the hippocampal expression of GLAST and GLT-1 and rescues the metabolic disorder-associated depression in mice.
THE TREATMENT AND REHABILITATION OF FUNCTIONAL NEUROLOGICAL SYMPTOM (CONVERSION) DISORDERS AND DISSOCIATIVE DISORDERS AFTER MILD TBI

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Objectives: Patients with mild traumatic brain injury (TBI) constitute the majority of patients with TBI (the silent epidemic). Psychiatric disorders accompanying mild TBI contribute to mild TBI prognosis. Limited research was devoted to the linkage between mild TBI and dissociative disorders and functional neurological symptom (conversion) disorders (Markowitsch and Staniloiu, 2016). This partly that for a long time, dissociative and conversion disorders were “dissociated” from the research arena. Similarly to the mild TBI, these disorders have been evolving and at times controversial diagnostic entities.

Purpose: The current presentation aims to increase the awareness and understanding of the relationship between mild TBI and dissociative disorders and functional neurological symptom (conversion) disorders by summarizing diagnostic, epidemiological, pathophysiological, neuropsychological and neuroimaging information on these disorders, reviewing explanatory paradigms of the relationship between mild TBI and dissociative disorders and summarizing the status of art of treatment and rehabilitation of these disorders.

Methods: Literature review and own clinical data, obtained with psychiatric, neuropsychological and various brain imaging methods.

Results: Functional neurological (symptom) disorders and dissociative disorders often have their onset after a mild TBI; their emergence contributes to the delayed recovery from postconcussion symptoms. Furthermore patients with mild TBI who score high on the Dissociative Experiences Scale (DES) have worse outcomes than patients who score low on the DES.

Conclusions: At least 10-15 % of mild TBI have chronic trajectories. Preliminary data identify dissociative and functional neurological symptom (conversion) disorders as risk factors for delayed recovery from mild TBI. Timely (early) multidisciplinary treatment and rehabilitation, including symptom focused cognitive-behavioural therapy, are needed to cure, and prevent chronicity and substantial disability associated with both mild TBI and functional neurological (conversion) and dissociative disorders.

Literature Reference
LITHIUM AMELIORATES SLEEP DEPRIVATION-INDUCED MANIA-LIKE BEHAVIOR, HPA AXIS ALTERATIONS, OXIDATIVE STRESS AND CYTOKINES IN THE BRAIN AND SERUM OF MICE
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Objectives: The goal of the present study was to investigate the effects of lithium (Li) administration on behavior, oxidative stress parameters and cytokines levels in the periphery and brains of mice subjected to an animal model of mania induced by paradoxal sleep deprivation (PSD). Purpose: Understanding the relationship between sleep deprivation, manic-like behaviors and HPA axis and inflammatory system changes, all seen in bipolar disorder (BD). Methods: The mice were treated for a period of seven days with saline solution or Li. The animals were subject to the PSD protocol for 36 h. Locomotor activity was then evaluated using the open-field test. The parameters of oxidative stress, HPA axis and inflammatory system were subsequently evaluated in the hippocampus, frontal cortex and serum of mice. Results: The results showed that PSD induced hyperactivity in mice, which is considered a mania-like behavior. PSD increased lipid peroxidation and oxidative damage to DNA, as well as causing alterations to antioxidant enzymes in the frontal cortex, hippocampus and serum of mice. In addition, PSD increased the levels of cytokines in the brains of mice. Treatment with Li prevented the mania-like behavior, oxidative damage and cytokine alterations induced by PSD. Conclusions: The present data demonstrated that PSD induces HPA-axis alterations, increases in the levels of cytokines and oxidative stress parameters. Therefore, it can be suggested that circadian rhythms alterations observed in BD may be related to the alterations in the HPA-axis, activation of the inflammatory system and oxidative stress; all these parameters are also observed in the animal model induced by PSD. In addition, Li could reverse the neurochemical alterations induced by PSD, suggesting that this mood stabilizer could act on the mechanisms controlling the circadian rhythms, and protect the brain and serum against HPA-axis alteration and increases in the levels of oxidative stress and cytokines.
DEVELOPMENTAL STUDY IN THE EKER RAT MODEL OF AUTISM

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Objectives: Behavioural abnormalities resembling human autistic spectrum disorder have been observed in adult male Eker rats (Waltereit et al., 2011). Here we test Eker rats of both sexes from birth to adolescence, with special focus on vocalizations and social behavior.

Purpose: The goal was to find out when the autistic phenotype first occurs, and how it changes during ontogeny.

Methods: We tested rat pups of both sexes, carrying the Eker mutation (inactivation of TSC2 gene) and their healthy littermates. We recorded isolation-induced vocalizations at P5, P7, P10 and P13. Furthermore, we performed simple tests of sensorimotor development in a subset of the animals. Preadolescent rats were tested in the open field and social interaction tests adapted for young rats.

Results: Eker rat pups are not different from their healthy siblings in the amount of isolation-induced vocalizations, and exhibit virtually no differences in the open field test. Social interactions before puberty was comparable to control animals.

Conclusions: We present longitudinal study of development in the Eker rat model. TSC2 mutation present in the Eker rats has surprisingly mild phenotype, compared to analogous transgenic mouse models or patients with tuberous sclerosis complex carrying mutation of the same gene. Our study failed to uncover any profound effects prior to puberty, implying that the previously described impairments probably develop later, and may also be sensitive to the exact experimental settings. Results from pubertal and post-pubertal rats will be discussed in the poster.

THE ABSENCE OF THE GLUN2C SUBUNIT ATTENUATES THE PSYCHOTOMIMETIC EFFECTS INDUCED BY KETAMINE AND OTHER NMDA ANTAGONISTS

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Objectives: Non-competitive NMDA-R antagonists like phencyclidine (PCP), ketamine and dizocilpine (MK-801) are used as pharmacological models of schizophrenia in rodents. Previous studies proposed that these compounds activate thalamo-cortical circuits after the blockade of NMDA-R in reticular thalamic GABAergic neurons. The GluN2C subunit of NMDA-R is densely expressed in thalamus and cerebellum.

Purpose: To study the involvement of the GluN2C subunit in the psychotomimetic effects (hyperlocomotion and stereotypical behavior) induced by NMDA antagonists under the hypothesis that those effects will be reduced in the absence of the GluN2C subunit.

Methods: Male wild-type (WT) and GluN2C receptor subunit knockout (KO Gln2C) mice were used. Mice were placed in the open field during a 30-min (ketamine) or 2-h trial (MK-801 and PCP). Distance moved (cm) was automatically calculated and behavioral signs were observed and scored by an experimenter blind to mice genotype as previously described (Scorza et al, 2010).

Results: The administration of ketamine (3mg/kg), MK-801 (0,10 and 0,25mg/kg) and PCP (5mg/kg) enhanced locomotor activity of both WT and KO GluN2C mice in a similar way. However, stereotypical behavior was attenuated in the KO GluN2C mice. Thus, ketamine (3mg/kg), MK-801 (0,25mg/kg) and PCP significantly increased the number of falls in WT compared to KO GluN2C mice (p<0,01). Moreover, ketamine (3mg/kg) decreased the number of rearings against the wall in WT mice and in a lesser extent in KO GluN2C mice (p<0,05), suggesting that KO GluN2C mice had less motor impairment, as also observed with the number of falls.

Conclusions: Overall, the GluN2C subunit is not implicated in the hyperlocomotion induced by the NMDA antagonists. However, it appears to be strongly involved in the stereotypical behavior. Further, the dramatic difference in the number of falls between WT and KO GluN2C mice suggests the involvement of GluN2C-containing NMDA-R in cerebellum, a key brain structure for the control of motor coordination.

Literature Reference
DISSOCIATION, EMOTIONAL AND COGNITIVE PROCESSING, AND HEMISPHERIC LATERALITY IN NORMAL SUBJECTS

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Objective: To study the relationship between dissociation and both emotional and cognitive hemispheric laterality, autobiographical memory and thought suppression in normal subjects.

Purpose: To develop scientific knowledge on the psychological and hemispheric mechanisms involved in dissociation in normal subjects, by comparing psychological performance of high-versus low-dissociators as measured by the Scale of Dissociative Tendencies (DES; Bernstein and Putnam, 1986)

Methods: Four experiments about hemispheric laterality and dissociation in normal subjects were carried out.- 100 subjects (50 high-dissociators -scores higher than 20 in the DES, and 50 low-dissociators –scores lower than 10 in the DES) run experiments on Dichotic Listening for linguistic and emotional stimuli, Divided Visual Field for linguistic and emotional stimuli, and both Central and Lateralized, Standard and Emotional, Stroop tasks. Two complementary studies on Autobiographical Memory and Thought Suppression were conducted.- 46 normal subjects (23 high-dissociators and 23 low-dissociators) completed the Autobiographical Memory Test (AMT; Williams and Broadbent, 1986), and the White Bear Suppression Inventory (WBSI; Wegner and Zanakos, 1994)

Results: Dichotic Listening.- ANOVA DESxEarxStimuli, d’: F(1,98)=4,75; p<0,05.
          Divided Visual Field.- ANOVA DESxValencexField, d’: F(1,92)=5,27; p<0,05.
          Standard and Emotional Lateralized Stroop.- ANOVA DESxStimulusxField, RT F(1,79)=2,23; p<0,09. High Dissociators group.- ANOVA StimulusxField, RT, F(1,39)=5,64; p<0,01.
          Autobiographical Memory Test.- ANOVA DESxMemories Number, F(1,44)=9,01; p<0,01.
          White Bear Suppression Inventory.- F(1,44)=7,27; p<0,05.

Conclusions: Our results on dissociation and hemispheric laterality demonstrate that dissociation in normal subjects is related to deficits in emotional processing, associated to a potential dysfunction in the right hemisphere. Dissociation in normal subjects is also associated to deficits in autobiographical memory, as well as to high tendency to suppress undesired thoughts. As a whole, these results suggest the relevance of developing research on the relationship between dissociation in normal subjects and either, changes in emotional and cognitive processing; and alterations in hemispheric laterality, particularly related to deficit in emotional processing. The study has implications at both basic and clinic research (e.g. PTSD)
NO SPONTANEOUS SEIZURES AND DEPRESSIVE-LIKE BEHAVIOR OCCUR FOLLOWING CONVULSIONS IN FASTED RATS AFTER ATROPINE TREATMENT AND FOOD INTAKE

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Objectives: Prolonged convulsions as well as brief single or repetitive seizures cause spontaneous seizures in animals. Locomotor hyperactivity, anxiety- and depression-like behaviors and cognitive impairment have been demonstrated after seizures. Convulsions developed in fasted mice and rats after antimuscarinic treatment and food intake appear in the form of single and short seizures that may evolve recurrent or long lasting seizures (1).

Purpose: This study aimed to assess whether spontaneous seizures and behavioral changes occur following convulsions in fasted animals.

Methods: Rats treated i.p. with saline (control) or 2.4 mg/kg atropine and given food after 24-h of fasting were grouped according to the seizure scores. Starting 24 h after convulsions, the animals with seizure score 1-2, 2+ or 3-5 were observed for the development of spontaneous seizures for 30 days. Observations were repeated 5 days per week for a minimum of 2 h each day. Using the open field and forced swimming tests, all animals were tested for the rearing and depression-like behavior 4 and 7 days after convulsions, respectively. Decreased rearing frequency in the novel environment reflects both anxiety-like behavior and reduced motor activity.

Results: The incidence of convulsions in atropine-treated animals was significant in comparison to control rats. During the observation period, no episodes of seizure activity were visually observed in any animal. The animals did not show differences in the duration of immobility when compared with the control animals. There were also no significant differences between the groups with respect to the number of rearings.

Conclusions: This study showed that spontaneous seizures and depression- or anxiety-like behaviors do not develop following convulsions induced by atropine treatment and food intake in fasted rats. These results are in accordance with our unpublished findings and other researchers’ that immobility in the forced swimming test and spontaneous activity in a novel cage remained unchanged after repeated seizures in rats (2).

Literature References:
Sensory and Motor Systems
AUDITORY SUBSTITUTION OF VISION IN A SIMULATED LANE-KEEPING TASK
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It has been shown that sensory substitution devices facilitate acquisition of novel perceptual skills (e.g., shape discrimination using soundscape). In the present study, we examined sensory substitution in sensorimotor skill acquisition. In a simulated driving task, the lateral lane position of a car was given to participants as an auditory cue by binaural balance of volume of white noise. Four groups of participants (N = 15 for each group) were subjected for lane-keeping training of 40 minutes in the different conditions: the participants in the control group performed the training in a normal driving condition; in the auditory substitution (AS) group, the lower part of lane landscape was visually occluded and instead the auditory cue for lateral lane positions was provided; in the restricted vision (RV) group, the lower part of lane landscape were occluded but no auditory cue was provided; and in the sound only (SO) group, the auditory cue was provided alone without any visual stimuli. The effect of training was assessed by the same lane-keeping task (with 5 minutes) as in the normal driving condition before and after training for participants in all groups. Lane-keeping accuracy (i.e., the root mean square of deviations from the lane center) was used as a performance measure. Results showed a significant training effect in all the groups except for the RV group, suggesting that the lower part of lane landscape is critical for lane-keeping skill acquisition. A training effect in the AS group was greater than that in the SO group, and comparable to that in the control group, suggesting that the auditory cue for lateral lane positions can be used as the substitution of occluded visual information in lane-keeping skill acquisition. In conclusion, our data demonstrate a possibility of sensory substitution in sensorimotor skill acquisition.
EFFECT OF ATTENTION ON AUDITORY PROCESSING OF MULTIPLE SOUND SOURCES
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Objectives: In a complex acoustic environment, the ability to selectively attend to a particular sound source while filtering out others is important. Although the phenomenon is well-known (‘cocktail party effect’), its neural mechanisms have remained unclear. This project aimed to reveal neural correlates of auditory processing when two speech sounds were presented simultaneously at same or different positions and to investigate neural effects of attention on auditory processing.

Methods: 20 healthy adults participated and their brain images were acquired on a 3T MRI. By combining 3 sound source locations and 3 attention directions, 9 experimental conditions were created. In each trial, participants were instructed to focus on the certain direction and to count the number of times a target word appeared.

Results: Enhanced neural activity for the multiple sound source locations was found in superior temporal gyrus (STG), precuneus, and inferior colliculus (IC). Compared to the baseline conditions, 1) the inhibition conditions activated precuneus, middle frontal gyrus (MFG), left lingual gyrus, right middle occipital gyrus and right angular gyrus, 2) the divided attention conditions activated precuneus and IC and 3) the selective attention conditions activated precuneus, STG, MFG and IC. The analyses for the effects of attention direction showed that the posterior STG is activated by the contralateral attention direction.

Conclusions: Successful auditory processing of multiple sound sources require auditory stream segregation and sound localization. Enhanced activity found in the STG and IC may reflect those processes. The involvement of precuneus in inhibition, divided attention and selective attention indicates that the critical role of the precuneus is in orienting spatial attention to the target sound. Differential activity in the posterior STG related to attention direction demonstrates that the sound localization process in the posterior STG is modulated by attention direction.
HOW DO LATER ADOLESCENTS AND ADULTS WITH AUTISM SPECTRUM DISORDER USE GAZE CUE WHEN THEY TRACK MOVING FACE IMAGE?

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Objectives: Autism spectrum disorders (ASD) is characterized by impairments of social interaction communication and imagination, and recent studies suggest that these functions are tightly linked to sensori-motor functions. To develop a better training program for improvement of communication skills, it is important to clarify the sensori-motor functions in individuals with ASD.

Purpose: Eye gaze is essential information for understanding others’ intention, so the current study recorded eye movements toward sequentially presented face images with or without gaze cues to investigate whether the ASD could perform the task in a prospective manner according to the cues.

Methods: Participants (ASDs and TDs) were seated comfortably on a chair in front of a laptop PC and the distance between the eyes and a screen was approximately 60 cm. Each line-drawn face image (= 257 × 221 pixels) was sequentially presented for one second on a laptop PC (14 inch, screen resolution = 1280 × 720 pixels). The number of potential presentation positions was 15 (i.e., 5 × 3), and the face images shifted from side to side and up and down. Two conditions were tested; 1) the gaze of face image was directed to participants (No Cue condition), 2) the gaze of face image was directed to the position where the next face would be presented (Cue condition). 16 sequences of gaze tracking were included in one trial and the experiment session in each condition consisted of 10 trials. Participants were required to track the moving face images without instructing the specific parts where they should fixate. A Japanese version of the Autism Spectrum Quotient (AQ) was administered to all participants.

Results: Although the ASD participants less looked at the eyes area in the face image, they could shift their gaze earlier according to the cue of face image in the Cue condition. This gaze effect was more evident in the second half of the session in comparison to the first half. The significant relationship between this gaze behavior and the score of the sub-scale ‘imagination’ in Autism-Spectrum Quotient (AQ) was also found by pooling both data of ASDs and TDs.

Conclusions: The current study demonstrated that individuals with ASD could use the social cue for the efficient tracking performance, and that the score of the ‘imagination’ could predict the performance.
EFFECT OF HYPERTHERMIA-INDUCED SEIZURES ON MOTOR COORDINATION AND GAIT IN BOTH ADOLESCENT AND ADULT RATS
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Febrile seizures (FS) is one of the most common convulsive disorders in infants and young children that only occurs in children between 3 months and 6 years-old, when the cerebellum is still developing.

In the present work, we have analyzed the consequences of febrile seizures on motor coordination and gait from adolescent and adult rats using balance beam and footprint test. In balance beam test motor coordination and balance were analyzed by measuring the ability of the rat to traverse a graded series of narrow beams to reach an enclosed safety platform in balance beam test. On the other hand, footprint test was used to compare the gait in different rats. The hind- and forefeet of the rats were inked with orange and pink nontoxic paints, respectively, and the rats were allowed to walk along a 50-cm-long, 10-cm-wide runway (with 10-cm-high walls). The footprint patterns were analysed in terms of the following parameters: a) stride length that represent the average distance of forward movement between each stride; b) Hindpaw and forepaw base that correspond to the average distance between left and right hind footprints and left and right front footprints and c) forepaw/hindpaw overlap, the distance between forepaw and hindpaw print, was used to measure uniformity of step alternation.

Results obtained have shown that in adolescent rats the time required to cross the 18 mm-round section and 12 mm-round section beam were significantly higher in hyperthermic group than in control animals. Similar results were obtained in adult rats when 35 mm-square section was used. Concerning footprint test, forepaw/hindpaw overlap resulted significantly higher in adolescent rat whereas stride length, forepaw and hindpaw base were altered in adult rats exposed to HIS.

We conclude that hyperthermia-induced seizures evoked fine motor coordination impairment and gait disturbances in both adolescent and adult rats.
A COMPARATIVE ANALYSIS OF HAND KINEMATICS USED TO OBTAIN STATIC VS. DYNAMIC OBJECTS OF VARYING SIZE: INSIGHT INTO THE ACTION-PERCEPTION THEORY

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Objectives: The action-perception theory, which proposes dorsal stream mediation for on-line action and ventral stream mediation for perception, is supported by hand-shaping differences associated with actual vs pantomime reaches. The generality of the theory to other hand use behaviors has not been evaluated, which was the objective of the present study.

Purpose: The present study compared reach-to-grasp movements with catching movements for balls of three different sizes during actual and pantomime conditions.

Methods: The experiment consisted of two parts: Part-I (static) monitored participants hand movements during a reach-to-grasp task for balls of three sizes (small/medium/large) in both an actual and pantomime condition. Part-II (dynamic) required the participants to catch and pantomime catch the same three balls. Two-high speed cameras and electromagnetic sensors attached to the participant’s thumb, index, and wrist recorded hand movements throughout each trial. Trials were presented in a counter-balanced design for both experimental parts, with participants performing three trials for each of the three ball sizes for both conditions. Kinematic and video data were analyzed using a repeated measures ANOVA.

Results: Part-I of the experiment exhibited hand-shaping calibrated to object size for actual but not pantomime conditions. In Part-II, the opposite was found; hand-shaping correlated to object size during pantomime but not for actual conditions. A comparison between Part-I and Part-II revealed highly correlated hand-shaping behaviour for pantomime, but not actual movements.

Conclusions: The experimental results suggest that pantomime movements made with respect to both static vs dynamic tasks are influenced by the perceptual features of the task and do not closely mimic the actual on-line movements. This finding is consistent with the action-perception theory. Further, the results support the broad applicability of the theory to varying hand movements. One explanation of the results is that in pantomime, participants monitor only the intrinsic properties of the object while neglecting their extrinsic properties.
INTERHEMISPHERIC CONNECTIONS BETWEEN OLFACTORY BULBS IMPROVE ODOR DETECTION
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In most sensory systems, bilateral arrangement of the pair of sensory organs is important for detecting the stimulus direction and location. The interhemispheric inhibitory interactions that use contralateral information from these two separate sensory channels are widely agreed to be important for generating delay lines across sensory organs. In most of these models, the delay between the arrival of sensory stimulus to the bilaterally arranged sensory organs are suggested to be utilized to suppress the signal coming from the contralateral sensory organ via contralateral inhibition. Such contralateral inhibition is therefore proposed to be important to increase the relative strength of the signal on the ipsilateral side, where the sensory stimulus is located, which facilitates the localization of the stimulus source.

We used anatomical tracing and functional brain imaging in adult zebrafish to show that two olfactory bulbs exhibit both inhibitory and excitatory connections. We demonstrate that the inhibitory interhemispheric connections are established via diffuse projections of the olfactory cortices onto contralateral olfactory bulb interneurons. Moreover, we showed that mitral cells send spatially organized direct excitatory connections to their functionally identical sisters in the contralateral olfactory bulbs. Functional recordings suggest that this glomeruli specific direct contralateral excitation can be recruited even by relatively weak olfactory stimuli and it is more sensitive than the polysynaptic contralateral inhibition. Finally, we showed that the combination of spatially organized contralateral excitation together with the spatially diffuse contralateral inhibition, improves the detection of specific odor signals against a broad background odor, by broadly subtracting background noise while compensating for the intra-bulbar mixture suppression.

We propose that such interhemispheric connections are not only useful for localizing stimulus sources, but also provide a novel mechanism that can improve the detection of odors activating only few glomeruli, such as reproductive pheromones, social or alarm cues.
Integrative Systems:
Neuroendocrinology,
Neuroimmunology
GOAL-DIRECTED LEARNING AFTER CHANGES IN THE ACTION-OUTCOME CONTINGENCY IS REGULATED BY CHOLINERGIC INTERNEURONS (CINs) OF THE POSTERIOR DORSOMEDIAL STRIATUM (pDMS).

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It is known pDMS is an essential structure for goal-directed actions, which critically depend upon encoding of specific action-outcome associations. Often these associations do not stay static throughout time, but are overwritten according to changes in environment. Neuroplasticity must remain flexible, integrating new and existing learning with the least possible interference. pDMS CINs play a key role in this process controlling goal-directed learning. They receive excitatory signals from the parafascicular thalamic nucleus (Pf), constituting an essential pathway for integrating action memories, encoding new and existing action-outcome contingencies (Bradfield et al., 2013). New and existing memories loss is a typical feature in certain pathologies such as Parkinson's disease, where neuroinflammation has been shown to play a crucial role. Thus, we used an inflammatory stimulus, lipopolysaccharide (LPS), to assess the hypothesis that inflammation in Pf affects pDMS CINs blocking integration of new and old goal-directed memories. To confirm CINs involvement we used pharmacological cholinergic activity blockade in pDMS. Long Evans rats received either an LPS injection in Pf and oxotremorine, a cholinergic agonist, in pDMS controlaterally or ipsilaterally. Sham rats received saline infusions in Pf and pDMS controlaterally. Two weeks after LPS injection rats were trained to press right and left levers for pellets or 20% sucrose solution and this contingency learning was analysed by a devaluation test for both reinforcers. Subsequently, levers were reversed, re-training the animals for the new contingency, with oxotremorine or saline infusion in pDMS. New contingency learning was analysed through another devaluation test for both reinforcers. It was observed that learning remained intact for all groups after initial contingency, however, learning was impaired in the contralateral treatment group after levers reversal in presence of oxotremorine. This could confirm that pDMS CINs are unable to integrate new and old goal-directed memories once there is neuroinflammation in Pf.

INNATE ATTRACTION FOR SEXUAL PHEROMONES APPEARS AT PUBERTY IN FEMALE MICE: CORRELATION WITH CHANGES IN OXYTOCINERGIC NEURONS

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Sexual pheromones play a major role in reproductive behavior in rodents. In mice, females show an innate attraction towards male chemosignals present in male urine. However, this attractive response appears with puberty, and in fact prepubertal females tend to avoid the male-derived sexual stimuli present in urine. To investigate possible neurobiological differences between pre- and post-pubertal females that may underlie the behavioral change from avoidance to attraction, we have focused in the oxytocin and arginine-vasopressin circuits of the “socio-sexual brain”, which are important in the control of social behaviors.

First, we performed preference tests in 8 prepubertal and 8 postpubertal females in which they chose male- vs female-soiled bedding. We calculated a preference score as the ratio between time spent investigating male chemosignals divided by total time investigating both stimuli. Subsequently, we performed an immunohistochemical detection of oxytocin and vasopressin in those brains.

The results of the preference tests matched previous literature, as prepubertal females mainly showed avoidance whereas postpubertal ones mostly showed preference for the male stimuli. A t-Student test revealed significant differences on the behavioral responses between both groups of females, (p=0.025). Furthermore, the study of the oxytocinergic circuits showed significant differences between the groups in the paraventricular hypothalamic nucleus (p=0.012). Moreover, the oxytocin immunoreactivity at the paraventricular nucleus showed a positive correlation with the preference score in the prepubertal group (Pearson coefficient=0.890; p=0.017). In contrast, the vasopressinergic circuits did not show between-group qualitative differences.

In conclusion, oxytocin immunoreactivity increases in the paraventricular nucleus of female mice during puberty, and this increase may be related to the female shift from avoidance to attraction towards male chemosignals.

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DON'T TOUCH MY PUPS! AGGRESSIVE RESPONSES AGAINST MALE INTRUDERS IN CD1 DAMS INCREASE WITH EXPERIENCE

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Maternal behaviour comprises physiological and behavioural adaptations that help the dams to successfully raise their offspring. This behaviour is expressed in a wide range of vertebrate species and can be parsed in two main components, namely pup-directed (i.e. maternal care), and non-pup-directed behaviour. Among the latter, maternal aggression against intruders has a huge adaptive value due to its direct relation to offspring survival. Given the importance of maternal aggression, it is important to understand its neural basis and the possible behavioural changes occurring throughout lactation. Thus, the main goal of this study was to investigate the behavioural profile of maternal aggression in the early post-partum period, specifically the possible changes in the structure of dams’ behaviour after several encounters with male intruders, i.e., whether aggression is enhanced after repeated testing. Previous studies have shown that virgin females housed with dams, that we name godmothers, share pup care and display similar levels of maternal care to those of dams, but no maternal aggression. Thus, we exposed two groups of CD1 female mice (lactating females, n=8; godmothers, n=8) to a male intruder during the post-partum day 4 to 6. Our results reveal that the total duration and number of attacks that dams displayed towards male intruders increased across testing, whereas the latency to attack decreased between post-partum 4 and 5. Moreover, the duration of individual attacks changed, so during the first testing day, dams displayed numerous short attacks (≤0.5s) but they rarely displayed long attacks (≥5s), whereas the third day the percentage of long attacks was maximum. By contrast, godmothers did not attack the intruders, but interacted with them, sniffing their bodies and ano-genital zone. Our findings show that repeated testing increases the duration and modifies the structure of the attacks in maternal aggression, a behaviour that is only exhibited by dams. This suggests that this aggressive behaviour arises after the hormonal changes linked to pregnancy and lactation. It is likely that prolactinergic signalling in the central nervous system contributes to the onset and expression of this adaptive behaviour that contributes to the survival of the offspring.

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FLUOXETINE TREATMENT AFFECTS THE INFLAMMATORY RESPONSE ACCORDING TO THE QUALITY OF THE LIVING ENVIRONMENT

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Objectives: It has been hypothesized that SSRIs, the most common treatment for major depression, affect mood through changes in immune function. However, findings concerning the effects of SSRIs on inflammation are contradictory showing that these drugs act either as pro- or anti-inflammatory compounds [1]. Since previous studies showed that SSRI effects are moderated by the quality of the living environment [2].

Purpose: We investigated whether the environment determines the effects of SSRI treatment on inflammation.

Methods: We treated C57BL/6 adult male mice with either fluoxetine or vehicle while exposing them to either an enriched or a stressful condition, following a chronic stress period aimed at inducing a depression-like phenotype. In the whole hippocampus, we assessed expression levels of IL-6, TNF-a, IL-1b and IFN-g, which are pro-inflammatory cytokines, and IL-4 and TGF-b, two anti-inflammatory cytokines. In isolated microglia, we performed RT-PCR analysis to assess the expression levels of a number of pro- and anti-inflammatory-related genes.

Results: As compared to vehicle, fluoxetine decreased TNF-a mRNA expression level in the stress condition but did not affect it in the enriched condition. Whereas IL-1b mRNA expression was increased by treatment in enrichment but not affected in stress. The change in IL-1b mRNA levels was paralleled by concordant modifications of IL-1b precursor and mature protein levels, fluoxetine-treated subjects showing a decrease in pro-IL-1b and an increase in mature IL-1b compared to vehicle. IFN-g expression levels were modified by fluoxetine as compared to vehicle only in the stressful condition, treated mice showing decreased mRNA levels compared to controls. RT-PCR analysis revealed that in microglia fluoxetine treatment administered in the enriched condition increased pro-inflammatory and decreased anti-inflammatory-related genes expression, in particular, iNOS, cd86, IL-15, IL-1b and IL-23 mRNA levels were increased, while arg-1, ym-1, IL-10, IL-1ra were reduced compared to vehicle. An opposite effect was found when fluoxetine treatment was administered in the stressful condition, specifically: Arg-1, cd206, ym-1, TGF-b, socs3, IL-10, IL-1ra, fizz-1 mRNA levels were increased, while iNOS, TNF-a, IL-1b, IL-6 and IL-23 levels were decreased compared to vehicle.

Conclusions: The present findings show that the effects of SSRIs on inflammation depend on the quality of the environment and provide a possible explanation for the inter-individual differences in SSRI action and effects. The increased understanding of the molecular mechanisms underlying this interplay may allow for more effective personalization of antidepressant treatment strategies based on the quality of the living environment of the depressed patient.

Literature Reference

DISRUPTION OF SOCIAL RECOGNITION IN RATS BY RELAXIN-3 AGONIST TREATMENT: TARGET NEURONS AND ERK ACTIVATION IN THE EXTENDED AMYGDALA

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Various neuropeptides can modulate social behaviour through specific areas of the extended amygdala. This area is also targeted by the nucleus incertus in the pontine tegmentum which contains GABA neurons expressing the neuropeptide relaxin-3. The nucleus incertus is the primary centre of the mammalian CNS expressing this peptide and the amygdala, septum and hippocampus receive prominent inputs from the nucleus incertus. **Purpose.** We hypothesized that relaxin-3, acting via its cognate G-protein-coupled receptor, RXFP3, might modulate social recognition behaviour. **Objective.** Our goal is to study the effects of the central administration (icv) of a relaxin-3 agonist at different stages of a social recognition test in adult male rats in the 3-chamber paradigm. **Methods.** During the first trial, the test rat was allowed to explore a conspecific subject and an object; and during the second trial it was allowed to choose the same familiar subject or a novel conspecific rat. Test rats explored the conspecific for longer than the object during the first trial and the novel rat for longer than the familiar subject during the second trial. **Results** While prior agonist infusion did not affect the outcome of the first trial, administration prior to the second recognition trial reduced the differential in time spent exploring the familiar and novel conspecifics. In situ hybridization has revealed that RXFP3 mRNA is expressed by GABA neurons in the extended amygdala that express combinations of CRH, somatostatin and prodynorphin. Furthermore, neurochemical studies revealed that RXFP3 agonist-treated rats display an increase in ERK phosphorylation in specific nuclei of the amygdala. However further studies are required to determine the relationship of these effects to specific behavioural processes and particular cell types. **Conclusions.** These data indicate that relaxin-3/RXFP3 signalling can alter social recognition and this modulation may occur via specific neurons in various regions of the extended amygdala.
INACTIVATION OF THE NUCLEUS INCERTUS DISRUPTS SOCIAL RECOGNITION THROUGH PROJECTIONS ON HIPPOCAMPUS, AMYGDALA AND SEPTUM IN ADULT MALE RAT

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Modulation of hippocampal and amygdala function depends on ascending subcortical projections. Both, hippocampus and amygdala receive ascending projections from the nucleus incertus (NI) in the pontine tegmentum. NI uses GABA as neurotransmitter that colocalizes with the neuropeptide relaxin-3 (RLN3). RLN3 belongs to the superfamily of relaxin and insulin peptides. Tracing studies suggest that NI pathways may play a relevant role in the integration of information related to memory and attention.

PURPOSE. The aim of this work is to demonstrate an effect of NI inactivation in social recognition by using the 3 rooms maze.

METHODS. Adult male wistar rats were NI lesioned by stereotaxic infusion of quinolenic acid. The social recognition of three chambers was developed in two trials. On the first trial, the subject problem was allowed to explore between an inanimated object and another subject. On the second trial, the problem subject was allowed to explore the familiar and the new subjects.

RESULTS. Both, lesioned and sham animals were able to differentiate between the subject and the object on the first trial. However, during the second trial while sham animals spent more time exploring the novel subject comparing to the familiar one, the lesioned animals were unable to differentiate between them.

Regarding to c-Fos expression levels, there were a significant difference between sham and lesion group in the horizontal limb of the diagonal band and in the nucleus triangularis septalis of the septum, on piriform cortex and central nucleus of the amygdala. Also, there were significant differences between both groups in CA1, CA2 and CA3 fields of the hippocampal formation.

CONCLUSIONS. We have demonstrated that NI facilitates the mechanisms of social recognition in rats, and this modulated is being done through the amygdala, septum and hippocampus.
DIAGNOSIS AND PROGNOSIS OF ANGIO-CEREBRAL-RENAL DYSFUNCTION IN ISCHEMIC STROKE
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Objectives: Ischemic stroke (IS) and chronic kidney disease (CKD) are the important global medico-social problems in the world because of high prevalence among adult population. Patients with CKD have a high risk of stroke development, and the presence of CKD in stroke often worsens the course and prognosis of this acute cerebrovascular disease. Although stroke is an emergency disease sharing the same atherosclerotic and vascular risk factors with ischemic heart disease, the association of renal function and stroke is poorly investigated. Moreover, there were no studies on renal dysfunction (RD) in ischemic stroke (IS) depending on pathogenic heterogeneity yet.

Purpose: to evaluate the development of angio-cerebral-renal dysfunction in IS with the development of diagnostic and prognostic criteria and methods of diagnosis and prediction.

Methods: A total of 302 patients with first-ever IS were examined. The degree of stroke severity was assessed according to Scandinavian, Orgogozo and Original (Gusev-Skvortsova) stroke scales. To determine IS subtypes, the scale and algorithm for differential diagnosis of IS pathogenetic subtypes developed by us (Patent for invention No. IAP 04956, 2014) was used. To assess renal dysfunction (RD), serum creatinine and urea levels were determined, glomerular filtration rate (GFR) was calculated according to CKD-EPI formula (2011), a comprehensive urine analysis was performed using Combina 13 test strips (dipstick methodology), albumin/creatinine ratio (A:C) was calculated, ultrasound of the kidneys was performed. To study angiogenesis and endothelial dysfunction, the levels of VEGF and endothelin-1 in blood serum were determined by enzyme immunoassay. Statistical processing of the results was carried out using variational parametric and nonparametric statistics.

Results. Depending on IS subtypes, atherothrombotic subtype (ATS) was determined in 40.4%, lacunar (LS) - in 39.1%, cardioembolic (CES) - in 12.3%, IS of another determined or mixed etiology (ADS) - in 3.6%, cryptogenic stroke (CS) - in 4.6% of patients. Depending on renal functional state, all patients with IS were divided into two main groups: 1 group (RD +) - 196 (64.9%) IS patients with RD and 2 group (RD -) - 106 (35.1%) IS patients without concomitant RD. The highest peak of RD was observed in acute and acute periods of IS, decreasing in the late recovery period. Most often RD was noted in ATS (41.3%) and LS (39.8%), and in 5.6% of cases in CS (RR=1.98, AtR=0, OR=2.04, EF=49.6). At RD the disease was characterized by medium-severe course and more frequent consciousness impairment. The markers of angio-cerebro-renal dysfunction in IS were pelvic disorders, ataxia, bulbar or pseudobulbar syndrome, high values of blood pressure, especially diastolic BP, cognitive disorders, hypercreatininaemia, uremia, decreased GFR, microalbuminuria, proteinuria, leukocyturia, hematuria and signs of endothelial dysfunction.

Conclusions. Thus, angio-cerebro-renal syndrome in IS has been described for the first time. Its clinical manifestations vary in IS different heterogeneous subtypes. To diagnose and predict angio-cerebro-renal dysfunction in IS, markers with high diagnostic sensitivity, specificity and prognostic significance have been identified, diagnostic and prognostic criteria have been developed. The computer program developed by us (№DGU 03786, 2016) will be helpful tool in monitoring and treating such patients, allowing predicting development of angio-cerebro-renal dysfunction in patients with stroke.

Literature Reference
BLUNTED BASAL CORTICOSTERONE PULSATILITY PREDICTS POST-EXPOSURE SUSCEPTIBILITY TO PTSD PHENOTYPE IN RATS
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Objectives: Glucocorticoids are characterized by both circadian and pulsatile patterns of secretion. Pulsatility of glucocorticoids has been determined to be critical for optimal transcriptional, neuroendocrine, and behavioral responses. We used an animal model of PTSD to assess whether stress-induced impairment of behavioral responses is mediated by an aberrant secretion of corticosterone.

Purpose: Examine whether PSS-induced impairment of behavioral responses is mediated in part by aberrant secretion of corticosterone.

Methods: Serial blood samples were collected manually via the jugular vein cannula during the light-(inactive)-phase in conscious male rats at 20-min intervals for a period of 5 h before and 6.5 h after exposure to predator scent stress. The outcome measures included behavior in an elevated plus-maze (EPM) and acoustic startle response (ASR) 7 days after exposure. Individual animals were retrospectively classified as having "extreme", "partial", and "minimal" behavioral responses according to pre-set cut-off criteria for behavioral response patterns. Corticosterone secretion patterns were analyzed retrospectively.

Results: Under basal conditions, the amplitude of ultradian oscillations of corticosterone levels, rather than the mean corticosterone level or the frequency of corticosterone pulsatility, was significantly reduced in individuals who displayed PTSD-phenotype 8 days later. In addition, extreme disruption of behavior on day 8 post-exposure was also characterized by a blunting of corticosterone response to the stressor. Animals with behavior that was only partially affected or unaffected displayed none of the above changes.

Conclusions: Blunted basal corticosterone pulse amplitude is a pre-existing susceptibility or risk factor for PTSD, which originates from prior (life) experiences and may therefore predict post-exposure PTSD-phenotype in rats. Further studies confirming these findings in animals and in human subjects are required to ascertain whether dysregulation in pulsatility indeed predisposes individuals to, or in fact underlies, faults in the HPA-axis response to stress and renders them vulnerable to PTSD.
CORTISOL AWAKENING RESPONSE AND SLEEP DURATION, BUT NOT SEX HORMONES, INFLUENCE STARTLE RESPONSE IN LATE PREGNANCY

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Objectives: To investigate the relation of startle response with cortisol awakening response (CAR), sleep duration as well as gonadal hormones in pregnant women.

Purpose: To further understanding of correlates of sensorimotor response as a neurophysiological process related to endocrine and physiological alterations in women in their late pregnancy.

Methods: Totally, one hundred and three pregnant women in gestational week 35-39 were recruited between January 2010 and May 2013. The startle response was measured as the blink response to an acoustic startle-eliciting stimuli delivered binaurally. All the participating women were screened for ongoing psychiatric disorders. Salivary cortisol levels were used to estimate the area under the curve with response to increase in cortisol following awakening, whereas the women where asked about sleep duration the night before the session. A venous blood sample was taken before the session to measure progesterone and cortisol levels. To investigate the relation of startle magnitude with AUCi and sleep duration, Pearson correlation tests (r) were performed.

Results: Our preliminary analyses show that startle magnitude was higher in pregnant women with greater AUCi (r = 0.270; p = 0.005) and short sleep duration (r = -0.19; p = 0.06). No association was found between startle magnitude and blood levels of progesterone (p = 0.617) or cortisol (p = 0.503).

Conclusions: Increased startle magnitude in pregnant women with higher cortisol awakening response may be interpreted as heightened neurophysiological reactivity, likely associated with altered stress system functioning. Furthermore, increased startle magnitude in pregnant women who slept less corroborate previous findings on the association between impaired sensorimotor gating and sleep deprivation in postpartum women. The lack of association between startle response and hormonal levels of progesterone and cortisol, suggests that endocrine responsiveness rather than hormonal levels is relevant to the startle response.

THE EFFECT OF NICOTINE AND MENSTRUAL CYCLE PHASE ON DECISION-MAKING IN WOMEN PERFORMING THE IOWA GAMBLING TASK
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Objectives: To investigate Iowa gambling task (IGT) performance in relation to menstrual cycle phase and acute nicotine administration in young women.

Purpose: The purpose of the project was to deepen knowledge on how reward-based decision-making is affected by sex hormones and nicotine in healthy women.

Methods: To date, twenty-two healthy, naturally cycling, non-smoking women completed the IGT in two randomized sessions (i.e. baseline and after intranasal administration of 0.5 mg nicotine) during the same menstrual cycle phase. In both sessions, women reported symptoms of anxiety and depression. The outcome measures were total net score, choices of decks, amount of earnings and losses per block, frequency of loss scores, and total score per block (learning curves). Estrogen and progesterone levels were inferred from self-reports on menstrual cycle phase. Repeated measures one-way analysis of variance models, followed by Tukey’s post-hoc test, were used to assess the interaction effect of nicotine with sex hormones on IGT performance.

Results: Out preliminary findings suggest that women performing the test in a phase of the menstrual cycle characterized by low estrogens and progesterone levels selected advantageous over time. Oppositely, high levels of estrogens (mid- to late follicular phase), alone and in combination with high levels of progesterone (luteal phase), to disrupt the expected IGT learning curve. Regarding nicotine, our findings indicate a tendency to choose more advantageous cards following exposure to nicotine.

Conclusions: The expected shift from explorative behaviour in the beginning towards an exploitative strategy seemed to be disturbed by estrogen and progesterone fluctuations. Ongoing analyses will investigate interaction effects between sex hormones and nicotine in a larger sample.

Literature Reference
Cognition and Behavior
ENVIRONMENTAL ENRICHMENT AS A THERAPEUTIC AVENUE FOR ANXIETY IN AGED WISTAR RATS: EFFECT OF CAT ODOR EXPOSITION AND GABAergic INTERNEURONS

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The use of more ethological animal models to study the neurobiology of anxiety has increased in recent years. We assessed the effect of an Environmental enrichment (EE) protocol (24h/day over a period of two months) on anxiety-related behaviors when aged Wistar rats (21 months old) were confronted with cat odor stimuli. Owing to the relationship between GABAergic interneurons and the anxiety-related neuronal network, we examined changes in the expression of Parvalbumin (PV) and 67 kDa form of glutamic acid decarboxylase (GAD-67) immunoreactive cells in different brain regions involved in stress response. Behavioral results revealed that enriched rats traveled further and made more grooming behaviors during the habituation session. In the cat odor session, they traveled longer distances and they showed more active interaction with the odor stimuli and less time in freezing behavior. Zone analysis revealed that the enriched group spent more time in the intermediate zone according to the proximity of the predator odor. Regarding the neurobiological data, the EE increased the expression of PV positive cells in some medial prefrontal regions (cingulate and prelimbic cortices), whereas the GAD-67 expression in the basolateral amygdala was reduced in the enriched group. Our results suggest that EE is able to reduce anxiety-like behaviors in aged animals even when ethologically relevant stimuli are used. Moreover, GABAergic interneurons could be involved in mediating this resilient behavior. In our opinion, our study is innovative and it has shed some light on the effect of EE on anxiety-related behaviors when it is started at advanced age. In general, we achieved our aims and we showed that EE is able to reduce anxiety-related behaviors, even when more ethological stimuli are used. One implication of our results is the possibility to develop intervention programs, similar to EE in rodents, to promote resilient behaviors in aged people.

EFFECT OF GTF2IRD2 ON VISUOSPATIAL SKILLS AND SOCIAL COGNITION IN WILLIAMS SYNDROME
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Williams syndrome (WS) is a rare genetic disease that results from a heterozygous deletion in the 7q11.23 cromosomal region. Usually, the affected region in 92% of cases - typical - contains 1.55 Mb of sequence and codes for 25 genes. The other 8% has a deletion greater than 1.8 Mb - atypical - and affects 2 other genes, one of them the GTF2IRD2. Currently, there is no consensus on the cognitive-behavioral phenotype/genotype relationship of patients with Williams syndrome, since there is a large number of genes about which we have little knowledge about their role in the clinical characteristics of the behavioral phenotype. The present study aimed to identify the role of GTF2IRD2 in the cognitive behavioral profile of WS patients. Participants were 8 patients with no deletion of GTF2IRD2 and 3 patients with deletion of this gene. Patients were between 7 and 16 years and were clinically diagnosed by a geneticist. The size of the deletion was determined by the Optimal CytoScan microarray technique and for the cognitive and behavioral performance a neuropsychological battery was used. The results indicate that patients with GTF2IRD2 deletion have greater visuospatial difficulties (p <.05) and greater behavioral problems associated with the construct of social cognition (emotional recognition, empathy and theory of mind) (p <.05). Our findings agree with Porter et al. (2012), who found behavioral alterations similar to those reported in this study. In addition, these findings provide new evidence of the implication of GTF2IRD2 on behaviors that are related to social cognition and visuospatial skills, since this gene has been associated to the development of cerebellum and dorsolateral and orbitofrontal prefrontal areas (Tipney et al., 2004).

Keywords: Williams syndrome, Genotype, Cognitive-behavioral phenotype, Neuropsychology, Genetics

Literature Reference:
ORAL AND WRITTEN RECALL IN THE SHORT-TERM MEMORY TASK IN ADULTS WHO STUTTER: A POSSIBLE ROLE OF DORSOLATERAL PREFRONTAL CORTEX IN ANXIETY-RELATED MEMORY IMPAIRMENT

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Objectives: The participants should be able to recognize the role of the right dorsolateral prefrontal cortex in the anticipation anxiety in adults who stutter. Also, the presentation should shed more light on the process of short-term memory testing using The Digit Span task (DST) in adults who stutter.

Purpose: To quantify the effect of anticipation of oral response in DST on recall accuracy and on EEG power spectra changes in beta (13-30 Hz) frequency bands in adults who stutter (AWS).

Methods: The EEG was recorded during a forward DST in 20 AWS and 20 peers who do not stutter (AWNS). The DST had three levels: three, five and seven digits to be remembered. The trials were randomized in memory load level and response modality. After stimulus presentation, the participants were instructed to recall digits in either oral or written response modality. The 5-second retention period taken from EEG trace after stimulus presentation and recall modality requirement, and recall was analyzed using spectral analysis (Fast Fourier Transform) and source localization (sLORETA).

Results: AWS had lower accuracy during oral response in DST compared to AWNS. Written response modality yielded no difference between AWS and AWNS. Increase in EEG beta (13-30 Hz) spectral power in right dorsolateral prefrontal (rDLPFC) region (F4 region in 10/20 International system for electrode placement) was found during anticipation of oral response in AWS. A negative correlation was found between EEG beta (13-30 Hz) spectral power increase in rDLPFC and verbal recall accuracy in AWS.

Conclusions: AWS show a drop in performance on orally tested short-term memory, which could be connected to anxiety due to anticipation of verbal response. Increased EEG beta (13-30 Hz) spectral power could be response modality- and not load-related in DST. Further experimental studies exploiting possibly diverse cognitive tasks and not only short-term memory, in task-induced anxiety are needed.
A DOG OR BETTER A CAT? HEMISPHERIC DOMINANCE AND CATEGORIZATION IN PIGEONS
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Objectives: Cerebral asymmetries in the vertebrate brain are implemented as differences in the preferential encoding strategies of the two brain halves. These differences require mechanisms entailing the dominance of one hemisphere controlling response selection and behavioral output in case of conflicting information processing. This metacontrol is mediated by intra- and/ or interhemispheric neuronal mechanisms, which presumably differ depending on cognitive complexity of the particular tasks.

Purpose: For a deeper understanding of the underlying mechanisms, we explored metacontrol in pigeons when confronted with an ambiguous categorization task.

Methods: We trained pigeons simultaneously on two categories (cats or dogs, respectively) whereby each hemisphere learnt only one of the categories. During learning phase, the animals had to discriminate sets of photographs that depicted scenes with (S+) or without (S-) dogs or cats, respectively. Each eye (and hence, the contralateral hemisphere) was trained once a day with a set of stimuli representing the hemispheric-specific category and training alternated between the seeing conditions each day. After reaching the learning criterion and passing monocular transfer tests that verified successful categorization, the binocularly seeing animals were confronted with ambiguous stimulus pairs that combined a picture with a cat (S+ for one hemisphere) and a picture with a dog (S+ for the other hemisphere). Pecking onto one of the stimuli indicated the hemisphere taking charge of the pecking response and hence, dominates choices.

Results: Our data demonstrated that the hemispheres did not differ in acquiring the two categories but displayed stable individual hemispheric dominances in conflict choices. Control experiments investigated in how far metacontrol depended on the available strategies to solve the task.

Conclusions: The individual dominance pattern was especially pronounced when a categorization strategy was necessary for decision. The observed response patterns provide important insight into the functional organization of a lateralized brain.
SPECIFIC INVOLVEMENT OF THE CAUDAL HIPPOCAMPUS IN THE CONTROL OF EXPLORATORY BEHAVIOR IN MICE AND VOLES
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Exploratory behavior is a necessary component of cognitive mapping which is hippocampal dependent (O'Keefe & Nadel, 1978). Complete lesion of the hippocampus usually results in hyperactivity and impaired exploration in rats, but effects of partial hippocampal lesions were not always found, especially after ventral hippocampal lesions (e.g. Bannerman et al., 2003). The role of different hippocampal subregions in the control of exploration in mice and other rodents is poorly studied, although species-specific features of the functions along the septotemporal axis of the hippocampus are possible. The involvement of the caudal hippocampal subregion was assessed in a series of experiments where different aspects of locomotion in various types of open field were studied in C57BL/6 mice and bank voles (Clethrionomys glareolus). Using c-Fos as a marker of neuronal activity showed that the caudal hippocampus, including ventral and intermediate subregions is specifically activated during exploration. Selective cytotoxic (NMDA) lesions of this part significantly affected the character of locomotion in both species, and this alteration was context-specific, marked impairment (hyperactivity, decreased tortuosity, rearing, a change of path segment characteristics and others) was found in a large (220 cm diameter) arena. The size of the arena influenced only caudal hippocampal subfields; c-Fos expression was high in CA3 and dental gyrus in mice tested in the large arena. In the experiments with the large arena with contrasted context zones (wall/center, shadow/light and food/nofood) no decreased anxiety was found in caudal hippocampal lesioned mice, however they demonstrated a sharp nonflexible change in activity depending on the availability of food and especially arena lighting. Recent naturalistic experiments showed increased activation in both whole dental gyrus and the caudal CA-fields after homing in bank voles. These findings suggest a specific role of this hippocampus region in the control of exploration and context-dependent movement.
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DEVELOPMENT OF A BRIEF CONGNITIVE TEST FOR ASSESSMENT OF OLDER PEOPLE IN HONG KONG
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**Objectives:** Readers will learn from this poster presentation about a new brief cognitive test for assessment of older people with low educational level.

**Purpose:** To develop and validate a brief cognitive test for assessment of older people with low educational levels.

**Methods:** The new cognitive test was developed based on an extensive review of the literature, as well as the views of an Expert panel. Items with paper and pencil were avoided to decrease the influence of education.

Three groups of subjects aged 65 or above were recruited: normal older people recruited in elderly centres, people with Mild NCD (Neurocognitive Disorder) and people with Major NCD (Neurocognitive Disorder). Clinical diagnosis of Major NCD and Mild NCD according to DSM-5 were made by experienced psychiatrists. All subjects were included in the study after they gave written consent.

The brief cognitive test and Mini Mental State Examination (MMSE) were administered to the subjects. The performance of the new Chinese cognitive test in differentiating subjects with Major NCD, Mild NCD and normal elderly were compared with the clinical diagnosis and the MMSE.

**Results:** In total, 359 subjects were recruited, with 99 normal controls, 132 subjects with major NCD and 128 with minor NCD.

Inter-rater reliability, test-retest reliability after 6 weeks, of the new cognitive test are good. The internal consistency of the new cognitive test was satisfactory.

The mean MMSE and new cognitive test scores showed significant differences among the 3 group of subjects. In the ROC curve analysis of the new cognitive test in differentiating normal subjects from those with cognitive impairment (Mild NCD + Major NCD), the area under the curve (AUC) was 0.942 with an optimal cut-off score of 12/13, sensitivity was 0.85 and specificity 0.87. The performance of MMSE in differentiating normal from cognitively impaired subject is inferior to the new cognitive test, with an AUC of 0.904, with an optimal cut-off score of 24/25, sensitivity was 0.83, specificity 0.84.

**Conclusions:** We have developed a brief cognitive instrument useful for cognitive screening in populations with low educational level. Further cross-validation studies involving a larger number of subjects are required.
NEURAL MECHANISMS FOR DELAY-DISCOUNTING IN HIPPOCAMPUS
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Dysfunctions of the hippocampus or medial prefrontal cortex (mPFC) can lead impulse control disorders, characterized by mistimed actions or decisions without due consideration of their consequences. However, it is not well known the activity especially in hippocampus associated with impulsive disorders. Here, we characterized unit activity in hippocampal CA1 of mice performing a delay-discounting task with comparing the activity in mPFC.

A delay-based decision task was performed in an automated T-maze. The delay length in the large-reward arm was progressively increased in each block (0, 5, 10, 20 and 40 s). Place-dependency in the delay-activated neurons was also investigated by switching delayed arm with non-delayed arm. We compared firing rate between before and after reward size decreased. Finally a mutant line, knock-out of NMDA receptor in CA1 excitatory neurons, showing impaired delay-discounting was subjected to electrophysiological study in CA1.

Sizable amount of CA1 and mPFC excitatory neurons showed significant increases (about 40%) or decreased (about 50 %) in their firing rates during long (>20 s) delay periods. Numerous (about 70 %) delay-activated neurons found in CA1 were location-selective (neurons specifically fired on one side) whereas majority of neurons in mPFC were location-unselective. Firing rate was decreased in CA1 but more widely varied in mPFC by decreasing reward size. The distribution of delay-activated and -suppressed neurons in mutants was significantly different from controls.

Our findings indicate that although hippocampal neurons sensitive to delay similarly to mPFC, hippocampal neurons encode the specific and integrated information for value, positions and delay compared to the mPFC neurons.
TIME-OF-DAY IMPACT ON SPATIAL MEMORY IN YOUNG AND AGED RATS

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Purpose: To study the effects of day-time and aging on spatial learning in the elevated plus-maze test in rats.

Methods: Young (2-months) and old (18-months) male Wistar rats, kept under a 12h light/12h dark cycle (lights on from 09:00-21:00 h), were exposed to the elevated plus-maze test, in the morning (10:00-11:30), early afternoon (14:00-16:00) and late afternoon (19:00-20:30). On the first training day, the animals were placed individually at the end of one of the open arms of the elevated plus-maze and the transfer latency to enclosed arms was noted (max 2 min). The test was repeated 24 h (young and old animals) and 45 days (young animals) later on. A long latency period to reach the enclosed arm indicated poor retention compared to significantly shorter latencies.

Results: In the morning and in the early afternoon, the young rats showed significantly decreased transfer latency time on the 24h retention trial but significantly increased on the 45-day trial. In all the tested periods, the latency time on the 24 h retention trial was significantly lower in the young rats, compared to the old ones. In both ages, the lower transfer latency time on the 24 h retention trial was in the early afternoon.

Conclusions: There were significant effects of the time-of-day on spatial memory in young animals but not in the old ones. Furthermore, in young animals the long-term memory seems to be more affected in the late afternoon, while forgetting is more pronounced in the morning and early afternoon than in late afternoon. This study indicates that the period of day affects differently the long-term memory formation and forgetting process.

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BENEFICIAL INTERACTION BETWEEN B VITAMINS AND OMEGA-3 FATTY ACIDS IN SLOWING BRAIN ATROPHY AND COGNITIVE DECLINE IN SUBJECTS WITH MILD COGNITIVE IMPAIRMENT (MCI)

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Introduction: Raised plasma homocysteine (tHcy) and low intake of omega-3 long chain fatty acids (FA) are risk factors for Alzheimer’s disease (AD). In subjects with MCI the VITACOG trial showed that B-vitamin treatment reduced the brain atrophy rate and slowed cognitive decline. We now show that these effects of B-vitamins are influenced by baseline plasma omega-3 FA concentrations.

Method: The effects of B vitamin intervention in VITACOG subjects was analysed according to baseline omega-3 FA (DHA and EPA) concentrations.

Results: There was a significant interaction (P = 0.024) between B-vitamin treatment and plasma omega-3 FA on brain atrophy rates. In subjects with high omega-3 FA, B-vitamin treatment slowed the atrophy rate by 40% compared with placebo, whereas B-vitamins had no effect on atrophy in subjects with low omega-3 FA. A similar interaction was found between omega-3 FA and the beneficial cognitive effects of B-vitamin treatment: high baseline omega-3 FA levels enhanced the slowing of cognitive decline following B-vitamin treatment.

Conclusion: The beneficial effect of B-vitamin treatment on brain atrophy and cognition was found only in subjects with high plasma omega-3 FA. The results highlight the importance of identifying subgroups likely to benefit in clinical trials. A clinical trial is needed to see if a combination of B-vitamins and omega-3 FA will slow conversion from MCI to AD.
MONOSODIUM GLUTAMATE TREATMENT IN MICE ELICITS HISTOPATHOLOGICAL AND BEHAVIOURAL FEATURES OF ALZHEIMER’S DISEASE
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Objectives: Although monosodium glutamate (MSG)-induced neurotoxicity has been recognized for decades, the potential similarities of MSG model to AD-type neuropathology have only been recently investigated.

Purpose: The present study investigated species-typical behaviours, biochemistry and histopathology in MSG-treated mouse model of AD.

Methods: 4-weeks old male mice (N=14) received 5 subcutaneous MSG (2g/kg) injections on alternate days, or saline vehicle (N=12). At age 9-11 weeks, mice were subjected to neurobehavioral tests for species typical behaviour and working memory. At age 12 weeks, mice were killed and brains excised. Accumulation of hyperphosphorylated tau protein (phospho S214; Abcam ab170892) was assessed in cortical neurons by immunohistochemistry. Concentrations of P-tau231P and β-amyloid peptide were measured in cerebral cortical homogenates.

Results: A 78% increase in cortical concentrations of phosphorylated tau protein was observed in MSG mice (P=0.046). Immunohistochemical staining showed intraneuronal neurofibrillary tangles immunostained by Anti-tau monoclonal antibodies. Nest-building behavior was significantly impaired in MSG-treated mice, (P=0.023), while digging and burrowing were not. Spontaneous T-maze alternation was impaired in MSG-treated mice (P=0.009), suggesting defective short-term working memory. MSG induced also a 56% reduction in exploratory head dips in a holeboard (P=0.009).

Conclusion: The reduction in T-maze alternation, nest building and holeboard exploration resembles the behavioural profile of the cytotoxic hippocampal lesion model of AD. This, and the presence of hyperphosphorylated tau, suggests that MSG-treated mouse replicates aspects of AD, although the MSG administration regimen requires optimisation.
PHARMACOLOGICAL BLOCKADE OF LYSOPHOSPHATIDIC ACID LPA\textsubscript{1} RECEPTOR WITH Ki16425 MODULATES THE EFFECTS OF ETHANOL ON THE BRAIN AND BEHAVIOR

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Background: The lysophosphatidic acid (LPA) is an ubiquitous lysophospholipid that is implicated in the modulation of emotional and motivational behaviors. Recently it has been suggested a relevant role for the LPA/LPA\textsubscript{1} receptor signaling system in alcoholism.

Purpose: This pre-clinical study investigates whether systemic LPA\textsubscript{1/3} receptor blockade with Ki16425 would modulate the neurobehavioral effects of ethanol.

Methods: Male Wistar rats or mice (Swiss, C57BL6/J or hybrid C57BL/6J×129X1/SvJ background) were treated with Ki16425 (20 mg/kg, intraperitoneal) or vehicle solution and used in four experiments: 1) oral ethanol self-administration, 2) loss of righting reflex, 3) ethanol-induced conditioned place preference (CPP) and 4) ethanol-withdrawal behavioral symptoms.

Basal neuronal activity and adult hippocampal neurogenesis were studied by immunohistochemistry for the expression of \textit{c-fos} and proliferating-cell-nuclear-antigen/doublecortin, respectively.

Plasma concentrations of corticosterone, autotaxin and LPA were determined using ELISA kits. Furthermore, mRNA levels related to the glutamate neurotransmission system in the medial prefrontal cortex and the hippocampus were determined by quantitative real-time PCR.

Results: Acute Ki16425 reduced motivation for ethanol, but not for saccharin, in chronically self-administering rats. In mouse experiments, Ki16425 treatment preceding intraperitoneal ethanol injection reduced ethanol-induced sedation, ethanol reward (CPP) and ethanol-withdrawal behavioral symptoms. Specifically, Ki16425 attenuated the impact of ethanol on nest building, physical signs and spatial working memory; but Ki16425 did not affect corticosterone levels or anxiety-like behaviors after ethanol. Regarding brain measurements, immunohistochemistry revealed that Ki16425 protects from the actions of ethanol on basal neuronal activity in the medial prefrontal cortex and on adult hippocampal neurogenesis. Furthermore, quantitative real-time PCR for glutamate-related genes showed unique neuroadaptations in the mice chronically treated with both Ki16425 and ethanol. In plasma, ethanol reduced circulating autotaxin concentrations, while Ki16425 increased LPA levels.

Conclusions: These results reveal the potential usefulness of systemic LPA\textsubscript{1/3} receptors antagonists as a novel treatment for alcohol-related disorders.
A PRECLINICAL MODEL FOR IDENTIFYING RATS AT RISK OF ALCOHOL USE DISORDER
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Objectives: The underlying factors for individual vulnerability to develop alcohol use disorder (AUD) have not been completely elucidated, but neuroscience-based clinical phenotypes could advance genetic studies of etiology and treatment.

Purpose: Implementing a novel approach to identify rats exhibiting high risks of losing control over alcohol intake following the model developed by Deroche-Gamonet et al ¹.

Methods: Inter-individual vulnerability to alcohol abuse was evaluated in rats daily trained for 80 days by modeling the operational definitions of DSM criteria: inability to abstain from alcohol seeking during signaled periods of reward unavailability, increased motivation to consume alcohol assessed in a progressive effortful task and persistent alcohol taking despite aversive foot shocks. Further, effects of Baclofen on ethanol seeking were evaluated. Reinstatement paradigm after a period of forced abstinence was also tested.

Results: Factor-analysis showed that the three addiction criteria loaded on one underlying construct accounting for 62% of variability indicating that they represent an underlying latent construct of addiction trait. Addiction trait-positive (A+) rats had higher scores on all three criteria compared to addiction trait-negative (A-) rats. A+ rats displayed an increased pre-morbid motor impulsivity, assessed in a 5-choice serial reaction time task. A+ rats exhibited a dose dependent decrease in motivation to seek ethanol under Baclofen treatment (2mg/kg, ip) and a persistent alcohol seeking compared over a 3-month period of abstinence, in contrast to A- rats.

Conclusions: The present model confirms that addiction-like trait develops in a small proportion of individuals exposed to ethanol. Further, development of this addiction trait not only requires prolonged exposure to alcohol but also depends on individual vulnerabilities or endophenotype like impulsivity that predispose individuals to lose control over alcohol consumption. The inter-individual differences of response to Baclofen points towards the rationality and the necessity of personalized treatment.

Literature Reference:
SYMPATHETIC ACTIVATION MEDIATES THE STRESS-INDUCED IMPAIRMENT OF COGNITIVE FLEXIBILITY
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Objectives: Cognitive flexibility emerges from the interplay of multiple cognitive systems, of which lexical-semantic and executive are thought to be the most important. Yet this has been largely ignored by previous research demonstrating that such forms of flexible thought deteriorate under acute stress.

Purpose: Motivated by this shortcoming, the purpose of this study was to evaluate several specific neurocognitive mechanisms implied to mediate the impairing effects.

Methods: Fifty-seven healthy adults were randomly assigned to psychosocial stress or control condition and assessed for performance on cognitive flexibility, working memory capacity, and semantic fluency. Stress response was indicated by changes in skin conductance, hearth rate, cognitive interference, and state anxiety.

Results: The results showed that stress impaired cognitive flexibility and this effect could be completely explained by the increased sympathetic activation. On the other hand, sympathetic activation was positively related to semantic fluency. Although working memory capacity was also impaired under stress, this effect was unrelated to sympathetic arousal.

Conclusions: The findings indicate that the impairment of cognitive flexibility is mediated by stress-induced sympathetic activation, which presumably modulates semantic retrieval. Specifically, stress level of arousal may decrease the ability to access and integrate remote ideas but enhance the retrieval fluency of close ideas represented in lexical-semantic and associative networks. The results also indicate that the impairment of cognitive flexibility and working memory are plausibly mediated by distinct neurobiological mechanisms.
ELECTROMAGNETIC FIELDS AND RECENT VS. REMOTE SPATIAL MEMORY IN YOUNG AND ADULT RATS
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Objectives: The exponential increase in the use of cellular mobile communication leads populations to be actively or passively exposed to electromagnetic fields (EMFs). Clinical and experimental studies showed that EMFs exposure may or may not induce cognitive changes. The impact of EMFs on long-term memory, i.e., consolidated at the systems level, has not yet been explored.

Purpose: Our project proposes to study the effects of a chronic EMFs exposure on the formation/persistence of a spatial memory in young (1-4 months) and adult (6-9 months) rats.

Methods: 72 Long Evans male rats were exposed to EMFs [LTE - 4G, 900 MHz, ~61 V/m, DASwhole body = 0.33 W/kg] in a reverberation chamber (4 h/day, 5 days/week for 3 months). Three groups were considered: chamber with EMFs (EMF) or without EMFs (Sham) and no chamber (Control). Subsequently, rats were tested in a Morris Water Maze (MWM) to assess learning and long term spatial memory at recent (1 day) and remote (25 days) delays. Anxiety (elevated plus maze) and horizontal locomotor activity in the home cage were also analyzed.

Results: In the MWM, no impact of EMF vs Sham was evidenced on learning and long-term spatial memory (1 day, 25 days), whatever the age. In adults, Control rats did not remember the platform location at 25 days while Sham and EMF rats did. In addition, in the 2 age-groups, there was no effect of EMFs exposure on anxiety and locomotor activity, when compared to Sham rats, but nocturnal locomotor activity was reduced in Controls as compared to EMF- and Sham rats.

Conclusions: A 3-month exposure to mobile phone EMFs (LTE, 4G) had no impact on spatial learning & memory retrieval, anxiety, and locomotion. Young rats did not show differential sensitivity to EMFs exposure supporting no evidence of age-dependent susceptibility. In adult rats, the behavioral effects of the exposure to the chamber (EMF & Sham vs Control) on locomotor activity and remote memory performance remain to be elucidated.

This project will be continued with the addition of a group of old rats (18-21 months). The determination of hippocampal and prefrontal gene expression and their potential epigenetic modulation are also under investigation. This study, using for the 1st time a 4G EMFs signal to investigate memory and its underlying mechanisms at various ages in the Rat, will bring new knowledges in the productive, still expanding and debated field of research on the possible impact of environmental EMFs on health.
ADULT VITAMIN D DEFICIENCY IMPAIRS LONG TERM POTENTIATION IN CA1 HIPPOCAMPAL NEURONS OF ADULT MALE BALB/C MICE
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Objectives: Adult vitamin D deficiency (AVD) is associated with cognitive decline in later life. We have reported in male BALB/c mice that dietary AVD results in reduced γ-aminobutyric acid and glutamate in the brain, as well as reduced attention [1,2], and increased latency to avoid shock zone during active place avoidance (unpublished). This impairment in spatial learning implicates dysfunction in hippocampal neurotransmission or long term potentiation (LTP). However, the neuronal mechanisms mediating impaired memory are unknown.

Purpose: We aimed to determine if hippocampal neurotransmission and LTP induction in CA1 neurons is inhibited by AVD.

Methods: Twenty week male BALB/c mice were fed a vitamin D deficient diet and compared to control mice fed the same diet supplemented with 1 IU/g vitamin D. After 20 weeks, mice were transcardially perfused with artificial cerebrospinal fluid (ACSF), and 400 μm coronal slices including hippocampus were superfused (ACSF, 32°C, 2 mL/min, >3h). Field excitatory postsynaptic potentials (fEPSPs, 0.05 Hz) were recorded from CA1 molecular layer (6-7 slices from 2-3 animals/group) or dentate gyrus (DG, 3-4 slices from 3 animals/group) by stimulating the stratum radiatum or medial perforant pathway, respectively. The recruitment of synaptic input and release probability was assessed by increasing stimulus intensity and the interval between two stimuli (50–2.5 Hz), respectively. In a subset of CA1 slices (3-4 from 2-3 animals/group), LTP was induced by applying 3 × 1 s, 100 Hz trains at 5 min intervals and the fEPSP slope was measured for 60 min.

Results: There was no effect of AVD on recruitment or release probability of synaptic input to CA1 or DG. AVD impaired LTP in CA1 for 60 min after induction relative to baseline (p < 0.05, Student’s t-test).

Conclusions: AVD did not affect fast-ionotropic neurotransmission to CA1 or DG, however it impaired LTP to CA1 neurons. This is consistent with increased latency to avoid shock during active place avoidance and provides evidence to suggest AVD is impairing memory formation. Ongoing research will determine the cellular mechanisms mediating impaired LTP in AVD.

Objectives: Recent studies have revealed that object-based attention plays key role in retaining bindings in working memory (WM).

Purpose: In the current study, we examined whether the consumed resource by the secondary task would return back to the WM task after the completion of the secondary task (recovery time) and led to binding recovery.

Methods: We manipulated the duration of the recovery time (500 ms vs. 1400 ms) and the type of the attention (object-based attention vs. space-based attention) consumed by the secondary task.

Results: By giving 900 ms of additional time, a significant binding performance-recovery was demonstrated. Such selective binding impairment and recovery, however, were absent when a space-based visual-search task. Moreover, modeling studies shows that this recovery was not due to increasing the resolution of the representation, but was attributed to increased probability of storage. This EEG studies showed that after the completion of the secondary task consuming object-based attention, a significant beta (13-18 Hz) activation was observed and lasted for at least 600 ms; while such enhanced beta was absent after the secondary task consuming space-based attention.

Conclusions: These results together imply that WM and external object-based attention share one resource pool, and a trade-off exists between the two. What new knowledge was gained from the project and what change(s) happened as a result?
OBJECTIVES: Given the accumulating evidence on the factors responsible for inducing drug cravings in the abstinent, the scope of cues investigated in the cue-reactivity paradigm has increased considerably. Yet, few studies have examined the effects of the intensity and endurance of different types of cues on their ability to induce craving. (50 words or less, at the conclusion of this presentation, the participants should be able to...e.g. demonstrate, recognize, diagnose, treat, etc.)

PURPOSE: Through comparing the abilities of the different types of cues in inducing craving, we could enhance our understanding of the underlying mechanisms of addiction and relapse behaviors.

METHODS: This study investigated differences among drug-related cues, negative physiological cues, and negative social cues in the induction of drug cravings among persons abstaining from heroin. The sample consisted of 74 males from three addiction rehabilitation centers in China, who were abstaining from heroin. They were assigned to short-term, medium-term, and long-term abstainer groups, based on their lengths of abstinence, and they completed a stress-imagery task.

RESULTS: The cravings induced by negative social cues were stronger than those induced by the other types of cues, and there was a significant interaction of cue type and abstinence length. Craving induced by negative physiological cues declined within approximately 6 months and the effects of drug-related cues decreased within 15 months, whereas craving induced by negative social cues remained after an abstinence period as long as 26 months.

CONCLUSIONS: Consistent with our prediction, different cues provoked different levels of craving. Craving induced by the three types of cues differed by length of abstinence. Negative social cues may be a primary factor in the relapse of heroin abstainers after a long period of abstinence.
SELECTION OF MICE FOR MORPHOLOGY AND BEHAVIOR TRAITS. EFFECTS ON COGNITIVE ABILITIES AND ANXIETY IN LABORATORY MICE
Olga Perepelkina, Alexandra Tarasova¹, Nadejda Ogienko, Irina Lilp, Inga Poletaeva.
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Two selection experiments were performed - the selection for large and small relative brain weight resulted in 15% brain mass, while the selection for high capacity to solve the cognitive task (the ability to extrapolate the direction of stimulus movement) resulted in creation of strain Ex (in comparison to control unselected mice – CoEX). The battery of behavioral tests applied demonstrated several significant differences between these strain pairs which were consistent selection. LB mice were significantly superior than SB in puzzle-box burrowing task, extrapolation task and T-maze task acquisition and demonstrated the lower level of anxiety in open field and EPM test as well as lower hyponeophagia in the special test. EX mice were significantly superior to controls in puzzle box task and hyponeophagia test, while their anxiety (EPM and light-dark test) was higher.

The comparison of mice from 4 strains mentioned above permits to demonstrate that anxiety indices obtained in different tests are not uniform, but heterogeneous by their mechanisms. The experiments demonstrated that the mouse ability to solve the cognitive tasks of different kind requires from an animal the expression of optimal ratios of anxiety, caution and explorative behaviors. As the differences revealed in these selection experiments are held in the selection generations these pairs of strains could be regarded as the plausible model for effects of pharmacological agents (drug capacity to modulate the expression of cognitive traits) in the search of means for behavioral correction.

The work was performed using the guidelines of EC Declaration 2010 (2010/63/EU). Partly supported by RFBR, grant N 16-04-01169 and State Registration Programm “Neurobiology of animal behavior” N NIOKTR AAAA-A16-11602166055-1.”
THE ASSOCIATIONS BETWEEN BRAIN-DERIVED NEUROTrophic FACTOR AND WATERPIPE SMOKING AMONG ADOLESCENTS: THE IRBID TRY

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Objectives: The current study examined the relationship between waterpipe (WP) smoking and circulatory BDNF among adolescents.

Purpose: Finding out the association, if any, between BDNF levels and waterpipe smoking will help in predicting the cognitive function of adolescents who smoke waterpipe.

Methods: The validated Arabic version of the YRBS was used to obtain self-reporting of tobacco patterns, while serum BDNF was determined with ELISA using commercially available kits (Human BDNF Duoset Kit R&D system, USA). Data were collected in 195 WP and 288 none smokers, of which 264 were females. The students were recruited from 7th (n=132), 8th (n=120), 9th (n=136), and 10th (n=94) grade.

Results: Simple linear regression analysis revealed that BDNF was related to WP smoking (p<0.0001), gender (p<0.0001), BMI (p<0.04), location (urban versus rural) (p<0.0001), but not age (p<0.3). Subsequent stepwise regression that included WP smoking, gender, BMI, and location, showed that only WP smoking (p<0.0001) and gender (p<0.0001) were related to serum BDNF. Also, the ANCOVA found a main effect for WP smoking (p<0.0001) and gender (p<0.0001) with lower BDNF in male WP smokers.

Conclusions: Circulatory BDNF was significantly diminished in adolescent WP smokers. This might impact cognitive function and predispose adolescents for behavioral changes include aggression, drug abuse vulnerability, attention deficit, and hyperactivity pattern.
MCI EVALUATION THROUGH EYE MOVEMENT’S ANALYSIS
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Objectives: Evaluate the relationships between eye movement during reading and Mild Cognitive Impairment (MCI).

Purpose: To develop a technique for accurate, objective, precise, non-invasive and economic MCI evaluation.

Methods: We analyzed the eye movement behavior during reading Spanish regular and highly-predictable sentences using an eyetracker.

The control group consisted of 35 elderly adults (24 Female and 11 Male), mean 70 years old (SD=6.2), with no known neurological and psychiatric disease and no evidence of cognitive decline or impairment in daily activities. The AD group; consisted of 22 Females, 13 Males; mean 68 years old (SD=6.4). The diagnosis of probable AD were based on DSM-IV. All AD patients underwent a detailed clinical history, physical/neurological examination and thyroid function test. Patients were excluded if they suffered from any medical conditions that could interfere with their cognitive decline.

Using the eye movement information data and linear mixed models we analyzed the effects of previous words properties (predictability, length, frequency) in the gaze and fixation duration.

Results: In Controls, changes in predictability significantly affected fixation duration along the sentence; noteworthy, these changes did not affect fixation durations in AD patients (t-value>3.5) [See reference].

Contextual-word predictability, whose processing require memory retrieval, only affected reading behavior in healthy subjects. In AD, this loss might reveal impairments in brain areas such as those corresponding to working memory and memory retrieval.

Conclusions:
Our study provides a test-bed for initial research on cognitive impairments linked to semantic, working and retrieval memory deficiencies. We were able to prove that deficits in the capacity for processing complex information are linked to memory guided eye movements. Early detection and monitoring opportunities in AD patients will be improved by this test. Furthermore, the results obtained with this novel methodology could become in time a simple marker for early disease detection.

Literature Reference

www-ebbs-meeting.com
Development of Wearable Device-Based Attention and Behavior Assessment (WD-ABA) System for Children

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Objectives: The wearable-devices (e.g. smart-watch) can be used conveniently for children as a tool measuring various behaviors such as attention and hyperactivity. Thus, we developed the wearable device-based attention and behavior assessment (WD-ABA) system to measure children’s attention and off-task behaviors in real-life setting.

Purpose: The purpose of this study was to develop WD-ABA, and to examine the validity of it.

Methods: We developed wearable device-based visual continuous performance tests (CPT) using signal detection theory. On CPT 1 target is yellow sun, non-targets are yellow moon and star. On CPT 2 target is pink heart with non-targets of green heart and pink diamond. Next, we administered the WD-ABA and standardized neurocognitive tests including attention subtests of Wechsler Intelligence Scale for Children, children's color-trails test, Stroop color and word test, and computerized attention test for children to 293 young children aged 5 to 7 years to examine the construct and concurrent validity of WD-ABA, and then established the age norms.

Results: Children showed the developmental trend of attentional abilities with age. The omission error, mean and standard deviation of response time measured by WD-ABA tended to decrease with age. These results suggested the construct validity of it. And there were significant differences in commission error and standard deviation of response time between boys and girls. Significant correlations were found between performances of WD-ABA and scores of standardized neurocognitive tests, suggesting its concurrent validity. In addition, activity (hand moving) levels during the WD-ABA were significantly correlated with omission errors of the CPT.

Conclusions: This study demonstrated that the wearable device-based attention and behavior assessment is valid, and would be an easy and convenient tool for assessing young children’s attention as well as hyperactivity in real-life setting.
TYPE OF REWARD INFLUENCES STRATEGY IN A PROBABILISTIC CHOICE TASK
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Objectives: The goal of this project was to compare decision strategies when mice are offered a natural reward or alcohol.

Purpose: We wanted to test potential differences in reinforcement associated with natural rewards vs. alcohol.

Methods: We have developed a novel method to assess behavioral strategy employed by mice when selecting between options associated with different probabilities of receiving a reward. A group of animals is implanted with radiofrequency chips and introduced to a sensor-equipped cage, where their activity is continuously recorded. After a period of adaptation, mice are offered access to saccharin or alcohol, and additionally free access to water. Initially, there is a 90% chance that access to saccharine or alcohol solution is granted after 2 seconds. As the procedure progresses, the probability changes periodically between 90% and 30% and cycles through all possible combinations.

Results: We tested choice between solutions 0.1% (w/v) saccharin, 4% (v/v) ethanol or a combination of them. In case of the sweetened water reward, the main factor affecting choice was time elapsed from last decision. The effect of the outcome of the previous choice was also significant, but overall smaller. In case of the alcohol solution, the effects of time and previous outcome were weaker, animals were more likely to repeat previous choice. We also observed that irrespective of strategy choices follow a specific time pattern, with majority occurring at discrete intervals.

Conclusions: The type of reward strongly affected animals’ behavioural strategy. Probabilistic access to sweetened water was associated with high probability of switching between choices, while access to alcohol solution led to frequent repeating of the same choice.
EMOTIONAL CONTAGION IN A RODENT MODEL OF AUTISM SPECTRUM DISORDER
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Objectives: To test emphatic abilities of a Fmr1KO(FVB) mouse, by checking whether these mice are capable of transferring the emotional information between familiar conspecifics.

Purpose: Proving an impairment in this domain would further validate Fmr1KO(FVB) mouse as a model of ASD and allow for future studies of the molecular mechanisms of such an impairment.

Methods: Animals were tested using the between subject transfer of emotional information protocol. In this paradigm, mice are housed in pairs for three weeks, one labelled as a Demonstrator, and the other as an Observer. In the test session, the Demonstrator is subjected to a series of aversive stimuli outside of the home cage, while the Observer remains there undisturbed. Then, the Demonstrator is returned to the home cage, where it can freely interact with the Observer. The following interactions are recorded and then analysed using BehaView software.

Results: Fmr1KO(FVB) Observers, unlike their WT counterparts, did not display an increase in social behaviours (i.e. the number and duration of side approach and anogenital area sniffing) upon being exposed to the stressed Demonstrators. In contrast to the Fmr1WT(FVB) mice, the Fmr1KO(FVB) Observers from the experimental group also had increased duration of self-grooming.

Conclusions: Here we report, based on the behaviour of the Observer from experimental group, that the Fmr1KO(FVB) mice, which are considered a monogenic animal model for autism spectrum disorder (ASD), have impaired empathic responsivity. This results, in correspondence to the previous studies, supports the Fmr1KO(FVB) mice as a model for ASD, and gives us an opportunity to study molecular mechanisms of emphatic response, but only in its simplest forms.
COGNITIVE AGING IN THE MARMOSET MONKEY (*CALLITHRIX JACCHUS*): A BEHAVIORAL STUDY USING A NATURALISTIC-LIKE APPROACH

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Objectives: Marmoset monkey, a small New World primate, is increasingly used in several fields of research, particularly in neuroscience and behavioral studies. The present study investigated the effects of aging on different cognitive processes, by using two tasks to test learning abilities, executive processes and response strategies in a naturalistic-like approach.

Purpose: Investigate the cognitive decline processes in the context of aging in the marmoset model.

Methods: Thirty six marmosets (2–14 years old) were tested in their home cages, unconstrained and without privation, in presence of their congeners. They had free access to an infrared touchscreen to perform shape discrimination reversal learning and delayed matching-to-position (DMTP) tasks. In addition to classical statistical methods, data analysis used the method proposed by Gallistel et al. (2004) to determine early changes in learning curves and predict the age at which a relative abrupt cognitive decline may appear.

Results: Cognitive impairment features were observed in middle-aged and older subjects concerning mainly perseverative responses, learning latency (number of trials to learning criterion) and response strategies. The learning latency was longer for older monkeys in the reversal task. From the age of 7, they made significantly more errors and showed perseverative responses before reaching the learning criterion.

In addition, the proportion of correct responses decreased with age in the DMTP task. This decline appeared at 6 years old. Furthermore, the proportion of win-stay and lose-shift strategies decreased significantly with age in both tasks.

Conclusions: Our study originally explored cognitive aging in the common marmoset. It reveals cognitive impairments related to inhibitory processes, cognitive flexibility, and spatial working memory for old and even middle-aged (6 – 7 years old) individuals. In line with anatomical neurodegenerative features (amyloid plaques and hyperphosphorylated tau (Rodriguez-Callejas et al. 2016)), we propose the common marmoset as a promising model of primate cognitive aging in a naturalistic-like context.
NEURAL FUNCTIONAL, MORPHOMETRIC, METABOLIC ABNORMALITIES ASSOCIATED WITH RECOGNITION DEFICIT IN OBSESSIVE–COMPULSIVE DISORDER
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Objectives: Obsessive–compulsive disorder (OCD) causes the neural dysfunction associated with cognitive deficit and emotional dysregulation. Although a few studies have revealed working memory (WM) impairment in OCD using anatomical/functional neuro-imaging and neuropsychological methods, the neural correlates of brain functional change and anatomical deficit remain unknown.

Purpose: This study assessed the neural correlates between brain functional change, anatomical deficit, and metabolic abnormality in patients with OCD using the combined functional MRI, voxel based morphometry (VBM), and MR spectroscopy.

Methods: Eighteen patients with OCD and 18 healthy controls matched for age, sex, and education level underwent high-resolution T1-weighted magnetic resonance imaging (MRI), event-related functional MRI (fMRI), and proton magnetic resonance spectroscopy (¹H-MRS) at 3 T.

Results: In fMRI, OCD patients showed lower activities in the cerebellum (Cb), inferior temporal gyrus, orbitofrontal gyrus (OFG), dorsolateral prefrontal cortex (DLPFC) and calcarine gyrus compared to the controls. In VBM, the patients showed significantly reduced GM volumes, especially in the Cb, hippocampus and superior temporal gyrus. As for the comparison of WM volumes, the patients showed significantly reduced volumes in the retrolenticular part of internal capsule, DLPFC and OFG. In MRS, the ratios of NAA/Cr and Cho/Cr were significantly lower in the DLPFC of the patients than in the controls, whereas the ratio of β-γ-Glx/Cr was significantly higher in the patients than in the controls.

Conclusions: Our findings will be helpful for understanding the neurocognitive impairment in OCD, as well as enhancing the diagnostic accuracy by additional information on the combined brain functional deficit, brain volume change and metabolic concentration.
FUNCTIONAL CHANGES IN THE DORSOLATERAL STRIATUM IN LOSS OF CONTROL

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Objectives: Loss of control over substance use is a hallmark of addiction. One of the neural mechanisms that has been proposed to contribute to loss of control over substance use is exaggerated involvement of the dorsolateral striatum (DLS), which mediates habitual behaviour.

Purpose: This study examines how changes in DLS function contribute to loss of control over reward seeking.

Methods: First, we assessed the effect of long-term exposure to alcohol on synaptic plasticity in acute brain slices of the DLS. Voluntary home-cage alcohol consumption was monitored in outbred Lister-Hooded rats in a two-month intermittent alcohol access paradigm, whereby substantial individual variation in alcohol intake can be observed. Animals were then bilaterally injected with an adeno-associated Channelrhodopsin virus (AAV5-CamKII-Chr2-eYFP) targeted at the motor cortices projecting to the DLS. Whole-cell patch clamp recordings were performed to measure optically induced excitatory post-synaptic currents. In parallel, we assessed whether activation of the DLS is sufficient to drive loss of control over reward seeking. To this aim, rats received bilateral injections of an adeno-associated DREADD-virus (AAV5-hSyn-hMD3q-mCherry), to chemogenetically enhance neuronal activity of the DLS. Loss of control over reward seeking is examined in a novel model. Here, compulsive seeking is operationalized as continued responding during presentation of a conditioned cue that predicts probabilistic footshock punishment.

Results: Our preliminary results indicate increased facilitation of paired-pulse responses in the DLS in rats that show a high voluntary alcohol consumption. This increase is caused by reduced amplitude of the first response, indicative of a reduced release probability. Moreover, presentation of the footshock-predictive cue profoundly suppresses responding for both alcohol and sucrose.

Conclusions: Long-term exposure to large quantities of alcohol seems to modulate short-term synaptic plasticity in glutamatergic cortical inputs onto the DLS presynaptically. We expect that activation of the DLS will induce loss of control over reward seeking.
THE ROLE OF THE PRELIMBIC PREFRONTAL CORTEX IN COMPULSIVE REWARD SEEKING

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Objectives: Loss of control over substance use is a hallmark of addiction, but the underlying neural circuits are still poorly understood. Elucidating these neural underpinnings is a crucial step towards developing innovative treatments. Dysfunction of the prefrontal cortex is thought to contribute to loss of control over substance intake.

Purpose: The aim of this study was to develop a novel paradigm to study control over substance use and subsequently test the hypothesis that prelimbic prefrontal cortex (PrL) activity is essential to maintain control over reward seeking behaviour under threat of adversity.

Methods: We developed a novel model to capture reward seeking under threat of adversity. In this within-subject paradigm, rats are trained to lever press for a reward (i.e. alcohol, cocaine or sucrose). Subsequently, they are confronted with a tone during reward seeking that functions as a warning sign since lever pressing during tone presentation results in a probabilistic footshock. We expect seeking behaviour to be suppressed during sessions in which the tone is presented. In ongoing experiments, we use chemogenetic and pharmacological inactivation of the PrL to determine the involvement of the PrL on behaviour in this task.

Results: We observed reduced responding in sessions during which the tone is presented. This reduction was observed when rats were lever pressing for either alcohol, cocaine or sucrose, although the reduction in responding for cocaine was less pronounced compared to the other substances.

Conclusions: We have established a model that captures behavioural control over substance seeking in the face of adversity that allows for within-subject comparisons. This model enables us to unravel the neurobiological mechanisms involved in loss of control over substance use.
THE NEUROPROTECTIVE EFFECTS OF THE HYPERICUM PERFORATUM L. HYDROALCOHOLIC EXTRACT AGAINST Aβ25-35-INDUCED AMNESIA AND OXIDATIVE STRESS IN A RAT MODEL

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Objectives: To study the effects of the Hypericum perforatum L. extract on memory formation and oxidative stress balance in the Aβ25-35 rat hippocampus.

Purpose: The neuropharmacological effects of the Hypericum perforatum L. extract administration (50 mg/kg and 100 mg/kg, i.p., for 21 days after neurosurgery) on memory performance and oxidant-antioxidant balance in the rat hippocampus were assessed in Aβ25-35-treated rats.

Methods: The Alzheimer’s disease (AD) rat model was produced by intraventricular delivery of Aβ25-35. Rat were treated with the extract (50 mg/kg and 100 mg/kg, i.p.), for 21 days after neurosurgery, and were subjected to behavioral assays such as Y-maze and radial arm maze test for assessing memory performance. Also, the antioxidant activity in the hippocampus was assessed using superoxide dismutase, catalase, glutathione peroxidase specific activities and total content of reduced glutathione, malondialdehyde and protein carbonyl levels. In addition, the acetylcholinesterase activity in the rat hippocampus was also assessed.

Results: The Aβ25-35-treated rats exhibited the following: decrease of spontaneous alternations percentage within Y-maze task and increase of working memory and reference memory errors within radial arm maze task. Administration of the hydroalcoholic extract significantly improved memory performance and exhibited antioxidant potential.

Conclusions: These findings suggest that the extract could be a potent neuropharmacological agent against Aβ25-35-induced dementia via modulating cholinergic activity and promoting antioxidant action. Therefore, the hydroalcoholic extract could be a potential candidate for further preclinical study aimed at the treatment of cognitive deficits in AD.

Acknowledgements
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Adult neurogenesis plays a critical role in hippocampal-dependent memory, however its role in complex forms of memory such as episodic memory has not yet been explored. First, one of the biggest challenge is to dispose of adequate animal models amenable to neurobiological investigation. We recently developed a new episodic memory task that provides means to quantitatively evaluate the ability of rats to form and recollect a combined knowledge of What happened (odor-drink associations), Where (locations) and in Which context/occasion (multisensory environments) after limited encounter of specific episodes during their daily life. Analysis of individual recollection profiles show that rats can form and recollect, in a hippocampal-dependent manner, an accurate, long-term integrated episodic memory that can last at least 24 days. Placing rats in a contextually challenging recollection situation at recall reveals the ability for flexible use of episodic memory. In this challenging situation that might appeal to pattern separation function of the hippocampus, we evaluated the implication of adult neurogenesis using a model of focal irradiation of the hippocampus. Analysis of recall performance 24 hours after exposures to the episodes showed that irradiated rats were not able to recollect an integrated episodic memory, forgetting either the odor-location association of the tested context or the entire episode. Furthermore, cellular imaging of immediate early genes activation in different brain structures indicates disruption of the hippocampal-prefrontal network implicated during recall. These results suggest that adult hippocampal neurogenesis underlies the consolidation and faithful recall of episodic memory. Supported by ANR-2010-BLAN-1413-01.
EFFECT OF MEMANTINE AND RILUZOLE ON SPATIAL LEARNING DEFICIT IN QUINPIROLE-SENSITIZATION MODEL OF OBSESSIVE-COMPULSIVE DISORDER

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Objectives: The objective of this study was to test effects of treatment with drugs decreasing glutamatergic activity in an animal model of obsessive-compulsive disorder (OCD) induced by chronic sensitization with quinpirole, a dopamine D2-like receptor agonist.

Purpose: The purpose of this study was to test the validity of quinpirole-induced model of OCD, with regard to cognitive deficit induced by the sensitization.

Methods: Adult male Long-Evans rats were sensitized by ten injections of quinpirole spaced by one-day interval on a circular open-field arena. The dose of the drug was 0.25 mg/kg. Animals were tested for acquisition in a place avoidance task on a rotating arena (Carousel) and during testing memantine (1 mg/kg and 5 mg/kg) and riluzole (1 mg/kg and 5 mg/kg) were co-administered with quinpirole during behavioral testing.

Results: Quinpirol at the tested dose induced a deficit in acquisition of the active place avoidance task, marked by inability to avoid a hidden sector and hyperlocomotion. Higher dose of the drugs (5 mg/kg) exacerbated this deficit, whilst lower dose (1 mg/kg) did not change it significantly, although a trend of improvement was seen.

Conclusions: We conclude that quinpirole-sensitization model of OCD exhibits relatively low reactivity to the drugs interfering with glutamatergic neurotransmission. Further studies on these influences are underway in our laboratory.

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THE RECOGNITION OF A NOVEL-OBJECT IN A NOVEL CONTEXT LEADS TO HIPPOCAMPAL AND PARAHIPPOCAMPAL C-FOS INVOLVEMENT

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Objectives: Contextual memory implies recognition based on the association between past and present events experienced. It is important for daily functioning and dysfunctional in many neuropsychological disturbances. The network related to this memory is still open for debate, even though it has been associated with medial temporal lobe regions, including the perirhinal, entorhinal and temporal association cortices, as well as the hippocampus and prefrontal cortex. Purpose: Our work tries to elucidate whether a change in the context, such as differences in the amount of stimuli presented on the walls and floor of an open field during object exploration, affects the recognition of an object that has been experienced before, and whether this context manipulation could be linked to changes in c-Fos expression.

Methods: We used a one-trial novel-object recognition task. The animals were divided into two different experimental conditions; in the OR-NORMAL group, the sample and probe test were performed in the same context. However, in the OR-CONTEXT group, the probe test was performed in a different context. Results: Our results showed that the OR-NORMAL group presented a greater exploration of objects than the OR-CONTEXT group. However, both groups presented significant exploration of the novel object. To label the brain regions involved in novel-object recognition under these conditions, we marked the expression of c-Fos protein. Results suggest that a neural circuit that includes the hippocampus, entorhinal and temporal association cortices is involved in the recognition of the novel-object in a novel context. Conclusions: Our work revealed that there was interference caused by changing environmental conditions in a novel-object recognition task, suggesting that a neural circuit that includes the hippocampus and entorhinal and temporal association cortices is involved in recognition in a novel context. These results could highlight how a dysfunction in this network may affect contextual memory, which is important not only for daily functioning, but also because it is altered in many disorders.
EFFECTS OF CLONIDINE ON DECISION-MAKING AND MOTIVATION IN MONKEYS
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Objectives: Among neuromodulatory systems, the noradrenergic system is one of the least understood. In this study, we aimed at testing directly several theories that have pointed out its implication in behavioural or cognitive flexibility and more recently, its potential role in motivation, with a strong role in effort processing.

Purpose: We designed a sequential effort-based decision task to test the causal role of noradrenaline in both behavioural flexibility and motivation in monkeys.

Methods: We used a quantitative approach to identify precisely the cognitive processes of interest and we manipulated central noradrenergic level using systemic injection of clonidine, an alpha-2 noradrenergic receptor agonist, which reduces central noradrenaline levels.

Results: Clonidine had two distinct effects. First, in line with the role of noradrenaline in behavioural flexibility, clonidine dose-dependently decreased choice volatility: monkeys' choices were more consistent under clonidine, but there was no effect on the cost-benefit trade-off. Second, in line with the role of noradrenaline in motivation and effort, clonidine dose-dependently reduced force production during the task. Because the effects on behavioral flexibility and motivation were statistically independent, they cannot be accounted for by a common confounding factor or a non-specific effect on arousal and vigilance.

Conclusions: Altogether, these results support the global implication of noradrenaline in facing challenging situations in two complementary ways: i) by increasing behavioural volatility, which would facilitate adaptation in a labile environment and ii) by enhancing the mobilization of resources to face immediate challenges.
AN FMRI STUDY ABOUT DISEMBODIMENT OF ADULT INTERNET GAME OVERUSERS
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Objectives: The aim of this study was to investigate the difference of brain activity between adult internet game overuser and normal controls in a disembodiment-provoking state.

Purpose: This study was to investigate the neural correlates about disembodiment of adult internet game overusers.

Methods: The fMRI images were taken while the internet game overusers and the controls were asked to perform the task composed with ball-throwing animations. The task reflected on either self-agency about ball-throwing or location of a ball. And each block was shown with either different (changing viewpoint) or same animations (fixed viewpoint). The disembodiment-related condition was the interaction between Agency task and Changing viewpoint.

Results: 1) In within-group analyses, the control group exhibited higher brain activation in left precentral gyrus, left inferior frontal gyrus, left insula. And the overuser group exhibited higher activation in right cuneus, left posterior middle occipital gyrus, left parahippocampal gyrus.
2) In between-group analyses, the control group exhibited higher activation in right posterior superior temporal gyrus. And the overuser group exhibited higher activation in left cuneus, left posterior middle occipital area.

Conclusion: These results show that the disembodiment-related brain activation of adult internet game overusers is different from that of normal persons.
JUDGMENTS OF EXPERIENCED EMOTIONAL INTENSITY DISTINCTIVELY MODULATE NODES OF THE AUTOBIOGRAPHICAL MEMORY NETWORK DURING THE SEARCH AND ELABORATION OF MEMORIES

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Autobiographical memory (AM) retrieval chiefly consists of searching for specific personal episodes and upon that, elaborating the details into a vivid construct. We used functional MRI to examine whether and how judgments about the emotional intensity experienced at the original time of the event distinctively modulate activity in the nodes of the AM network during the search and elaboration of memories. Participants provided a list of emotional and neutral events that they had experienced, and were invited to extensively evaluate various phenomenological qualities about those memories. Participants returned on a subsequent day to undergo scanning (3T Siemens Trio); a cue was shown for 3 seconds at the beginning of each trial (which lasted 17 seconds), and participants were asked to retrieve the episode associated with the cue (search phase), signaling completion with a button-press. Participants were also instructed to mentally relive the event for the remaining of the trial (elaboration phase). After each trial, participants rated the emotional intensity experienced at the original time of the event, as well as the negative and positive affects experienced at recall time. After screening for exclusion criteria, 26 subjects were included in the analysis (14 females, 20-25 years old). A parametric modulation analysis was conducted using the ratings collected in the scanner. Regions-of-interest were derived from the Harvard-Oxford structural atlases. Small-volume correction was applied within each region to determine significant modulation of BOLD activity levels (p<.05, family-wise-error correction) during both phases. Though the vmPFC was modulated by emotional intensity ratings during search and elaboration, activity in the hippocampi, amygdalae and precuneus was only modulated during elaboration but not search, whereas areas in the temporal gyri showed the reverse pattern. Overall, these results indicate that the engagement of AM network nodes during search and elaboration is distinctively modulated by subjective judgments of experienced emotional intensity.
SOCIAL BUFFERING SUPPRESSES FREEZING RESPONSE DURING FEAR EXTINCTION SESSION BUT DOES NOT IMPROVE FEAR EXTINCTION MEMORY

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Social support during the exposure-based psychotherapy has been suggested to have an important influence on the course of exposure treatment; however the mechanisms of such influence remain unknown. To study neuronal correlates of social buffering during fear extinction, a model of exposure therapy, we have developed a rat model. In this model pair-housed rats are separately fear conditioned to the tones and then subjected either to fear extinction or merely exposure to the experimental cage. Next, the rats are placed in the experimental cage, in separate compartments, and presented to conditioned tones in pairs or separately. We observed a clear difference in the level of freezing between the rats that were not fear extinguished and tested separately or with a partner. Testing rats together resulted in much lower freezing response than testing them separately. However, the effect was transient, when fear memory was measured on the next day there was no difference between rats exposed to the conditioned tones together or separately. To investigate whether the mechanisms underlying social buffering effect we observed are similar to the ones involved in fear extinction, we compared activation of the prefrontal cortex and amygdala, the structures critical for extinction of conditioned fear. We found lower activation of the anterior cingulate cortex, and prelimbic and infralimbic parts of the prefrontal cortex in animals tested together, whereas no differences were observed in the basolateral and central amygdala. The inhibition of the anterior cingulate and prelimbic cortices resembles the pattern of activation observed in rats subjected to fear extinction; however activation of the infralimbic cortex related to low level of fear after fear extinction was not observed here. Taken together, these results suggest that the mechanisms of social buffering of conditioned fear can only partially rely on the neuronal circuits involved in fear extinction.
DOPAMINERGIC CONTROL OF INDIVIDUAL DIFFERENCES IN APPETITIVE LEARNING
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Objectives: Inter-individual differences in learning have particular relevance in the context of drug addiction and relapse. They can be studied in animals using appetitive conditioning in rats, where the same training situation can result in widely differing patterns of conditioned responses. Some individuals termed sign-trackers (ST) are attracted to the Pavlovian conditioned stimulus (an inactive lever) while others, termed goal-trackers (GT) are directly attracted to the unconditioned stimulus (the magazine for reward delivery). Still, the origin of these differences remains unclear.

Purpose: In this study, we address the algorithmic nature of ST and GT responses and their dependence upon dopaminergic signaling.

Methods: M. Khamassi and colleagues developed a computational model of ST/GT results in terms of the balance between concurrent learning processes, and derived a series of testable predictions (Lesaint et al., 2015). As a first step, we examined the emergence of ST and GT subpopulations. We then investigated the contribution of tonic dopaminergic signaling to ST and GT behaviors, using a CAV2 viral vector harboring Cre-dependent hM4Di DREADD infused in the ventral striatum of TH-Cre transgenic rats.

Results: Rats trained with two different levers, only one of which was predictive of food developed into roughly equivalent populations of STs and GTs, the latter interacting with the food magazine for the whole duration of CS presentation. In a new group of rats trained with only one lever, lever-pressing responses emerged in nearly all rats while magazine interactions occurred mainly at the onset of the CS and gradually disappeared. Inhibition of mesolimbic dopaminergic projections by systemic Clozapine-N-Oxide during Pavlovian training was found to maintain responses to the food magazine without markedly impairing the development of lever-pressing responses.

Conclusions:
- These results indicate that nearly all rats are susceptible to acquire lever-directed ST responses, although at different learning rates.
- They reveal a new role for dopamine signalling in the gradual elimination of GT responses.
- They suggest the existence of quantitative rather than qualitative differences between ST and GT individuals.

Literature Reference
Maternal care emerges postpartum to ensure welfare of the offspring, and involves the acquisition of a high motivation towards infants. However, since virgin female mice show nearly-spontaneous pup retrieval and care it seems that motivation cannot further increase during motherhood. The main goal of this work is to characterise maternal motivation in dams and virgin females. Maternal behaviour is commonly assessed measuring pup retrieval, but this approach presents some limitations when performed in a familiar, non-challenging environment (home-cage). Herein, we present a novel behavioural design for motivated pup retrieval in which pups are separated from the females by a 10cm-high barrier that constitutes a true challenge for the females to retrieve them to the nest. We also seek to analyse the role of prolactin and oxytocin in the medial preoptic area (key site in the control of maternal behaviour) in maternal motivation for pups.

Three experimental groups, lactating dams (n=9), pup-exposed virgins (n=10) and pup-naïve virgins (n=10) underwent three daily motivated pup retrieval trials, starting on postpartum day 2. Dams displayed significantly lower latencies to retrieve than either of the virgin groups, demonstrating that full maternal motivation is only developed after pregnancy. Regarding virgins, although initially both groups show no retrieval behaviour, pup-exposed virgins did improve significantly through the experiment. This indicates that continuous pup exposure leads to maternal sensitisation also in virgins females.

Brains were then processed for the immunohistochemistry of oxytocin and pSTAT5 (prolactin-derived signalling marker) in the AC/ADP cell group of the preoptic hypothalamus. Dams showed significantly increased levels pSTAT5 immunoreactivity in the AC/ADP. Furthermore, the number of oxytocin cells of the AC/ADP correlated negatively with motivated pup retrieval performance in dams and pup-exposed virgins. These findings suggest that prolactin modulates the AC/ADP during lactation and that AC/ADP oxytocin is not directly involved in maternal motivation, but might rather subserve other functions, such as stress or anxiety regulation.

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TRANSCRIPTIONAL CO-REPRESSOR SIN3A ENHANCES LONG-TERM MEMORY BY MODELING NEURONAL SYNAPTIC PLASTICITY MARKERS

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Consolidation of short-term memories into stable long-term memories requires a coordinated program of gene transcription. Recent data suggest that epigenetic mechanisms are important for the consolidation of long-term behavioral memory. Indeed, histone acetylation, which is associated with transcriptional activation, increases at select learning-induced genes. Moreover, pharmacological enhancement of histone acetylation with histone deacetylase (HDAC) inhibitors improves long-term memory formation (Hawk et al., 2011). DNA methylation in gene regulatory elements is an epigenetic modification associated with transcriptional repression. Prior to learning, DNA-methylation recruits inhibitory complexes containing HDACs and the transcriptional co-repressor Sin3A to memory-promoting genes. We previously showed that a mutation of Sin3A enhances long-term potentiation in hippocampal slices, and also exhibit enhanced long term (but not short-term) contextual fear memory (Bridi et al., submitted). In the aim to highlight the role of this transcriptional co-repressor in hippocampus-dependent memory, we examined spatial object memory in a conditional mutant mouse line with forebrain-specific deletion of Sin3A protein. As expected, our results indicate an enhancement in long- but not short-term spatial memory performance in adult Sin3A mutant mice in comparison to the wildtype littermates. We next explore the cellular and molecular mechanisms underlying this enhanced long-term spatial memory. We found that mice with forebrain Sin3A deletion showed (i) an increase of Zif268/Egr1 expression in CA1 pyramidal cells, and (ii) a transcriptional modifications of genes involved in learning, memory and synaptic plasticity. Determining the genes marked by epigenetic modifications and the mechanisms that link these modifications to the regulation of gene expression during long-term memory formation and maintenance will provide critical insight into the role of these modifications in memory storage and provide targets for treatment of the brain disorders.

Bridi M.S., Schoch H., Florian C., Poplawski S.G., Banerjee A., Hawk J.D., Hahn C.G., Havekes R., Spruston N. and Abel T.G. The transcriptional co-repressor SIN3A regulates hippocampal synaptic plasticity via Homer1/mGluR5 signaling (submitted)
NEURAL PROCESSES SUPPORTING THE BIAS TOWARDS POSITIVE INFORMATION IN BINOCULAR RIVALRY
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Binocular Rivalry (BR) consists of the conscious perception of one of the two competing images presented to each eye. This phenomenon has been used with pairs of neutral-emotional images and a BR bias towards emotional images has been behaviorally shown. However, information on the neural mechanisms underlying this bias has not been provided yet. We aimed to find the neural correlates of the emotional bias by employing behavioral and ERP indices, using an endogenous attention task with BR and normal vision conditions. We showed pairs of scenes containing animals (of positive, negative and neutral emotional valences) in one eye and objects (of neutral valence) in the other eye within a BR paradigm and the same images with regular, unrivaled binocular vision. Participants (n=30) were asked to indicate, through key presses, whether the image contained an animal or an object. This task allowed us to detect emotional biases without explicitly revealing the scope of the study, an advisable strategy in the study of emotional processes. Our behavioral results show that positive images were more likely to gain conscious perception in the BR condition, and they had a smaller error rate and were detected faster than the other emotional valences in the regular binocular vision condition. At the neural level, the LPP, a positive wave peaking around 500 ms after stimulus onset, showed significantly greater positivity at frontoparietal areas for the positive valence in both visual conditions, although the effect was stronger for the normal vision condition. These results suggest that i) endogenous attention is a modulating factor in BR, ii) BR is biased towards positive emotional contents, and iii) LPP is a useful, objective electrophysiological index of the emotional bias in BR. Work supported by the Ministerio de Economía y Competitividad of Spain (PSI2014-54853-P).
NORM COMPLIANCE AFFECTS PERCEPTUAL DECISIONS THROUGH MODULATION OF A RESPONSE BIAS
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Adaptive decisions in social contexts depend on both informational and normative influences that potentially conflict when certain choices are beneficial for an individual, but societal rules mandate a different course of action. To accommodate the goal to decide optimally with the need to comply in social contexts, reliability of information has to be balanced against deleterious effects of non-compliance such as ostracism. In this study, we systematically investigated how interactions between normative and informational influences affect decision relevant cognitive processes. We extended a direction-of-motion discrimination task where participants combined their individual with social information, i.e. own percept with other players’ choices. Experimental prompts to decide either with or against the social information served as normative influence where compliance affected other players’ remuneration. Importantly, we manipulated norms in two separate experiments such that compliance signalled different degrees of prosociality. Behavioural analyses and computational models of perceptual decisions provided evidence for normative influences on a response bias that was established through social influences. Specifically, experimental normative prompts for compliance versus non-compliance affected this bias in opposite directions. Critically, these effects were augmented when the strength of normative influences was increased, indexing conditions under which norms effectively influence decisions. We provide an account of how higher order goals like norm compliance affect perceptual decisions that informs theories of social influence.
INDOMETHACIN COUNTERACTS THE EFFECTS OF INTERMITTENT CHRONIC ETHANOL ON EMOTIONAL MEMORY IN MICE
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Objectives: Considering that inflammatory responses to alcohol may contribute to alcohol-related brain damage and to explain the long-term cognitive consequences of binge drinking, the main objective of this study was to demonstrate the effectiveness of an anti-inflammatory treatment in counteracting the detrimental effects of ethanol administration on emotional memory in mice.

Purpose: The purpose of this study was to evaluate the effects of intermittent chronic administration of a high dose of ethanol on inhibitory avoidance learning in male and female periadolescent mice, and the possible counteracting action of the commonly used anti-inflammatory agent indomethacin.

Methods: Male and female CD1 mice were randomly divided into four groups in each sex: saline+saline; saline+ethanol; saline+indomethacin; and ethanol+indomethacin. According to their pharmacological group, all subjects were treated with saline, ethanol (3 g/kg) and indomethacin (10 mg/kg), being daily injected (i.p.) the first three days of each week, throughout a three week period. After checking that there were not significant differences in locomotor activity between groups, all subjects (n = 9 per group) were evaluated in inhibitory avoidance 96 h after the pharmacological treatment.

Results: Memory impairment was observed in the saline+ethanol groups, with even a lack of learning in the male group. Inhibitory avoidance learning (significantly longer test latencies than training latencies) was observed in the rest of groups, without differences between them.

Conclusions: As expected, intermittent chronic ethanol impairs emotional memory in mice and this impairment can be counteracted by the anti-inflammatory indomethacin. This study represents new evidence which supports the contribution of inflammation in the cognitive consequences of binge drinking and a useful guide for designing effective treatments for Alcohol Use Disorders.
THE ROLE OF ADULT HIPPOCAMPAL NEUROGENESIS IN SPATIAL MEMORY RECONSOLIDATION

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Reconsolidation is the process by which an established memory becomes stable again after being reactivated. Long-term memory stabilisation relies on structural modification and the cellular mechanisms of reconsolidation have been extensively studied. Despite the fact that new neurons are continuously added to the brain and that this adult neurogenesis play an important role in memory processes, reconsolidation has never been addressed in the context on ongoing hippocampal neurogenesis. The goal of this study is to determine the role of adult-born neurons in memory reconsolidation.

We used a behavioural protocol in the Morris water maze to demonstrate that spatial learning undergoes reconsolidation. We then found that, unlike neurons born during development, adult-born neurons that are mature or immature at the time of learning are activated by reconsolidation. In order to investigate a causal relationship between adult neurogenesis and spatial memory reconsolidation, we designed a DREADD retrovirus. When injected into the dentate gyrus of rats, this retrovirus allows us to specifically and reversibly inhibit new neurons during the reconsolidation process. Our preliminary data show that inhibiting, at the time of reactivation, mature neurons that were activated by learning, has no effect on memory retention. However, inhibiting, during reconsolidation, the population of new neurons that was immature at the time of learning and not activated by learning impairs memory retention. These results suggest that adult-born neurons may be necessary for remote memory reconsolidation. All together our results show a clear involvement of hippocampal neurogenesis in spatial memory reconsolidation.
EVALUATING A LIGHT-TOUCH BEHAVIORAL INTERVENTION FOR INDUCING AMNESIA FOR ACQUIRED FEAR MEMORIES
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There is a recent surge in research that tries to experimentally induce amnesia for previously established emotional memories, with the hopes of eventually developing novel therapeutic tools for the treatment of PTSD and other emotional disorders. This reconsolidation interference research has used a variety of approaches, including pharmacological reconsolidation blockade, memory updating after retrieval, administration of electroconvulsive shock, and others. However, existing experimental approaches either have characteristics that complicate their clinical translation or have defied robust replication. We conducted a study exploiting an original, light-touch behavioral intervention for inducing amnesia for acquired fear memories that aimed to avoid some of the problems associated with existing approaches. Utilizing a cued fear conditioning paradigm spread over three days, we conditioned participants on day 1 with two fear-relevant stimuli serving as the CSs and a mild shock to the wrist as the US. On day 2, following memory reactivation, participants were allocated to one of two groups. The cognitive load (CL) group (n=20) completed an emotional working memory task with high cognitive load, while the second group served as a no-task control (n=20). On day 3, all participants completed extinction training followed by a test for reinstatement of fear. We observed successful acquisition and reactivation in fear-potentiated startle (FPS) responding, skin conductance responding (SCR), and US expectancies in both groups. We failed to induce amnesia in the CL group as, contrary to our hypothesis, differential (CS+/CS-) responding was intact at the beginning of extinction, and performance of both groups was comparably sensitive to reinstatement. Thus, we obtained no evidence that the execution of an emotional working memory task after fear memory reactivation impairs reconsolidation.
EARLY LIFE STRESS INDUCES LOWER GENE EXPRESSION OF GLUCOCORTICOID RECEPTOR AND ITS MODULATOR FKBP51 IN MICE

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Early life stress (ES) has been associated with increased risk for psychopathologies later in life, and the HPA-axis malfunctioning seems to be the link between ES and brain disorders such as depression, bipolar disorder and PTSD. A translational approach is a keen strategy in the search for insights into the mechanisms behind this phenomenon; in this regard we evaluated the expression of glucocorticoid receptor (GR) and its modulator FK506 binding protein 51 (FKBP51) in brain tissue from mice subjected to an experimental paradigm of ES from P2 to P9, which has been associated with neuropsychiatry phenotypes.

At P9, mice from control and stress groups were decapitated between 8:00 and 9:30 immediately after the body weights were determined. Blood samples for corticosterone assessment were taken, and the brains were quickly removed and stored. Corticosterone levels were determined by RIA, brains were manually dissected to obtain a slice of tissue that included cortex, hippocampus, thalamus and hypothalamus. Relative quantification of gene expression was calculated using the CT2 method; GAPDH gene was used to normalize the expression of the target genes.

Mice subjected to stress, compared to controls, presented significantly reduced body weight (2.75 ± 0.13 g, N=21 and 3.89 ± 0.09 g; N=33; p<0.001) and increased corticosterone basal levels (5.41 ± 1.32 ug/dl, N=21 and 2.63 ± 0.18 ug/dl, N=26; p=0.0258). Moreover, stressed mice, compared to controls, showed significant lower expression of GR (0.35 ± 0.05, N=16 and 1.55 ± 0.24, N=31; p=0.0012) and FKBP51 (0.58 ± 0.08, N=15 and 1.14 ± 0.18, N=29). Our findings indicate that ES promoted lower GR and FKBP51 mRNAs expression whereas MR and CRH were not altered, pointing to an imbalance in this system. Future studies will assess whether targeting GRs at relevant time points is effective in preventing effects of ES on fear memories.
EFFECT OF GONADECTOMY ON THE SUSCEPTIBILITY OF MALE RATS TO THE SLEEP DEPRIVATION-INDUCED IMPAIRMENT OF BEHAVIOURAL AND SYNAPTIC PLASTICITY

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Objectives: In both human and animal studies, the effect of sleep deficiency on cognitive performances has mostly been studied during adulthood in males, but very little data exist concerning the effects of poor sleep in gonadal hormones-depleted status, such as aging or gonadectomized (GDX) male animal models.

Purpose: The present study investigated the potential modulatory effects of the endogenous male sex hormones on the 48 h REM sleep deprivation (SD)-induced cognitive and synaptic impairments by comparing the gonadally intact with castrated male rats, a rodent model of androgen-deprived male animals.

Methods: The multiple platform method was used for inducing REM-SD and spatial performances were evaluated using Morris water maze (MWM) task. Early long-term potentiation (E-LTP) was measured in area CA1 of the hippocampus and PCR and western blotting assays were employed to assess brain derived neurotrophic factor (BDNF) gene and protein expression in the hippocampus.

Results: Regardless of reproductive status, REM-SD significantly disrupted short-term memory and LTP, as well as hippocampal BDNF expression. The corticosterone levels were not significantly changed following REM-SD neither in intact nor in GDX male rats.

Conclusions: These findings suggest that depletion of male sex steroid hormones by castration does not lead to any heightened sensitivity of male animals to the deleterious effects of 48 h REM-SD on cognitive and synaptic performances. Although these findings failed to establish any significant difference in cognitive vulnerability of two reproductive conditions to sleep loss, however, it does not reduce the need to consider sex, age, or reproductive status when exploring the consequences of sleep disturbances on health.
ENVIRONMENTAL ENRICHMENT REVERSES COGNITIVE IMPAIRMENT, MOTOR COORDINATION, BALANCE DISTURBANCE AND DEPRESSIVE BEHAVIOUR AFTER ETHANOL CONSUMPTION DURING ADOLESCENCE

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Alcohol consumption during adolescence is one of the main problems that concern our society. An enriched environment (EE) has been shown to significantly facilitate recovery from brain injury due to important molecular, anatomical and functional changes that occur along brain development. Our aim is to investigate the potential positive effects of EE on the cognitive impairment, coordination, balance disturbance, anxiety and depressive behaviour caused in adult by excessive ethanol consumption (binge drinking) during the adolescence. Male C57BL6 mice were exposed to a 4 day drinking-in-the-dark procedure during adolescence. The animals were given free access to alcohol or water for 2-h sessions during three consecutive days, and a 4-h session on the 4th day. Then the animals during the withdrawal period (17 days) were reared under two different conditions: standard laboratory condition (SC) and EE. In the last four days of the withdrawal period, recognition, spatial and associative memory tasks as well as motor coordination, balance, depressive behaviour and anxiety tests were performed.
A significant lower recognition, spatial and associative memory was observed in the alcohol treated standard group (SC-OH) compared to the untreated shams. Besides, the SC-OH showed worse motor coordination skills and balance as well as and an increase in depressive behavior associated with adolescent ethanol consumption. However, enriched EE-OH group showed a significant recover of the three types of memory studied, as well as motor coordination and balance and an improvement in the depressive behaviour observed in SC-OH. No significant long-term anxiety changes were found between the different groups. In conclusion, these results suggest that an enriched environment may have potential benefits for the recovery of the behavioural impairment observed in adult after binge-drinking alcohol during adolescence.

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ADOLESCENT INTERMITTENT ALCOHOL EXPOSURE: LONG-TERM DEFICITS IN COGNITION, MOTOR COORDINATION, BALANCE AND DEPRESSIVE BEHAVIOUR

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Alcohol drinking, especially among adolescents, is a serious public health concern. However, the long-term effects in adult brain of intermittent ethanol exposure during adolescence (AIE) are not well established. Here, we investigated the AIE effects on recognition, spatial and associative memory, motor coordination, balance, anxiety and depressive behaviour in adult mice.

Male C57BL6 mice were exposed to intermittent ethanol intake (20% (v/v) in tap water) using a 4 days drinking-in-the-dark procedure during adolescence (PD 32 to 56). Animals were given access to ethanol (or water) for 2h sessions during 3 days, and 4h session on the 4th day. Ten days after withdrawal, the animals were subjected to behavioural tests (novel object recognition test, novel object localization test, object-in-place test, rotarod, beam walking balance test, light-dark box test and tail suspension test). Afterwards, they were sacrificed and the hippocampi were used for electrophysiology.

A significant lower recognition memory (P<0.001***), spatial memory (P<0.01**) and associative memory (P<0.001****) was observed after AIE. This loss of memory correlates with the absence of cannabinoid type 1 receptor-dependent excitatory long term depression after medial perforant path synaptic stimulation (P<0.01**). Also, a significant reduction in motor coordination (P<0.05*) and balance (P<0.05*) and a significant increase in depressive behaviour (P<0.05*) was observed in adult mice after AIE. However, no significant long term changes in anxiety-related behaviour were found.

In conclusion, repetitive exposure to ethanol during adolescence leads to a deficit in memory, specifically in recognition, spatial and associative memory, as well as in motor coordination, balance and depressive behaviour in adulthood. Anxiety-related behaviour seems not to be affected by AIE.

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CROSS-TALK BETWEEN OXYTOCIN AND VASOPRESSIN REGULATES FEMALE AGGRESSION IN RATS
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Objectives: To establish an aggression test for virgin female rats, and to elucidate the role of
the nonapeptides oxytocin (OXT) and vasopressin (AVP) in this behavior.

Purpose: To unravel the neurobiology underlying aggression in females and to search for
novel (pharmacological) treatments against pathological aggression in humans.

Methods: In our standard protocol, young adult virgin female Wistar rats were isolated for 3-
5 days (immediately after surgery if performed) and then trained in three consecutive daily
10-min Female Intruder Tests (FITs). This protocol yields high levels of aggression, which
can then be manipulated with pharmacological treatments.

Results: We performed 5 experiments (E1-5) in separate cohorts of isolated and trained
females. In E1, ICV infusion with OXT (50 ng) or AVP (0.1 and 1 ng) strongly reduced
aggression compared with vehicle (VEH, P < 0.05), whereas the selective OXTR-agonist
TGOT (100 ng) increased aggression (P = 0.069). In E2, pretreatment with a selective V1aR
antagonist (V1aRA), but not with a selective OXTR antagonist (OTA), was able to block the
anti-aggressive effects of OXT. In E3, bilateral infusions of AVP (0.1 ng) into the CeA
increased aggression compared with VEH (P = 0.0224), whereas intra-CeA TGOT (0.01 ng)
had no effect. In E4, bilateral infusions of AVP (0.1 ng) into the dorsal LS caused anti-
aggressive effects similar to ICV infusion (P = 0.017), whereas both OXT and TGOT (0.1 ng)
had no effect. Since AVP had the strongest behavioral effects in the FIT, we measured post-
FIT AVP concentrations in the cerebrospinal fluid (CSF) of highly aggressive isolated and
trained females and found that they were significantly lower than those of non-aggressive
group-housed, untrained females (E5). No differences were seen in post-FIT plasma AVP
concentrations.

Conclusions: In high aggressive (isolated and trained) females, the anti-aggressive effects of
ICV OXT and AVP are mediated by V1aR. Furthermore, high aggressive females showed
low post-FIT AVP levels in the CSF. In addition, the LS but not CeA may be the main brain
area where AVP inhibits female aggression. Our future aims are to monitor AVP release in
the LS of high versus low aggressive females and to define the neural pathways involved in
the anti-aggressive effects of AVP neurotransmission within the LS.
GRID CELLS FIRING PATTERN IS MODIFIED DURING GOAL-DIRECTED SPATIAL NAVIGATION
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Grid cells are neurons of the medial entorhinal cortex (mEC) that are active in multiple fields forming a hexagonal grid that spans the entire surface explored by the animal. Early studies have suggested that grid cells provide a universal metric map of the environment that supports path integration abilities. So far, no direct experimental evidence supports this hypothesis. Here we asked: i) whether the hexagonal firing pattern of the grid cells is modified in a goal-directed spatial navigation task; ii) whether the use of different navigation strategies (self-motion-based vs landmark-based navigation) modulates their activity. To investigate this issue, we recorded mEC neurons while rats were performing a continuous goal-directed navigation task. In this task, the animals have to reach and stay for two seconds in an unmarked goal zone within a circular arena, in order to receive sugar pellets that are randomly scattered on the floor. To assess the influence of self-motion-based and landmark-based navigation on grid cells activity, animals were tested in both light and dark conditions. Preliminary results indicate that during goal-directed spatial navigation, the metric properties of the hexagonal pattern are modified. In particular the field spacing is locally expanded near the goal zone. These results will provide new fundamental information on the role of entorhinal grid cells in spatial cognition.
RESTING STATE EEG CAN PREDICT BEHAVIORAL PERFORMANCE AND IT'S ERP CORRELATES DURING REPEATED TASK EXECUTION
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Objective of our research was to understand the relation between individual spectral characteristic of resting state EEG against task related brain activity and behavioral performance.

Methods: Healthy adults were tested twice (TEST and RETEST, two months apart) with a visual search task. EEG was recorded during task execution and preceding resting state session. During analysis, subjects were split into groups defined by high and low resting state amplitudes calculated of multiple frequency bands across 7 electrode clusters (F, FC, C, CP, P, PO and O). Reaction times (RT) and amplitudes of ERP components (readiness related CNV and attention related P300 waves) were compared with two-way ANOVA and subjected to correlation analyses.

Results: Significant differences in ERPs were observed between groups defined by resting frontal (F+FC clusters) beta (13-30 Hz) and gamma (30-44 Hz) amplitudes (high-BG, low-BG groups): i) during TEST there was no difference in RT between the high-BG and low-BG groups while the ERP amplitudes were bigger in high-BG participants; ii) during RETEST, ERP amplitudes in low-BG group reached the same level as in high-BG group; iii) in parallel, RTs decreased in low-BG participants below high-BG level during RETEST. Individual data in frontal low gamma group exhibited positive correlations between amplitudes of gamma band at resting state before TEST and RTs during TEST and RETEST (r =0.61, p < 0.001 and r =0.69, p < 0.001 respectively).

Conclusions: Low frontal beta and gamma amplitudes at the resting state predict shortening of RTs and increase of ERP amplitudes in the repeated visual search task. This finding exemplifies link between brain activity in the resting state and following processing of external stimuli.
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The selective vulnerability of the basal forebrain cholinergic neurons (BFCN) is responsible for most of the clinical alterations in learning and memory processes that are characteristic of the Alzheimer’s disease (AD).

It is necessary to develop and validate animal models that mimick the cognitive impairment associated to AD.

In the model used in the present study we induced a BFCN depletion in rat by intraparenchymal infusion of 192IgG-saporin (SAP) immunotoxin. We used new neuro-microsyringe, with a minimal needle diameter to avoid mechanical damage.

Different types of learning and memory are affected in AD patients, including spatial, and instrumental conditioning processes involving emotions. To evaluate these types of memories we performed the Barnes maze (BM) and passive avoidance (PA) test in the lesion model in rat, respectively.

The aim of the present study is to compare the recorded behaviour parameters to those observed in cognition in AD patients.

SAP rats had impairment in both spatial learning (time in the target quadrant SHAM: 89 ± 6 s; aCSF: 89 ± 3 s and SAP: 53 ± 3 s, p<0.05), and aversive stimulus learning (SHAM: 88 %; aCSF: 76 % s and SAP: 20 % positive responses, p<0.05). Furthermore the rat brains of the lesion model showed a decrease of 76 % in the number of BFCN that was in correlation to the mentioned parameters (r² = 0.72).

In conclusion, we observe behaviour parameters in the SAP model of cholinergic cortical deafferentation from BFCN, that resemble clinical correlates in AD patients, such as a exhibiting poor judgment, aberrant motor behaviour and non-productive deambulation associated to anxiety and fear, according to described in humans by McClive- Reed and Gellis (2011).
A NEW TASK TO DESCRIBE LONG-TERM EPISODIC MEMORY NETWORKS IN THE RAT
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The objective of this study is to develop a new paradigm in rodents to study episodic memory, a complex form of long-term memory. It has been initially defined by Tulving (1972) as the human ability to consciously recollect personal past events. Previous paradigms developed in birds and rodents demonstrated animal abilities to form and recollect life episodes. Indeed, they were shown to integrate different informations related to an episode: What happened, where and in which spatio-temporal context it happened (What-Where-Which). However, former studies presented some limitations. First, they are based on an extensive repetition of events to be remembered, which is never the case in humans. Secondly this memory has never been tested at very-long term whereas humans are able to recall single events for decades. We proposed a new behavioral paradigm as close as possible to human characteristics of episodic memory. Rats were exposed during different days to two episodes each characterized by a combination of rich contextual information (somatosensory, visual and auditory modification of the experimental arena) and of specific odor-place cues that were associated with the delivery of positive or negative reward (sugar or quinine in water). The accuracy of their recollection of these episodes was then tested at very long-term (1 month), either in a similar or in a more challenging recall situation than the one experienced during encoding. A fine analysis of rats behavior during recall session, confirmed that most of them were able to recollect fully or partially the What-Where-Which component (75%), even in a situation different from the initial life episode (70%). This new model, coupled with a set of multi-scale different methodological approaches, will be use to study which brain regions and dynamics are involved in remote episodic memory retrieval and how brain circuits are reorganized according to the age of memory.
INSULAR AND VENTROLATERAL ORBITOFRONTAL CORTICES DIFFERENTIALLY CONTRIBUTE TO GOAL-DIRECTED BEHAVIOR IN RODENTS
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The medial prefrontal cortex (mPFC) has long been considered a critical site in action control. However, recent evidence indicates that the contribution of cortical areas to goal-directed behavior likely extends beyond mPFC. Here, we examine the function of both insular (IC) and ventrolateral orbitofrontal (vlOFC) cortices in action-dependent learning. We used chemogenetics to study the consequences of IC or vlOFC inhibition on acquisition and performance of instrumental actions using the outcome devaluation task. Rats first learned to associate two actions with two distinct rewarding outcomes. Then, one of these outcomes was devalued and we assessed the rats' choice between the two actions. Typically, rats will bias their selection towards the action that delivers the still valued outcome. We show that chemogenetic-induced inhibition of IC during choice abolishes goal-directed control whereas inhibition during instrumental acquisition is without effect. IC is therefore necessary for action selection based on current outcome value. By contrast, vlOFC inhibition during acquisition or the choice test impaired goal-directed behavior but only following a shift in the instrumental contingencies. Our results provide clear evidence that vlOFC plays a critical role in action-dependent learning, which challenges the popular idea that this region of OFC is exclusively involved in stimulus-dependent behaviors.
INTER-INDIVIDUAL AND INTER-STRAIN COGNITIVE AND SOCIAL PROFILES AND THEIR CORRELATION TO SEROTONIN METABOLISM IN THE RAT BRAIN

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Considering a continuum between normality and pathology, the study of inter-individual differences and of the spontaneous expression of maladapted behavior are promising approaches to accurately model symptoms of human mental diseases in rodents. The development of therapeutic solutions will depend on finding the specific biological markers of these symptoms. Serotonin is a brain neurotransmitter involved in the modulation of symptoms of different mental diseases. Its hypofunction has been linked to poor decision making, impulsivity, cognitive inflexibility and increased aggression.

The Wistar Han (WH) strain of rat is the most commonly used in preclinical research. Inter-individual differences in behaviors and in central serotonin metabolism have been observed and characterized in this strain. In a healthy population of WH, the minority of them which spontaneously make poor decisions in the Rat-Gambling-Task (RGT) are also more sensitive to reward and risk, present higher cognitive inflexibility and motor but no cognitive impulsivity. Poor decision makers in the RGT present an imbalance in monoamine metabolism.

The Dark Agouti (DA) strain of rat was recently used to study serotonin function using transgenic approaches, but has not been characterized at a behavioral level yet. The goal of this study was to explore the socio-cognitive abilities and serotonin production in related brain areas of the DA in comparison to WH rats.

WH and DA rats were tested in a longitudinal study to assess decision-making ability, flexibility, delay and risk-based impulsivity and different aspects of social abilities. In each strain inter-individual differences were considered and behavioral profiles identified. Post-mortem measures of the serotonin levels in prefrontal and sub-cortical structures were determined using HPLC technique. This study revealed interesting similarities and differences existing between DA and WH rats in their cognitive and social abilities, and their correlation to serotonin metabolism in the brain.
THE ROLE OF THE ORBITOFRONTAL CORTEX/NORADRENALINE TANDEM IN BEHAVIORAL FLEXIBILITY

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Updating information is an essential ability for an organism to flexibly adapt to a changing environment. It implies a continuous knowledge about the causal relationship between its actions and consequences while assigning a value to these consequences. Numerous studies have highlighted the important role of the prefrontal cortex and its different sub-regions in these processes. In particular, recent work in our laboratory, using instrumental learning in which an animal must associate voluntary actions with the delivery of rewarding outcomes, have shown that the orbitofrontal cortex (OFC) is essential to quickly cope with changes in action-outcome associations. In other words, the OFC allows the animal to rapidly update the contingencies between actions and outcomes when they are modified and adapt its response according to these modifications. Yet, the mechanism by which this updating is processed remains unknown. Interestingly, some authors consider the locus coeruleus-noradrenaline (LC-NA) system as an input signal to the OFC that promotes new learning. Indeed, the LC sends independent noradrenergic projections to the different sub-regions of the prefrontal cortex, including the OFC, suggesting an independent modulation of their functions. Moreover, this system has been identified to play a role in flexibility-required tasks, which converges with a large literature and our findings about the role of OFC. Therefore, in our study we investigate this interaction between NA and OFC in a flexibility-required task. To do so, we bilaterally injected our rats with an anti-DBH (Dopamine-Beta-Hydroxylase: a specific enzyme of noradrenergic neurons) saporin in the OFC to selectively deplete LC-projecting noradrenergic neurons in this region. Then, two weeks after, rats performed an instrumental task which requires behavioral flexibility. Taken together, this set of experiments will shed new lights into the role of NA in the OFC for instrumental behavioral flexibility.
FRONTAL NEUROBIOLOGY OF DECISIONS TO CHECK
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Objectives: 1) Assess medio-frontal regions recruitment in decisions to check as opposed to a more standard externally guided decision and 2) test the causal role of the midcingulate cortex in such behaviors.

Purpose: Recent theories argue that midcingulate cortex (MCC) dynamically signals the value of environmental options to guide behavior away from default or routine actions, and explore other alternatives. Yet the qualitative nature of MCC signals and its specific contribution to behavior is still subject of intense debates as well as how and when it communicates with the dorsolateral prefrontal cortex (dLPFC).

Methods: We designed a so-called checking-task eliciting voluntary checks for information about an incoming reward bonus in trained monkeys. We performed single unit and LFP recordings in MCC (213 single units) and dLPFC (198 single units) in two monkeys doing the task [1]. We also tested the effect of injecting either a GABA agonist (2 µL of muscimol at 10 µg/µL) or a GABA antagonist (2µL of bicuculine methiodide at 15 µg/µL) in MCC on checking behavior in the same task (1 monkey, 8 sessions muscimol, 6 sessions bicuculine).

Results: We showed that MCC neurons contribute first, followed by dLPFC neurons, to decision to check. The opposite scheme was found for a classical cue-based categorization decision thus enlightening a specific frontal dynamic for checking decisions [1]. Interestingly, the MCC check-related population activity also encoded feedback. MCC inactivation by muscimol led to alteration of the frequency of checking but did not induce deficits in feedback integration. Despite not leading to huge checking deficit, muscimol and even more bicuculine disturbed the use of information gathered by previous checks to adapt on-going choices.

Conclusions: Combined electrophysiological and pharmacological data suggest a key role of the MCC in the maintenance and updating of relevant information used to regulate exploratory decisions. Our results also highlight the flexible and dynamical nature of medio-frontal regions recruitment in adaptive decision-making and suggest that MCC-dLPFC functional communication and influence over the other depends on the current task demand.

Literature Reference
SYNESTHESIA IN BIPOLAR AND SCHIZOPHRENIA PATIENTS: A STUDY OF ITS RELATIONSHIP WITH ABSTRACT THINKING
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Objectives: The neurological condition ‘synesthesia’ may explain the links underlying metaphor perception and comprehension of abstract concepts in humans. Schizophrenia and bipolar disorders share certain similarities regarding symptomology which often inhibits and attenuates differentiating between them. Individuals with schizophrenia have more pronounced structural brain and neuropsychological abnormalities than those with bipolar disorder. A unique characteristic of schizophrenics’ thought and language disturbance is concretism. In other words, schizophrenic patients fail to understand metaphors. On the other hand, an intellectual ability such as metaphor perception remains intact in bipolar patients.

Purpose: The aim of the current study is to determine (a) if patients with schizophrenia are weaker at metaphor comprehension than bipolar and normal individuals (b) if the patients with schizophrenia are weaker in synesthesia comprehension than bipolar and normal individuals (c) if bipolar patients can understand metaphors as well as healthy people, and (d) whether bipolar patients can understand synesthesia as well as healthy controls.

Methods: Twenty-eight schizophrenic patients, 28 patients with bipolar disorder, meeting diagnostic criteria, as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and 28 healthy controls, were analyzed in two subgroups of male and female participants, who completed Synesthesia battery and a designed metaphor task.

Results: The results of battery and the task in schizophrenic patients were significantly lower, in comparison with bipolar patients’ (p<0.01). The responses to the metaphor task were more literally comprehended in the schizophrenic group as compared with the bipolar and control groups. No significant differences were observed in the results between the healthy control and bipolar group tasks.

Conclusions: The results revealed a strong correlation between synesthesia and metaphor recognition which could stem from co-existing common neurological structures. Previous research has indicated that the formation of synesthesia occurs in the human brain before the ability to understand metaphors and abstract thinking develop. Thus, this condition may determine a causal role in the ability to develop understanding abstract concepts and abstract thinking.

Literature Reference
PERSONALITY FACTORS PREDICT NEUROFEEDBACK TRAINABILITY IN HEALTHY PARTICIPANTS

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Objectives: Studies on Neurofeedback (NF) have shown that people can learn to modulate aspects of their neural activity. However, one third of people do not achieve control over NF. Various factors have been related to individual’s success, but no theoretical framework is available and, thus, research within this context is needed.

Purpose: The aim of this study is to show that personality factors are significantly related to NF trainability.

Methods: Forty healthy volunteers were randomly assigned to one of three conditions: experimental (SMR/theta), sham and control. Locus of control, re-appraisal process performed by individuals and the two motivation systems (BIS/BAS) were assessed before volunteers underwent NF training (real or sham) or control task. Once NF training was complete, experimental participants were categorized as either NF respondents or non-respondents. Heart Rate (HR) was recorded transversally to show how NF influenced the Autonomic Nervous System (ANS).

Results: A tendency to significance was found between conditions regarding the subtraction of the amplitude of SMR [F(2, 37) = 2.29; n.s.] and theta [F(2,37)= 2.96; p = .06]. Specifically, only the experimental condition and, especially NF respondents, displayed important changes in SMR and theta [*t*(18)= 3.74; *p*=.002 and *d*= 1.59] amplitudes. Indeed, changes in EEG and HR results were related to personality factors. Respondent participants within the experimental condition showed that locus of control (r =-.56; *p*=.04) and re-appraisal processes (r = .58; *p*=.03) were related significantly to changes in EEG (SMR and theta). Also, these variables were evidenced to be significant predictors of the ability to gain control over brain activity and physiological changes (HR) throughout NF training.

Conclusions: Evidences in this study suggest that, indeed, personality factors such as locus of control and re-appraisal processes performed by individuals regarding the implementation of strategies through the session are related to the success in NF trainability. Even more, these variables could be acting as predictors of NF training performance. Additional research in the future would be of use to evidence if the predictions and relationships, obtained in this study, point towards a determinant nature of these personality factors, which would be of vital importance within the intervention in psychosomatic medicine and the clinical field in general.

Literature Reference


OBJECTIVES: Demonstrate the importance of oscillatory burst analysis to understanding cognitive control in frontal cortex, and to understanding of the general role of oscillatory phenomena.

PURPOSE: Reveal that cognitive control processes are differentially encoded in the properties of single trial oscillatory bursts in beta and gamma frequencies.

METHODS: Two monkeys learned a test of cognitive control in which they repeatedly moved between exploration and exploitation periods, using feedback to search for, find, and repeat rewarded responses. The monkeys provided chronic electroencephalographic (ECoG) recordings of both prefrontal and sensorimotor cortex. We extracted significant bursts of oscillatory power during the delay period of each trial, and then studied the effect of the cognitive control task on the length, frequency, timing, and power of the bursts at different epochs of the task, as well as the relationship between different frequency bands of bursts.

RESULTS: Frontal oscillations are discrete burst phenomena, and not sustained throughout the delay. Individual trials contain multiple bursts, with each burst showing individual properties that are not simply echoes of the first burst. In prefrontal cortex, the number and power of bursts at beta frequencies reflects cognitive control for that trial, similarly to trial-by-trial mean beta power. By contrast changes in burst duration but not power reflect the within session change in mean beta power. Separate cognitive information can be decoded from burst frequency, and from the relative timing of bursts across frontal cortex sites.

CONCLUSIONS: Analysis of cortical oscillations as single trial burst phenomena is essential to understanding the relationship between oscillations and behaviour. Specific properties of these bursts carry contrasting cognitive information, demonstrating how oscillations can multiplex information necessary for cognitive control.
BODY MASS INDEX AND COGNITIVE FUNCTION IN SAUDI ADULT POPULATION
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Objective:
To investigate the relationship between BMI and cognitive impairment.

Purpose:
The association between body mass index (BMI) and cognitive function is a public health issue. And we want to educate and aware our population.

Methods:
A cohort of 595 adults with normal cognitive function (MMSE≥26). The association between BMI and cognitive impairment which was assessed by the Cambridge neuropsychological Test automated battery (CANTAB) in Saudi adult population.

Results:
Cognitive impairment were identified in those with BMI≥25 kg/m² than normal-weight (18.5≤BMI<23 kg/m²) were marginally less likely to experience the development of cognitive impairment.

Conclusion:
In this nationally representative study, we found that obesity was associated with lower risk of cognitive decline among mid and old-age population.

Keywords: mild cognitive impairment, Alzheimer disease, body weight, body composition, body mass index, cognitive decline
TESTING CAUSALITY IN THE ASSOCIATION BETWEEN EXERCISE AND NEUROCOGNITIVE GAINS: A TRANSLATIONAL RESEARCH STUDY
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Objectives:
To test whether the regional increases in grey matter volume associated with aerobic exercise and/or progressive resistance training are being used during performance in cognitive tasks.
To investigate whether progressive resistance training increases grey matter volume and improves cognitive function to the same extent that aerobic exercise does.

Purpose:
Over the past years, the connection between exercise, brain health, and cognitive function has been garnering increasing research attention. It has yet to be shown that the regions in the brain where grey matter volume increases are causally contributing to the observed improvements in cognitive function.

Methods
We propose to conduct a multidisciplinary research study to investigate whether or not the grey matter volume changes that are observed after increased, intensive exercise are directly responsible for enhanced cognitive function.
To accomplish this, we used High-resolution anatomical images (voxel size, 1 mm³) of the whole brain acquired on a 3 T Siemens whole-body scanner equipped with a standard head coil for radiofrequency (RF) transmission and signal reception. Images used for voxel-based morphometry (VBM) analysis. These MRI-based measures of brain structure have been shown to be sensitive to change in previous longitudinal interventions.

Results
We examined training-related changes in functional connectivity (FC) default mode network DMN and central executive network CEN within and between networks.

Conclusion:
This investigation addresses a fundamental question that is of high relevance in the field due to its vast range of implications for athletic training, cognitive development, neurological disorders, age-related cognitive decline, and obesity.
CHARACTERISING GLIAL RESPONSE AND COGNITIVE DECLINE IN THE hAPP-J20 ALZHEIMER’S MOUSE MODEL
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Objectives: The need for early biomarkers in Alzheimer’s disease (AD) that precede the associated cognitive symptoms is recognised, with the focus shifting towards cellular changes in the neurovascular unit. The objective of the current study is to assess the timing of histopathological changes in relation to cognitive decline in an AD mouse model.

Purpose: The purpose was to provide a characterisation of astrocytes and microglia relative to plaque load in the hAPP-J20 mouse model, relative to wild-types, and compare this to recognition memory decline.

Methods: Male hAPP-J20 mice and aged-matched littermates were assessed at 3, 6, 9, and 12 months of age. The spontaneous object recognition (SOR) task provided a measure of memory decline with both a short delay (1 min) and a long delay (4 hrs) assessed. Immunohistochemistry of FFPE (formalin-fixed paraffin-embedded) brain tissue was used to characterise and quantify Aβ-deposition, and astrocyte and microglial responses.

Results: At all ages tested J20 mice had impaired long-term, but preserved short-term, recognition memory. Wild-types were able to demonstrate long-term memory up to 9 months of age, but showed preserved short-term memory at all ages tested. Plaque pathology in the J20 mice was present from 6 months onwards, with migration of reactive microglia and astrocytes to compact plaques. Astrocyte activation in the hippocampus was significantly greater in the J20 mice at 9 months, compared to wild-types.

Conclusions: The current study provides a key indication of both the pathological and cognitive mechanisms at play in AD. A deficit in retaining information over longer periods was present at early ages in this AD mouse model preceding the deposition of Aβ and glial responses. Defining early physiological changes in relation to cognitive decline could provide insight into new therapeutic targets early in the disease process, when intervention is most likely to effectively slow down progression.
SEROPTONIN 5-HT3 RECEPTOR ANTAGONISM POTENTIATES THE ANTIDEPRESSANT ACTIVITY OF CITALOPRAM

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Selective serotonin reuptake inhibitors (SSRIs) are able to regulate the activity of different neurotransmission pathways involved in depression. The administration of the SSRI citalopram increases serotonin release in terminal areas as the locus coeruleus (LC), which contributes to modulate noradrenergic function [1]. Serotonin 5-HT3 receptor (5HT3-R) activation in the LC reduces the firing activity of noradrenergic neurons and decreases noradrenaline (NA) in prefrontal cortex (PFC) [2]. Thus, the blockade of 5-HT3 receptors in co-administration with SSRIs could avoid this potential countertherapeutic effect of SSRIs on NA release.

The role of 5HT3-R in the effect exerted by citalopram was investigated by neurochemical in vivo evaluation of NA release (microdialysis), and behavioural studies (FST: forced swimming test and OFT: open field test).

Systemic administration of the 5HT3-R agonist SR57227 (10 mg/kg i.p.) increased NA in PFC (Emax=133±2%). This increase was enhanced in the local presence in LC of the 5HT3-R antagonist Y25130 (50 µM) (Emax=296±41%). Local administration in PFC of SR57227 (1-100 µM) increased NA in the area (Emax=815±148%). This effect was attenuated by the local presence of Y25130 (Emax=366±58%). These results support the existence of 5HT3-R in PFC that modulate local NA release and 5HT3-R in LC that inhibit LC firing activity.

Systemic citalopram (10 mg/kg i.p.) increased NA in LC (Emax=185±11%) and decreased it in PFC (Emax=-35±7%). When Y25130 was pre-administered locally in the LC (50 µM) or systemically (10 mg/kg i.p.) with citalopram (10 mg/kg i.p.), NA in PFC switched from an inhibition (Emax=-40±5%) to an increase (Emax=117±8%).

In FST, systemic coadministration of subeffective citalopram (2.5 mg/kg i.p.) and Y25130 (10 mg/kg i.p.) doses decreased the immobility time whereas no change of locomotor activity was observed in OFT.

These results show that the addition of a 5HT3-R antagonist to citalopram could represent a strategy to improve antidepressant response.

References:
PREVALENCE OF IMPAIRMENTS IN ATTENTION IN EUTHYMIC BIPOLAR PATIENTS

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Objectives: To evaluate the scope of (putative) attention deficits in euthymic BD patients.
Purpose: To prove the existence of permanent cognitive impairment in clinically asymptomatic BD.
Methods: The data presented are part of a study on cognition in BD during manic/mixed episode, euthymia, in first-degree relatives and in healthy controls examined with a battery of neurocognitive tests for the period January 2012 – January 2014. Here we summarize the results on the distribution of impairments in selective and sustained attention in the groups of HC and BDE patients tested with Stroop Colour and Word Test and Bourdon Cancellation Task. The groups comprised 24 and 28 individuals respectively, aged 18 to 65 years. The domain scores were normed and results at/below the 5‰ were considered deficient.
Results: None of the HC demonstrated impairment in the tested attention domains. 21.43% of the BDE patients performed at or below the 5‰ on at least one of both cognitive measures. 17.86% were impaired in one domain only while one participant scored below the defined range of impairment in both variables.
Conclusions: Deficits in different domains of attention are highly prevalent among BDE individuals. One of five in our sample suffered deficiencies in at least one attentional component. In other words, a significant proportion of “symptom free” BD patients suffer a clinically meaningful cognitive impairment. This knowledge can inform the clinicians in their everyday practical decisions.
ALTERED EXPRESSION OF MRNA ENCODING OPIOID PEPTIDES AND RECEPTORS IN DISCRETE BRAIN REGIONS OF THE VALPROIC ACID ANIMAL MODEL OF SOCIAL IMPAIRMENT
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Altered social behaviour and affect is a hallmark of psychiatric and developmental disorders. Animals prenatally exposed to the anti-epileptic valproic acid (VPA) exhibit reduced social interactive behaviour, and as such this is a useful model to investigate the neurobiological underpinnings of altered social responding. The opioid system is widely recognised to regulate and modulate social behaviour, with mu-opioid receptor agonists and kappa antagonists facilitating social play behaviour. However there is a paucity of studies examining if the endogenous opioid system is altered in models of social impairment.

Objectives: To determine if expression of mRNA encoding opioid receptors and peptides is altered in discrete brain regions of the rat VPA model of social impairment.

Purpose: To confirm social behavioural deficits in VPA-exposed animals, and if these are associated with altered opioid receptor and peptide mRNA expression in discrete brain regions.

Methods: Pregnant female Sprague-Dawley rats received VPA (600mg/kg s.c.) or saline on GD12.5 and social behaviour in the male offspring was assessed using the direct social interaction test and the 3-chamber sociability test during adolescence (PND36-43). Discrete brain regions were dissected from a separate cohort of behaviourally naive animals (PND36-40) and mRNA expression of endogenous opioid receptors and pre-pro-peptides was determined using qRT-PCR. Data were analysed using a t-test; P<0.05 was deemed statistically significant.

Results: Animals prenatally exposed to VPA spent significantly less time interacting in the direct social interaction test and exhibited reduced sociability and social preference in the 3-chamber sociability test, compared to saline controls. VPA-exposed animals exhibited significantly reduced kappa opioid receptor and pre-pro-dynorphin mRNA expression in the cerebral cortex, and reduced kappa and nociceptin/orphaninFQ mRNA expression in the hypothalamus. The expression of endogenous opioid receptors or pre-pro-peptide mRNA in the amygdala, hippocampus and striatum did not differ between VPA- and saline-exposed animals.

Conclusions: The data presented confirm the impaired social behaviour in adolescent rats prenatally exposed to VPA, an effect accompanied by reduced kappa and pre-pro-dynorphin expression in the cerebral cortex, and kappa and nociceptin/orphaninFQ expression in the hypothalamus. Further studies are required to determine if alterations in the opioid system underlie the aberrant social behaviour observed in the VPA model.
Objectives: To demonstrate a reliable measure of Pavlovian learning in macaques that can be used to study the neural bases of stimulus-reward learning.

Purpose: To compare the acquisition of changes in pupil diameter (PD) to a CS+ in rhesus monkeys (Macaca mulatta) that had sustained bilateral excitotoxic lesions of OFC (n=4) and unoperated controls (n=3).

Methods: Monkeys were trained on a task in which Pavlovian trace-conditioning of stimulus-reward associations was superimposed on instrumental conditioning of active visual fixation. The visually presented CS+ was followed by a 0.5-ml fluid reward delivered 500 ms (trace period) after the stimulus was turned off. The CS– was followed by an unfilled interval and no reward was delivered. PD was measured with an eye-tracking device. We chose to measure autonomic arousal with pupil responses because, under appropriate conditions, PD can be correlated with behavioral events with good temporal resolution (Mitz et al., 2017).

Results: Controls exhibited an increased pupil size to the CS+, compared to the response to the CS-, within a couple of training sessions (2 ± 1) and continued to show the conditioned pupil response in anticipation of reward across at least 4 consecutive sessions. By contrast, monkeys with OFC lesions required more sessions (14 ± 4 sessions) to acquire the conditioned autonomic response and three out of four failed to sustain it for 4 consecutive sessions even with an extended period of training (≥48 sessions on average).

Conclusions:

- Macaque monkeys exhibit a reliable change in PD to visual stimuli that have been paired with reward in the context of Pavlovian learning.
- In macaques, the OFC is necessary for acquiring Pavlovian autonomic responses to cues that predict positive events.
- Although studies of the neural substrates of stimulus-reward learning in rodents often rely on Pavlovian conditioning, measures of stimulus-reward learning in macaques lean heavily on instrumental tasks. Using PD as a measure of Pavlovian learning in macaques provides a commensurate measure, one which should aid cross-species comparisons of stimulus-reward learning.

Literature Reference:
EFFECTS OF MATERNAL DEPRIVATION AND ADOLESCENT COMPLEX HOUSING ON SOCIAL BEHAVIOUR AND IMPULSE CONTROL IN ADULT WISTAR RATS
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Objectives: Early life context and stressful experiences have an impact on the development of social interaction and the regulation of impulses and emotions, further fine-tuned by experiences in adolescence. Relatively unexplored are animal models of early life stress in this social field, that could explore biological underpinnings and windows of intervention.
Purpose: We have investigated early life stress effects and adolescent complex housing effects on later life behavioural inhibition and social behaviour in Wistar rats.
Methods: On postnatal day 3, part of the litters were deprived from maternal care for 24h, followed by reunion with the mother and standard upbringing until weaning. During early adolescence males were either pair housed or placed in a complex rearing environment. This consisted of large, two floor Marlau™ cages, where animals lived together with 10 conspecifics. Behavioural inhibition was measured in a 5-choice serial reaction time task and social interest and social recognition were measured in a social approach task.
Results: Maternal deprivation did not impair behaviour in the 5-choice task, but affected social recognition. Animals that were raised in a complex environment during adolescence showed a strong impairment in behavioural inhibition, but improved attention in the 5-choice task, regardless of early life environment. A slight decrease in social interest was seen in group-housed animals with a maternal deprivation background, but complex housing did not affect social recognition.
Conclusions: Our maternal deprivation protocol does not seem to influence impulse control in adulthood, but affects short term social recognition. Complex housing in adolescence does not moderate these effects, nor in itself affects social recognition. We did find strong effects of the complex housing environment on behaviour in the 5-choice task, suggesting a fast adaptation of these animals to changes in the environment, at the cost of lower behavioural inhibition.
PSYCHOLOGICAL AND PSYCHOPHYSIOLOGICAL FACTORS RELATED WITH SUICIDAL PROPENSITY IN PATIENTS WITH SCHIZOPHRENIA

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Objectives:
To investigate the relationship between suicide risk and electrodermal response to acoustic stimuli and investigate additional risk factors: mental pain and levels of anxiety and depression in patients with schizophrenia.

Purpose:
To examine possible differences among patients with high and low suicide risk.

Methods:
7 healthy individuals (M age = 43; SD = 10) were compared to 8 patients with paranoid schizophrenia (M age = 47; SD = 12). Suicide risk was assessed based on the SBQ-R scale. Mental pain, the level of anxiety and depression were evaluated. Participants were exposed to 10 consecutive tone stimuli, presented with the randomized ISI. During the exposition, electrodermal activity was measured.

Results:
Results showed significant (p < .05) differences in intensity of mental pain between controls, and patients. In the case of anxiety and depression, patients had significantly (p < .05) higher scores than the control group. In addition, there were significant U = 10, p = .037; differences in Mean SCR amplitudes in reaction to sound stimuli between patients (Mdn = .19) and controls (Mdn = .56). Patients with high and low suicidal tendencies differed in level of mental pain (M = 45.5, SD = 8.89 vs M = 20.17, SD = 4.83), t(8) = 5.9, p = .001 and level of anxiety and depression (M = 31, SD = 6.98 vs M = 10.38, SD = 6.07), t(10) = 5.3, p = .001.

Conclusions:
Individuals diagnosed with schizophrenia report experiencing more intense mental pain, anxiety, and depression than healthy individuals. Moreover, suicidal patients with schizophrenia scored higher on these scales than non-suicidal patients with the same diagnosis. Schizophrenic patients demonstrated reduced skin conductance amplitudes in response to sound stimuli, which is consistent with literature concerning psychophysiological processes in this population (Lim et al., 1999) and effects of neuroleptics.
BLOCKING NMDA RECEPTORS IN THE NUCLEUS ACCUMBENS INTERFERES WITH APPETITIVE CONDITIONING: WHAT ARE THE SPECIFIC EFFECTS ON LEARNING AND LEARNING-RELATED NEURONAL ACTIVITY?

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Various studies suggest that NMDA receptor activation in the nucleus accumbens (NAc) is necessary for reward-related learning to occur. This conclusion is drawn from the finding that blockade of NMDA receptors in the NAc during training impairs acquisition of different kinds of reward-directed behaviors. However, NMDA receptor antagonists might interfere with performance as well, which makes their specific effects on acquisition hard to interpret. The goal of this study was to specifically examine the role of accumbens NMDA receptors on learning by using an experimental design that addresses the abovementioned confound. In this study, animals in two groups received either infusions of an NMDA receptor antagonist (AP5 group) or saline infusions (yoked vehicle group) in the NAc core throughout training in a cued approach task. The behavioral paradigm was designed to ensure that both groups received the cue alone, or the cued paired with reward, the same number of times. As a result, any observed differences in learning between these two groups cannot be attributed to a performance deficit. By eliminating this confound, we observed that blockade of NMDA receptors in the NAc interferes with acquisition of cued reward approach behaviors independent of effects on performance.

Consistent with the behavioral observations, electrophysiological unit recordings in behaving animals demonstrated that cue-evoked excitations emerge in NAc neurons during task acquisition. These excitations are necessary for the cued approach response (Du Hoffmann and Nicola, J Neurosci 2014). We are using a novel technique that enables colocalized simultaneous unit recordings and local infusions to determine whether NMDA receptor blockade within the NAc prevents the appearance of these excitations in NAc neurons during learning, thus describing a mechanism by which NMDA receptor-dependent plasticity in the NAc facilitates the acquisition of cued approach. The results from this experiment will also be discussed.
Objectives: Recent studies have shown that inhibition of return (IOR) is characterized by a functional dissociation in the visual field with a stronger inhibitory magnitude in the periphery compared to the perifoveal visual field (Bao and Pöppel, 2007; Bao et al., 2011; Lei et al., 2012; Bao et al., 2013). The present study aims to further understand the spatial reference frames of perifoveal and peripheral IOR.

Purpose: By comparing whether IOR is bound to the retinotopic or environmental location, this study investigates whether perifoveal and peripheral IOR is controlled by the same or different reference systems.

Methods: Using a spatial cueing paradigm, both the perifoveal and the peripheral IOR were measured in young adults. The critical manipulation in the IOR task involved a gaze shift, i.e., after the presentation of a spatial cue the fixation point was shifted to a new location triggering a saccadic eye movement to this position. Then IOR effects for targets appearing at both the originally cued location and the new corresponding retinotopic location were examined.

Results: The results showed a clear difference of the IOR reference frame between the perifoveal and peripheral region. In the perifoveal region, an environmentally coordinated IOR effect was observed, while in the periphery both the environmental and the retinotopic coordinated IOR effect were observed.

Conclusions: This observation supports the concept of a functional dissociation of attentional control in the visual field. The different reference systems for perifoveal and peripheral IOR are presumably based on the different neuro-anatomical projections with a strong bias of the perifoveal region projecting to the lateral geniculate nucleus and from there to the striate cortex (V1), and more peripheral areas of the visual field having a stronger projection to the superior colliculus.

Literature Reference
ANIMAL MODEL OF SCHIZOPHRENIA INDUCED BY DIZOCILPINE (MK-801): SPATIAL AND INTERVAL TIMING STRATEGIES ON A ROTATING ARENA
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Objectives: The objective of this study was to test a rat model of psychosis induced by dizocilpine (MK-801) in a variant of active place avoidance task aimed at both spatial-based and temporal-based avoidance strategies. We expected that we will be able to separate both types of strategies in this animal model.

Purpose: The purpose of this experiment was to test a hypothesis that both aforementioned strategies in the task will be differentially affected by MK-801 treatment.

Methods: We used a modified active place avoidance task on a rotating arena for rats. Adult male Long-Evans rats were used. This task required the rats to localize a to-be-avoided sector defined in the stable room coordinate frame while the arena rotated. Normally, this task probes spatial learning and cognitive coordination. However, we introduced periodic intervals during which the spatial strategy usage was blocked by darkness and rats had to rely on temporal updating of the sector position in relation to arena rotation. After pretraining in 20-min daily session during four weeks, we have applied MK-801 and recorded changes in spatial and temporal performances in the final week.

Results: A specific dose of dizocilpine (0.12 mg/kg) disrupted timing strategy but not performance based solely on spatial integration. Rats were not able to avoid the sector during intervals of temporal strategy demands and displayed a higher number of errors in these phases.

Conclusions: The results corroborated the hypothesis that both types of strategies are separable. Notably, neural circuits affected in patients with schizophrenia are those important for interval timing and temporal strategies. However, interval timing deficits are often discrepant between models and real patients and our approach could serve as a useful tool for provide insight into deficits of information processing in models of schizophrenia, Alzheimer’s disease and obsessive-compulsive disorder. This work was supported by GACR grant 17-04047S and AZV grants 15-34524A and 17-30833A. Institutional support for IPHYS was provided by RVO: 67985823.

Literature reference:

NETWORK DYNAMICS OF MEMORY RECALL: HYPERACTIVITY OF PLACE CELL POPULATIONS IN HIPPOCAMPAL CA3
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Distinct memories, such as memories for different environments are stored as orthogonal patterns (e.g. different place cell maps) in hippocampal CA3 autoassociative network. Memory recollection requires hippocampal network to shift from whatever present state towards an activity pattern reflecting the new input information. Mechanisms underlying this process are largely unknown.

We examined neuronal activity of CA3 population during retrieval of memory for spatial context using ‘teleportation’ protocol, where memory recall is induced by sudden switch of environment-specific light cues. Previous study described the competitive nature of spatial map transition with network state temporarily alternating between activity patterns of the original (old) and correct (new) representation shortly after the context change.

We observed that teleportation-induced retrieval of spatial map was accompanied by transitory increased recruitment of place cells, which peaked at the time of reactivation of the new memory pattern and decreased to baseline level within the first five seconds, on average. This hyperactivity effect was specific to the correct representation as it was not present during flickering-based reactivation of the original activity state. We found that hyperactivity was caused by increased recruitment of place cells at the periphery of their firing fields. In consequence, during the first seconds after teleportation the decoded momentary spatial position from place cells’ activity rendered an increased coding error. Both the memory recall-related hyperactivity and the increased coding error corresponded in their time course.

These data show that during memory recall the activated memory pattern is initially undergoing a transitory period of population hyperactivity. Suddenly conflicting sensory inputs may contribute to the observed drop in precision of spatial coding after the switch of spatial contexts. Increased, though less spatially selective, activation of neuronal population may support the expression of retrieved pattern in competition with the original representation, facilitating an effective retrieval of correct memory trace.
ALTERED LEVELS OF DOPAMINE TRANSPORTER ACCOMPANIED BY BEHAVIORAL INFLEXIBILITY

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Learning and behavioral flexibility are subserved by the prefrontal cortex and the basal ganglia. Distinct regions of PFC mediate different forms of flexibility: medial prefrontal cortex plays a crucial role in shifting between strategies or attentional sets, while the orbitofrontal cortex (OFC) is implicated in reversal learning. OFC and dorsomedial striatum (DMS) form a functional frontocorticostrial circuit crucial for the mediation of flexibility during reversal learning via dopamine (DA) neurotransmission. The important regulatory control of temporal and spatial activity of released DA is provided by the dopamine transporter (DAT), which therefore likely plays a role in controlling the influence of DA on cognitive processes. We used a gene knockout mouse model to investigate the role of DAT in the performance on the Attentional Set-Shifting Task (ASST) stages dependent upon the OFC and the DMS. Additionally, behavior of mice after repeated administration of selective DAT inhibitor, GBR 12909, was examined. The animals were treated with the inhibitor to elicit a compensatory DAT up-regulation following withdrawal. DAT+/− mutant mice have shown difficulties during reversal learning and intra-dimensional shift stages of the ASST. GBR 12909-treated mice had deficits in reversals. Neuronal activation in the OFC and DMS during the ASST was examined with early growth response proteins 1 and 2 (egr-1, egr-2) immunohistochemistry. Densities of egr-2 labeled cells in the OFC were lower in mutant mice than in wild-types during reversal learning and the expression of the egr-1 was lower in mutant mice in the OFC and DMS during reversal and intra-dimensional shift stages. Mice with decreased DAT levels displayed behavioral difficulties that were accompanied by a lower task-induced activation of neurons in brain regions involved in the reversal learning. The study provides evidence that altered DAT function, specifically in OFC and DMS, underlies deficits in behavioral flexibility.

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THE IMPACT OF MAMMILLOTHALAMIC TRACT LESIONS ON HIPPOCAMPAL AND RETROSPLENIAL CORTEX MICROSTRUCTURE

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The medial mammillary bodies and its projections to the anterior thalamic nuclei via the mammillothalamic tract (MTT) are needed for normal hippocampal and retrosplenial cortex function. MTT lesions produce ‘covert pathology’ in these distal regions as evidenced by a reduction in markers of neural activity (e.g. the immediate early gene, c-fos). However, it is not known whether these functional changes are accompanied by, or even the result of, structural changes at the dendritic level. To address this, in Experiment 1 we examined dendritic arbor complexity in CA1, dentate gyrus, and retrosplenial granular b cortex (Rgb) and spine density in CA1 and Rgb after bilateral MTT lesions. Rats with MTT lesions (n=9) and sham operated controls (n=11) were tested on a reinforced T-maze alternation task, confirming impairment in the MTT lesion group. Subsequently, the brains were treated with Golgi-cox stain, and blinded Sholl analysis and spine density counts were performed on dendritic arbors. Spine density counts showed the MTT lesions significantly reduced CA1 spine density but not Rgb spine density. MTT lesions did not influence the number of intersections in CA1, dentate gyrus, or Rgb after Sholl analysis. In Experiment 2, we examined dendritic arbor complexity of immature neurons in dentate gyrus. Following surgery (MTT = 12, sham = 8), the efficacy of the lesion was confirmed with the same T-maze task then doublecortin staining and blinded Sholl analysis was performed. Sholl analysis of doublecortin stained neurons showed the MTT lesions significantly reduced the number of intersections. Our findings suggest that damage to the MTT produces changes in hippocampal microstructural integrity as shown by reduced spine density in CA1 and reduced dendritic arbor complexity in dentate gyrus which appears restricted to immature neurons. These findings provide novel evidence of the importance of ascending mammillary body projections for hippocampal integrity.
HIPPOCAMPAL ACTIVATION DURING POST-LEARNING SLEEP IS NECESSARY FOR REMOTE ITEM MEMORY CONSOLIDATION

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Objectives: 1) To investigate whether dorsal hippocampus contributes to consolidation of remote item memory during sleep. 2) To investigate the role of dorsal hippocampus on retrievals of recent and remote item memories.

Purpose: To gain insight into mechanisms underlying sleep-dependent consolidation of remote item recognition memory.

Methods: Rats underwent surgery for intra-hippocampal infusion of GABA\(\alpha\) receptor agonist, muscimol (MUS) to reversibly inactivate dorsal hippocampus. Bilateral guide cannulas were implanted and aimed to target CA1 region of dorsal hippocampus. Two frontal electrodes, two occipital references and two EMG wires were also implanted for monitoring sleep. Novel-object recognition (NOR) task was used to test item memory. In experiment 1, rats were introduced into an open-field to explore two identical objects and were then allowed to sleep for 2 hours after learning. Either MUS or vehicle (VEH) was infused when slow-wave sleep (SWS) was detected. Item recognition memory was tested 3 weeks later. In the test phase, one object was replaced by a novel object. In experiment 2, behavioral paradigm remained the same as experiment 1 except that intra-hippocampal infusion of MUS was performed 15-min prior to the 3-week NOR test. In experiment 3, NOR test was performed 30-min after learning and either MUS or VEH was infused 15-min prior to the test.

Results: In experiment 1, reversible inactivation of dorsal hippocampus during sleep impaired consolidation of 3-week NOR memory. MUS-infused rats failed to show preferential exploration of the novel object. In experiment 2, intra-hippocampal infusion of MUS right before the 3-week test did not impaired NOR memory. In experiment 3, MUS-infused rats and VEH-infused rats showed intact recent NOR memory.

Conclusions: Hippocampal activation during post-learning sleep is essential for consolidation of remote item recognition memory. However, retrieval of recent or remote item memory does not require functional hippocampus. These results provide first evidence how sleep enhances remote item memory.
HIIPPOCAMPAL DRR1 OVEREXPRESSION IS INSUFFICIENT TO CURB EARLY DETRIMENTAL EFFECTS OF ACUTE SOCIAL DEFEAT ON COGNITION IN MICE

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Objectives: Acute stress prepares the body for action by stress hormone secretion. A short-lasting stressor may cause temporary impairments but, when stress severity is within limits, homeostatic recurrence is anticipated. Identification of resilience factors and understanding early stress-coping may lead to novel insights into neurobiological mechanisms underlying chronic stress-induced detrimental sequelae.

Purpose: The actin-binding protein DRR1 has been described as a stress-resilience factor (Schmidt et al. 2011) but the direct potential of DRR1 to curb stress-effects has not been investigated yet.

Methods: We employed a novel model of acute social defeat (ASD) in mice and tested the animals ∼4h (ASD-early) and ∼8h (ASD-late) after social defeat in a novel, comprehensive -but brief- behavioral test battery for cognition, anxiety-like behavior and social behavior. We investigated the integral function of DRR1 expression as potential resilience factor in early stress-coping by studying ASD-induced hippocampal DRR1 expression levels and the subsequent effects of manipulating these DRR1 expression levels by viral targeting on ASD-induced behavioral impairments.

Results: Here we report on the role of hippocampal DRR1 in the behavioral effects of acute social defeat stress (ASD) early- (∼4h) and late (∼8h) after stress-induction in male mice. ASD-early resulted in hippocampal dependent cognitive impairments in the Y-maze and in the spatial object location test whereas ASD-late was not affected in these tests. Hippocampal DRR1 mRNA-expression was increased in both ASD-early and ASD-late whereas DRR1 protein levels were increased only in ASD-late. To investigate whether the absence of hippocampal DRR1 protein upregulation in ASD-early caused the associated cognitive impairments, we investigated the effects of virus-induced hippocampal DRR1 overexpression on stress-outcome. However, DRR1 overexpression did not ameliorate the hippocampal-dependent cognitive impairments induced by ASD-early.

Conclusions: We conclude therefore that hippocampal DRR1 protein expression alone is insufficient to protect from the detrimental cognitive effects following acute social stress at an early stage where perhaps a more global response in local actin dynamics, involving multiple stress-responsive actin binding proteins (van der Kooij et al. 2016) that act synergistically, was warranted.

Literature Reference:

THE ROLE OF THALAMOSTRIATAL CONNECTIVITY IN HUMAN BEHAVIOURAL FLEXIBILITY

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Objectives: To illustrate the contribution of thalamostriatal interactions in human behavioural flexibility.

Purpose: The study was designed to test the hypothesis that functional and structural connectivity between the centromedian-parafascicular thalamic complex (CM-Pf) and the caudate nucleus of the striatum is associated with successful adaptation during probabilistic reversal.

Methods: Multiband functional and diffusion magnetic resonance imaging were combined with a performance of a multi-alternative probabilistic learning task with a reversal component. Learning and reversal periods were modelled separately during analysis. Parametric modulation was used to assess the specificity of striatal subdivision involvement during reversal learning. Psychophysiological interaction (PPI) analysis was used to examine changes in functional connectivity between striatal and thalamic subdivisions.

Results: Dorsal striatal activation increased linearly during the perseverative period. Additionally, functional connectivity between the CM-Pf and the dorsal anterior caudate increased during the reversal period, but not during initial learning of contingencies. This effect was specific to this connection and was not seen between other thalamostriatal connectivity dyads.

Conclusions: These results are in line with prior evidence for the role of the dorsal striatum in behavioural flexibility. Moreover, we demonstrate for the first time that communication between the CM-Pf and the caudate is important specifically for reversal learning. Our findings are in line with evidence from the animal literature, providing further support for the role of thalamostriatal input in behavioural flexibility, and complement our prior data on the role of striatal cholinergic function in the same behavioural context.
UNRAVELING THE FUNCTIONAL CONTRIBUTION OF FKBP51 IN MONOAMINERGIC BRAIN AREAS TO STRESS VULNERABILITY


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Objectives: Both, environmental factors and genetic predispositions substantially contribute to an increased risk for the development of stress related psychiatric diseases. Polymorphisms of the FKBP51 gene, an important player in the negative feedback loop of the HPA axis, have repeatedly been associated with depression and PTSD.

Purpose: The aim of this project is to investigate the role of FKBP51 in the brain in more detail, utilizing pharmacological and genetic approaches in mice.

Methods and Results: First, we used in situ hybridization to analyze the regulation of FKBP51 expression in response to stress. We aimed to detect region specific changes in FKBP51 expression following chronic or acute stress. Second, we focused our experiments on two main monoaminergic brain areas (dorsal raphe, locus coeruleus) that show not only high FKBP51 expression, but also regulation following acute but not chronic stress. Unlike in the amygdala [1], viral overexpression of FKBP51 in these areas did not alter anxiety behavior under basal conditions. Third, we used SAFit2, a newly developed specific antagonist for FKBP51, to mimic behavioral effects observed in knockout animals. We showed that SAFit2 is a very potent modulator that specifically prevented the stress-induced increase in social avoidance behavior.

Conclusions: The effectiveness and specificity of this antagonist make it a very interesting compound and its investigation could potentially lead towards the development of drugs, antagonizing or otherwise manipulating FKBP51 in the brain. In future experiments, conditional brain region specific knockouts will enable us to not only ascertain the role of FKBP51 in different brain areas in much greater detail, but also shed light into underlying mechanisms or neuronal pathways.

Taken together, this project will advance our current understanding of the interaction of FKBP51 with stress vulnerability and potentially pave the way for the further development of novel treatment strategies for stress-related disorders.

The authors state that there is no conflict of interests to declare.

SLC6A15, A NOVEL STRESS VULNERABILITY CANDIDATE, REGULATES ANXIETY AND DEPRESSIVE LIKE BEHAVIOR THROUGH THE GLUTAMATERGIC SYSTEM

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Objectives: The aim of this study was to investigate the mode of action of the neuronal neutral amino acid transporter SLC6A15 and its effects on behaviour and neurochemistry in the hippocampus.

Purpose: SLC6A15, a neutral amino acid transporter predominantly expressed in neurons, has been recently suggested to play a role in the aetiology of major depressive disorder. The purpose of this study was to explore a putative mechanism of action of the transporter in the brain and to characterize behavioural and molecular changes following manipulation of SLC6A15 in mice.

Methods: To implement this aim, we analysed hippocampal neurochemistry and behaviour in animals with reduced, i.e. full knockout or acute pharmacological inhibition, or increased levels of SLC6A15, i.e. targeted overexpression in the hippocampus. We are furthermore investigating the effects of reduced SLC6A15 levels on glutamate synthesis, mitochondrial function and electrophysiology in primary hippocampal cell culture.

Results: Ablation of SLC6A15 reduced tissue levels of several substrate amino acids such as proline and leucine as well as glutamate levels in the hippocampus, while overexpression increased hippocampal glutamate levels. We observed an anxiolytic effect of SLC6A15 KO after chronic stress exposure and of SLC6A15 antagonist treatment under control conditions, an effect that was reversed by hippocampal overexpression of the transporter. Lack of the transporter was furthermore associated with alterations in sensorimotor gating.

Conclusions: In summary, our results implement SLC6A15 as a modulating factor for emotional behaviour and stress vulnerability. Our data show that alterations in SLC6A15 function affect neutral amino acid and glutamate content in the hippocampus, thereby possibly affecting glutamate synthesis in mitochondria, glutamatergic neurotransmission and metabolic functions.
FUNCTIONAL INTERACTION BETWEEN MEDIAL OR LATERAL ENTORHINAL CORTEX AND THE HIPPOCAMPUS DURING SPATIAL AND OBJECT NOVELTY DETECTION
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The ability to encode and retrieve past experiences relies on the activity of the hippocampus and the entorhinal cortex. A large amount of studies in the literature point to the existence of two parallel information processing pathways: the ‘what’ pathway, involving the lateral entorhinal cortex (LEC), and the ‘where’ pathway, involving the medial entorhinal cortex (MEC). Both pathways converge into the hippocampus (HPC), where episodic memory is supposed to emerge. Recent results, however, are not fully consistent with this model. We have recently shown that both medial and lateral entorhinal cortices contribute to spatial (where) as well as non-spatial (what) processing, thus suggesting that more complex interactions between these two areas exist during episodic memory formation. The purpose of our study is to further explore this issue by analysing how MEC, LEC and HPC interact during spatial- and object-novelty detection. Animals were implanted with electrodes and local field potentials were recorded simultaneously from MEC or LEC and HPC. LFPs were collected while the animals were engaged in an object exploration task, involving four 16-min sessions. In the first two sessions, two objects were presented in a 100cm-diameter arena; in session 3, one of the objects was modified (either replaced, or displaced or both), and such modification remained stable during session 4. We analyzed possible modifications induced by spatial and object novelty on theta oscillations within MEC, LEC and HPC. The results will reveal whether or not specific co-activations of MEC or LEC and HPC occur during spatial and object-novelty, thus allowing to refine our knowledge of the functional interaction between the hippocampus and the entorhinal cortex in episodic memory.
EFFECT OF MATERNAL AND OFFSPRING MTHFR DEFICIENCY ON ASD LIKE BEHAVIOR AND THE INHIBITORY SYSTEM
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Objective: Methylene tetrahydrofolate reductase (MTHFR), a critical enzyme in the one-carbon (C1) metabolism pathway, shows high prevalence of polymorphism in Autism-spectrum-disorders (ASD) patients. MTHFR-deficiency predisposes human and mice towards ASD-like behavior. Recent studies show significant alternations in the GABA pathway in ASD and animal models of ASD.

Purpose: Evaluate the influence of maternal and offspring MTHFR-deficiency on mice behavioral-profile and the brain GABAergic system.

Methods: Six groups of adult mice were divided by maternal:offspring genotype [MTHFR+/+(WT) and MTHFR+/- (HT)]-1.WT:WT 2.HT:WT 3.HT:HT. Behavior was evaluated by ASD related behavioral tests, after which the GABAergic markers Parvalbumin(PV+) and decarboxylase 67 (Gad-67+) were examined by Immunohistochemistry in their brains. In parallel, we examined the susceptibility to convulsion induction by PTZ injections.

Results: Open-field (general behaviour) - all groups moved a similar distance. Alternation was seen in anxiety related behaviour measured by distance moved in [center/(center+margin)] (G,p<0.05). Nest-building (welfare) - alternation in nest quality (G,p<0.05 MG,p<0.05). Social-proximity (sociability): alternation in number of aggressive (MG,p<0.05 G,p<0.05) and non-aggressive (G,p<0.01 MG,p<0.001) interactions. Three-objects test: a) restrictive interest - alternation in time spent with a preferred object (MG,p<0.05). b) recognition memory - test was repeated after 24 hours with one object switched - alternation in time spent with novel object was found (G p<0.05). Marble-burying (repetitive behaviour): decrease in the num. of buried marbles (G,p<0.05 MG,p<0.05).

The density of PV+ interneurons was increased by 30% in the cortex of HT:WT group compare to WT:WT (p<0.05) and of Gad-67+ was decreased by 40% in the frontal cortex of HT:HT compare to HT:WT. Susceptibility to convulsion was 10 times higher in the HT:WT group compare to WT:WT (p<0.001) and 2 times higher compare to HT:HT (p<0.001).

Conclusions: Both genotype and maternal genotype effect behavior and the inhibitory system, with a more robust effect of maternal genotype. This might be explained by the role of MTHFR in C1 metabolism and the importance of its products for the fetus development, interneurons survival and neurogenesis.
ECOCAPTURE: AN ECOLOGICAL WAY TO DIAGNOSE APATHY IN PATIENTS WITH NEUROLOGICAL DISORDERS

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Objectives: Apathy can be defined by a quantitative reduction of voluntary or goal-directed behavior (Levy and Dubois, 2006). The study’s objective is to offer a behaviorist approach by quantitatively and qualitatively measuring apathy in a short-time, near to real-life situation.

Purpose: The project’s purpose is to better diagnose apathy and to adapt the treatment to each patient’s apathy form.

Methods: We have developed an original method, called ECOCAPTURE, consisting in a multi-step scenario (45 min) taking place in a functional exploration platform equipped with different data acquisition systems (video and sensor) to capture behavior.

Results: Here, we report preliminary results in a small group of bvFTLD (behavioral variant of Fronto-Temporal Lobar Degeneration) patients (n = 6) matched for age, gender and level of education to healthy participants (n = 6), already demonstrating that discrete metrics strongly differentiate patients from controls. Besides, this study allowed introducing a 3 phases scenario (Free/Guided/Facilitated) in order to discriminate one’s ability to spontaneously (self-) generate behavior in response to a given ecological environment from that of organizing and controlling behavior in an externally–driven situation. This scenario also assesses behaviors related to effort/reward balance with positive and negative stimuli (food/sound).

Conclusion: The method called ECOCAPTURE is able to distinguish apathetic patients from healthy subjects especially regarding activity (no activity/exploration/activity) and body position (lying/seating/standing/walking) during the first 3 minutes. These results correlate with the Starkstein apathy scale score (Starkstein et al., 1992), which is a clinical apathy scale.

The project has reached its objective offering a new tool that can distinguish apathetic patients from healthy subjects, even in a very small population sample. Moreover it offers a stronger scenario that can be used for a larger study to differentiate and understand the different mechanisms underlying apathy and its different forms. We would like to validate this tool in a larger population in order to establish a behavioral signature for apathy distinguishing different forms and its transnosological ability applying ECOCAPTURE to different pathologies (bvFTLD/Parkinson/depression). Perspectives concern its adaptation to a patient follow-up at home and a potential therapy.

Literature Reference:
Objective: The objective of this study was to provide insight into a function of adult neurogenesis in the dentate gyrus of the hippocampus in the rat. Adult neurogenesis contributes to many behaviors, including pattern separation and cognitive flexibility, but the precise role of these newly-born cells is unknown.

Purpose: The purpose of this study was to develop a behavioral assay to test a hypothesis that adult-born neurons in the hippocampus contribute to integration of temporally close events during memory formation. Moreover, assessment of contribution of adult-born neurons to performance in this task was conducted.

Methods: Our novel test is a form of one-trial aversive trace conditioning. In short, light/dark shuttle-box environment was modified so that rats almost completely preferred dark compartment. After habituation, each animal was presented with a loud sound that was followed, after 2-sec interval, by an electric foot-shock. An escape to the light compartment terminated this foot-shock. Animals were re-tested after three days. In this test only sound has been presented and animal reaction has been recorded. We systemically treated Sprague-Dawley rats with cytostatic temozolomide (TMZ; n = 18) and compared frequency of avoidance to controls (n = 18) to assess a contribution of adult neurogenesis to this behavior.

Results: 10-30% of animals escaped immediately following sound during the task presentation; indicating formation of a trace-conditioned memory. We found a non-significant trend of adult neurogenesis ablation being associated with reduced frequency of avoidance (30% of control rats avoided compared to 10% of TMZ-treated rats).

Conclusions: Although we did not show that adult neurogenesis is essential in formation of this one-trial trace memory, we consider our paradigm to be a valid test of episodic-like memory. Despite the task does not meet traditional parameters, we propose that this test is a suitable tool to test mechanisms of episodic memories. Moreover, compared to other paradigms described as episodic-like, our novel test presents many advantages - including lack of a need for learning a particular rule but addressing temporal segregation of the stimuli and one-trail character.

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THE HIPPOCAMPUS-DEPENDENT EFFECT OF CLOMIPRAMINE IN THE QUINPIROLE SENSITIZATION MODEL OF OBSESSIVE-COMPULSIVE DISORDER (OCD) IN RATS

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Objectives: The objective of this study was to provide insight into effects of clomipramine and risperidone on a deficit of cognitive flexibility in quinpirole sensitization model of obsessive-compulsive disorder (OCD). Two different behavioural tasks were chosen to determine a potential dependence of effects on the hippocampal functions.

Purpose: The purpose of this study was to reveal whether an effect of clomipramine and risperidone on quinpirole sensitization was specific for learning task dependent on the hippocampus.

Methods: We induced behavioral sensitization in Long-Evans rats by a chronic intermittent treatment with dopamine D2/D3 receptor agonist quinpirole. In this model, we tested an effect of a tricyclic antidepressant clomipramine and an antipsychotic risperidone in several different combinations. At the end of the sensitization, animals were trained in place avoidance task on rotating arena and tested for the reversal learning. Separate groups of animals were tested in a hippocampus-independent two-way active avoidance task.

Results: Addition of clomipramine to quinpirole impaired acquisition learning to such a degree that reversal learning could not be tested. Risperidone alone was not effective in alleviation of reversal learning deficit and it also caused a mild deficit of acquisition. Combination of clomipramine and risperidone; however, significantly spared acquisition and reversal learning in quinpirole-sensitized rats. In the two-way active avoidance task clomipramine failed to have any effect on the performance.

Conclusions: This study showed that augmentation of clomipramine with a neuroleptic may help to reverse impairments of cognitive flexibility in the quinpirole sensitization model of OCD. We suggest that OCD patients who display cognitive deficits may profit from this treatment combination. The study also suggests that this animal model of OCD may represent a specific subgroup of OCD patients whose cognitive deficits are associated with the hippocampus.

This work was supported by AZV grant 15-34524A. Institutional support for IPHYS was provided by RVO: 67985823.
A CONTRASTING ROLE FOR THE ANTERIOR THALAMIC NUCLEI
IN VISUAL AND SPATIAL REVERSAL LEARNING
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Purpose: Consistent with its dense interconnections with the hippocampus, the anterior thalamic nuclei (ATN) are known to be involved in spatial learning and memory. The ATN are also reciprocally connected with frontal cortex, and recent evidence has revealed a role for these nuclei in behavioural flexibility (Wright et al., 2015). The present study evaluated the effects of ATN lesions on two complementary tasks that assessed strategy set-shifting and reversal learning.

Methods: Experiment 1 used an automated procedure in an operant chamber (Floresco et al., 2008). Rats with excitotoxic lesions in the ATN (n=13), along with their surgical controls (n=13), initially acquired a visual cue-based discrimination and were subsequently tested on their ability to switch to a response strategy. The rats also underwent reversals of both the visual and response discriminations. In Experiment 2, the same rats were tested on a series of two-choice visuospatial discriminations in a water maze. Platform location was first specified by a spatial response strategy which, subsequently, was reversed. Set-shifting was then tested by switching to a visual discrimination with a final visual reversal.

Results: In Experiment 1, ATN lesions did not affect initial learning of a visual-cue discrimination, the switch to a response strategy or the response reversal. However, the ATN lesions did facilitate visual reversal learning. Similarly in the water maze task (Experiment 2), ATN lesion animals learnt both the response and visual discriminations at the same rate as control animals. ANT lesions again facilitated a visual reversal but additionally impaired the reversal of the spatial response strategy.

Conclusions: Anterior thalamic lesions facilitated visual reversal learning but impaired spatial reversal learning. This dissociation points to distinct roles for the ATN in spatial and non-spatial cognition.

ROLE OF DORSAL AND VENTRAL HIPPOCAMPUS IN WORKING MEMORY LOAD CAPACITY

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Objectives: The hippocampus (HP) regulates working memory capacity (WMC) in conditions of high memory load (Sannino et al., 2012). Anatomic, genetic and behavioral studies suggested that the HP is subdivided into a dorsal (dHP) and a ventral (vHP) portion. Whether these two HP subregions differently regulate WMC is not known.

Purpose: Investigate functional differences between the ventral and dorsal hippocampus in regulating the limited capacity of working memory (WM).

Methods: Selective excitotoxic lesions of the dHP and vHP were performed in adult CD1 male mice. We tested control and lesioned animals in the different objects/identical objects task and in a modified version of the radial maze task (Olivito et al., 2016) to study object and spatial WMC, respectively. In the radial maze task the use of the sequential strategy to lower the memory load was prevented and allowed by the introduction and removal of a confinement procedure, respectively, in two consecutive phases of the task.

Results: Both dHP lesioned and vHP lesioned impaired spatial WMC; however, vHP also impaired egocentric navigation, when animals were allowed to use of the sequential strategy. The dHP, but not the vHP, impaired object WMC.

Conclusions: Our study reports that activation of the HP along its septo-temporal axis is necessary for spatial WMC, consistent with its role in allocentric navigation. The selective contribution of the dHP in object WM in condition of high memory load might be to support novelty detection processes in complex stimulus arrays. This suggests that a functional differentiation exists between the dHP and the vHP in regulating object WMC, but both subregions similarly regulate spatial WMC.

Literature Reference
According to the Shared Signal Hypothesis, (SSH, Adams & Kleck, 2005) processing approach-oriented facial expressions is facilitated when happy and angry faces are presented with direct eye-gaze as they share the motivational intent, whereas processing avoidance-oriented facial expressions is facilitated when sad and afraid faces are presented with averted eye-gaze. The present study investigated whether these predictions stand also when presenting emotional faces briefly and for faces, whose emotional expression is present only at low spatial frequencies and it is not clearly visible or whose motivational intent is unclear (i.e., surprised and neutral faces). In Experiment 1, afraid, angry, happy, surprised and neutral faces (referred as to “Full expression”) were presented with direct and averted gaze (averted left or right) for 300ms. In Experiment 2, hybrid versions of the faces from Experiment 1 were used. Hybrids are created by superimposing a neutral expression conveyed at high spatial frequencies onto the emotional expression conveyed at low spatial frequency. Participants (N= 32) categorized the faces as positive or negative based on their first impression. ANOVA results on the proportion of positive response showed significant main effects of Gaze and Expression for both Full (Exp. 1) and Hybrid expressions (Exp. 2). Importantly, the Gaze by Expression interaction predicted by the SSH was not significant for Full expressions, F(4,124)=.899, p=.476, η²=.028, as well as for Hybrid expressions, F(4,120)=.162, p=.957, η²=.005), indicating that gaze and expression are processed independently. Methodological differences between the present studies and past evidence as well as the meaning of the present findings in relation to the SSH are discussed.
RESTING STATE EEG ACTIVITY AS PREDICTOR OF SPATIAL WORKING MEMORY PERFORMANCE?
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Objectives: Resting state EEG activity has been reported to predict IQ and working memory performance in healthy individuals. However, the link between brain spontaneous activity and specific cognitive functions has been sparsely investigated. We tested the relations between resting-state EEG and allocentric spatial working memory in healthy 25-30-year-old and 64-75-year-old individuals.

Purpose: We aimed to characterize an electrophysiological signature of the brain resting-state activity, which could be used to predict spatial working memory performance in healthy individuals.

Methods: In this study, we recorded resting state EEG from 17 healthy participants (7 young adults 25-30 years of age, M=27.29, SD=0.84; 10 older adults 64-75 years of age, M=70.50, SD=1.23) and tested them in a real world allocentric spatial memory task.

Results: Our preliminary data showed age-related changes in alpha and theta peak frequencies and in gamma power, correlating with spatial working memory performance.

Conclusions: Describing potential biomarkers of memory abilities will allow to further our understanding on the neurobiological basis and organization of human memory functions.
CAUSALITY OF GHRELIN RESISTANCE IN STRESS-RELATED BEHAVIOR IN MICE
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Objectives: Acute stress increases ghrelin release, which stimulates food intake as a potential stress-coping mechanism. However, diet-induced obesity induces central ghrelin resistance, which in turn may deteriorate stress coping. We explored whether central ghrelin resistance is a causal factor in the association between obesity and stress-related psychiatric disorders.

Purpose: We investigated the effects of diet-induced ghrelin resistance on stress-related behavior in mice.

Methods: Male C57BL6/J mice were subjected to auditory fear conditioning and placed on a standard diet or high-fat diet for a total period of two months. One month after diet onset mice were subjected to behavioral tests for stress-related behaviors. We tested for fear memory expression and extinction in the fear conditioning paradigm, anxiety-like behavior in the elevated plus maze test, and reward processing in the two-bottle choice saccharin preference task. Central ghrelin resistance was evidenced by lower food intake following administration of a ghrelin receptor agonist.

Results: Mice placed on a high-fat diet gained significantly more abdominal fat, resulting in higher body weights compared to controls. Additionally, high-fat diet exposure was associated with sustained central ghrelin resistance as evidenced by the blunted feeding response following administration of a ghrelin receptor agonist. High-fat diet exposure did not affect anxiety-like behavior, fear memory expression, or fear memory extinction. However, high-fat diet-exposed mice displayed a decreased saccharin preference in a two-bottle choice test, demonstrating impaired reward processing.

Conclusions: Taken together, our data suggest that diet-induced ghrelin resistance per se does not affect anxiety or fear processing in mice. However, the observation of abnormal reward processing in high-fat diet exposed mice suggests that diet-induced obesity may aggravate emotional numbing and anhedonia in stress-related disorders.
SUBJECTIVE MEMORY COMPLAINTS AND PERSONALITY TRAITS IN INFORMAL CAREGIVERS OF CANCER PATIENTS
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Objectives: The role of the informal caregiver is considered a situation of chronic stress that produces harmful consequences on physical and mental health and could be associated with cognitive impairment. In prior studies, impact of chronic stress has been evaluated in caregivers of different pathologies as Alzheimer’s disease but the cognitive and psychosocial consequences of the caregiving of cancer patients have received little attention.

Purpose: Our main purpose was to evaluate if the chronic stress induced by the caregiving of cancer patients could have a significant impact on subjective memory complaints and the level of burden displayed by informal caregivers. We also evaluated the modulatory role of different personality traits assessed by NEO Five-Factor Inventory (NEO-FFI).

Methods: The present study was carried out with a sample composed by 1) Cancer Caregivers: informal primary caregivers of a relative with cancer (n=34); or 2) Non-caregivers: control group subjects without previous experience as primary caregiver of a dependent person (n=26). All subjects were evaluated with a battery of tests including: sociodemographic questionnaire, Memory Failures of Everyday (MFE –30), Zarit Caregiver Burden Interview (ZCBI) and personality traits assessed by NEO Five-Factor Inventory (NEO-FFI).

Results: Cancer Caregivers displayed higher level of subject memory complaints than Non-Caregivers (p<0.001). In Caregivers group, subjective memory complaints showed a significant positive relationship with neuroticism (r=.38, p<0.05) and level of burden (r=.44, p<0.01). Furthermore, burden measures indicated a positive relationship with neuroticism (r=.59, p<0.0001) and a negative relationship with extraversion (r=-.38, p<0.05) and conscientiousness (r=-.39, p<0.05).

Conclusions: Our results indicate that personality traits, specially neuroticism, extraversion and conscientiousness, could modulate the relationship between subjective memory complaints and level of burden in informal caregivers of cancer patients. These results suggest that in future interventions aimed to prevent cognitive and psychological effects of caregiving both personality traits and level of burden must be taken into account.

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THE EFFECT OF SLEEP DEPRIVATION ON THE EXPRESSION OF FEAR
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To gain insight into the high comorbidity between insomnia and anxiety disorders, we investigated the effect of sleep deprivation on the expression of fear in healthy participants. We used a conditioning paradigm with a fear acquisition phase (comprising one face stimulus that was always paired with an electric shock and another face stimulus that was never paired with an electric shock) in the evening and a test of fear expression (comprising the two face stimuli of the acquisition phase and a morph between these two as a generalization stimulus) in the subsequent morning. Between the acquisition and the test phase, participants were either kept awake for 12 hours in the laboratory (n = 19) or allowed one night of sleep at home (n = 20). Sleep deprivation relative to sleep led to overall increased subjective threat values as indicated by the shock expectancy ratings. These findings suggest that insomnia may play an important role in anxiety disorders by increasing fear. Future research should evaluate whether our results are due to sleep deprivation after learning or due to the sleep-deprived state during testing.
LOCAL CHARACTERIZATION OF SLEEP STAGES
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Objectives: Historically, sleep stages were characterized based on surface EEG recordings; however, local characterization of sleep stages in deeper brain areas remains as an open question. Therefore, our aim in this study was to compare the characterization of sleep stages in different brain structures.

Purpose: To determine the local characterization of sleep stages in different brain structures.

Methods: Two surface EEG electrodes were place above frontal and parietal lobes, respectively, in the left hemisphere; two local field potential (LFP) electrodes were placed in the medial prefrontal cortex (mPFC) and dorsal hippocampus (dHC) both in the right hemisphere; and one electromyogram (EMG) electrode were chronically implanted in 5 adult rats. The rats were recorded for 12 h during the light cycle. Sleep was scored using 10-s epochs. Each epoch was classified as awake, slow-wave sleep (SWS), pre-REM sleep or REM sleep. The characterization of sleep stages was performed independently for each EEG and LFP signal together with the EMG signal. Sleep characterization for EEG parietal, LFP mPFC and dHC, was compared with the characterization using EEG frontal as reference.

Results: Our results show that the characterization of the sleep stages was highly similar for SWS (97.2 ± 0.3%), across EEG parietal, LFP mPFC and LFP dHC, compared with EEG frontal. For REM sleep and pre-REM sleep, the similarity drops to 17.1 ± 9.9% and 78.1 ± 10.3%, respectively and they showed statistically difference (Kruskal wallis test, p=0.01 for pre-REM sleep and p=0.03 for REM sleep). We found that in 30% of the REM sleep episodes, this stage appeared first in dHC, and then come up in LFP mPFC (mean delay 3.6 ± 0.07 s) and after that in EEG frontal and EEG parietal simultaneously (mean delay 8.5 ± 0.05 s). This was accompanied by an increase in theta activity in dHC. Furthermore, this increased of theta activity was associated with a decrease in muscle tone.

Conclusions:
- In rats, it is possible to characterize SWS by using neuronal activity from different brain structures with high similarity.
- The characterization of pre-REM and REM sleep varies depending on the brain structure.
- There is a local appearance of REM sleep that comes up first in dHC and may spreads to the other cortical areas.
MODULATION OF FEAR PROCESSING BY A HALLUCINOGENIC SEROTONIN 5-HT2A RECEPTOR AGONIST

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Objectives: Hallucinogens are re-considered for therapeutic use in the treatment of anxiety disorders. Serotonin 5-HT2a receptors are a key target of hallucinogens but it remains unclear how their activation may core symptoms such as excessive fear. We aimed to elucidate the role of 5-HT2a receptors in hallucinogen effects on fear processing.

Purpose: We carried out this study in mice to establish neuroanatomical substrate and molecular target of hallucinogen effects on fear processing.

Methods: We investigated the effects of the synthetic hallucinogenic 5-HT2a receptor agonist 1-[2,5-dimethoxy-4-iodophenyl]-2-aminopropane (DOI) on fear learning and fear expression in wild-type and 5-HT2a receptor knockout mice using an auditory fear conditioning task. We studied the effect of DOI on neuronal activity by immunohistochemical analysis of c-Fos expression in the brain. Brain regions expressing the 5-HT2 receptor were identified by immunohistochemistry. Finally, local administration of DOI was performed to identify the brain region mediating its effects on fear processing.

Results: Systemic administration of DOI (2 mg/kg) before conditioning did not affect fear learning but administration before testing abolished fear expression. Specific 5-HT2a receptor involvement in the observed effects of DOI was demonstrated by the absence of effects in 5-HT2a receptor knockout mice. We found that systemic administration of DOI (2 mg/kg) induced c-Fos expression in the medial prefrontal cortex and in the amygdala. Both brain regions express 5-HT2a receptors. However, fear expression was unaffected by infusion of DOI into the medial prefrontal cortex but was suppressed by infusion of DOI (1 µg/µl) into the amygdala.

Conclusions: Our data demonstrate that the hallucinogenic DOI suppresses fear expression specifically through activation of 5-HT2a receptors in the amygdala. These data provide new insight in how hallucinogens modulate motional processing.
EFFECT OF MODULATING LEPTIN RECEPTOR EXPRESSING NEURONS IN THE LATERAL HYPOTHALAMUS ON MOTIVATION

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Objectives: Leptin is an anorexigenic adipose tissue-derived hormone which has been shown to reduce the increase in motivation for food reward caused by food restriction in rodents. Studying the role leptin plays in motivation may help in further understanding how decreases in body weight alter the incentive motivation towards food.

Purpose: In this set of experiments we will examine to what extent VTA and LH leptin receptor neurons (LepR) contribute to the behavioral effects of leptin on motivation using a chemogenetic approach in LepR-cre mice.

Methods: For behavioral studies adult male LepRcre mice were injected with AAV-DIO-hM3Dq (excitatory DREADD) which induces neuronal activation upon clozapine-N-oxide injection. Animals were tested on multiple behavioral tasks, such as the progressive ratio, open field and free feeding task, to assess effects on, motivation, locomotion and feeding, respectively.

Results: Immunohistochemistry done on LepR-cre/Rosa26-YFP mice showed that the LepR is indeed expressed in the VTA. However, only ~5% of the total amount of VTA DA neurons expresses the LepR and this represents ~25% of all LepRs in the VTA. Consistently, activating LepR neurons in the VTA did not affect locomotion, feeding or motivation. This suggested that leptin’s effects on motivation originate from leptin responsive areas that provide input to the VTA.

By injecting a cre-dependent retrograde virus into the VTA of LepR-cre mice, we showed that the LH contains the largest population of LepR neurons projecting to the VTA. Therefore, further behavioral studies were focused on the LH. Activating hypothalamic LepR neurons showed a trend towards an increase in performance on the progressive ratio task and locomotion, but not during free feeding.

Conclusion: Our anatomical and behavioral data support the idea that not leptin sensitive neurons in the VTA, but instead in the LH, mediate the increased motivation for food under conditions of negative energy balance.
UNTANGLING RHYTHMIC CONTRIBUTIONS OF THE HIPPOCAMPUS AND THE OLFATORY BULB TO PREFRONTAL CORTEX ACTIVITY
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Objectives: Oscillations are thought to mediate flexible, functional connectivity in the brain. Here we provide evidence for this hypothesis by studying prefrontal cortex (PFCx) interactions with the hippocampus (HPC) and the olfactory bulb (OB) in freely moving mice. We will also demonstrate the importance of accounting for volume conduction in this kind of analysis.

Purpose: The aim of this study is to determine how rhythmic inputs from the HPC and the OB influence PFCx activity depending on the behavioural state.

Methods: Mice were simultaneously implanted with LFP wires or multi-site silicon probes in the HPC, OB and PFCx. They were trained using an aversive sound-conditioning paradigm and brain activity was recorded during conditioned freezing and exploration. Methods of analysis include: spectral and coherence analysis, current source density analysis and unit-LFP coupling.

Results: The results presented here build on the study of OB oscillations at 4Hz seen in the PFCx during freezing and their causal implication in the cue fear conditioning paradigm (see poster by Lefort et al.)
Our results show that:
- PFCx coherence during freezing and exploration in different frequency bands with OB (4Hz vs 8Hz) and HPC (7Hz vs 9Hz)
- HPC and OB coherence in LFP recordings is eliminated by using local re-referencing or CSD analysis, suggesting a contribution of volume conduction
- Not accounting for volume conduction effects in the HPC LFP leads to erroneous conclusions concerning the frequency and the strength of HPC-PFCx coupling
- PFCx units are more strongly coupled to the OB LFP during freezing (4Hz) than during exploration (8Hz) whereas PFCx units coupling to the HPC does not change between exploration and freezing

Conclusions: These results show that during freezing the PFCx entrainment to by the OB but not the HPC is increased relative to exploration. It has previously been demonstrated that the 4Hz rhythm in the PFCx is involved in the generation of freezing in this paradigm (Karalis et al. 2016) whereas the HPC is not involved (Sanders et al. 2003). This suggests that this selective coupling between regions based on behavioural state is a functional mechanism involved in behavioural output. Moreover, these results underscore the importance of careful analysis of LFP signals and vigilance regarding effects of volume conduction by showing that they can bias classically used measures.

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THE IMPACT OF CHOICES AND ERRORS ON LONG-TERM DECLARATIVE MEMORY
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The ability to acquire long-lasting memories is driven by the extent to which predictions about future states match actual outcomes. Computationally, predictions can be updated and optimized by the calculation of an error term associated with their accuracy in light of incoming information – the degree of mismatch between expectation and reality. Indeed, one of the most successful theories in neuroscience is the reward prediction error (RPE) theory of reinforcement learning (RL), whereby action- or stimulus-outcome contingencies are learned over trials in accordance with the principles of PE based updating. Remarkably, despite the acclaim of this computational account, its applicability to the formation of long-term declarative memories has not been explicitly examined. We attempted to bridge this gap by carrying out a series of behavioural and neuroimaging studies of semantic knowledge acquisition, utilising feedback regarding the veracity of answers to questions concerning previously learned information, in order to engender PEs. By utilising two different error terms provided by subjective assessments and degrees of actual inaccuracies, we were able to compute trial-by-trial prediction error terms and assess their link to long-term memory strength. We demonstrate a striking relationship between PE and subsequent memory for information presented during feedback such that the larger the error upon initial retrieval, the better the learning from feedback in the long run. These data, supplemented by fMRI scanning, show that declarative learning follows similar rules to RL, sometimes with surprising and paradoxical consequences. Moreover, a network of brain regions, including ventral striatum and prefrontal cortex, known to govern non-declarative reinforcement learning, seem to similarly underlie the updating of declarative memory as a function of evaluated PE.
THE FUNCTIONAL ROLE OF THE OLFACTORY BULB IN THE FEAR-RELATED 4Hz OSCILLATIONS OF THE PREFRONTAL CORTEX

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Objectives: Whereas the amygdala has long been known to be associated with fear learning, more recent findings extend the fear network to also include the prefrontal cortex and the hippocampus and propose that slow oscillations (4Hz) drive synchrony between the areas. This 4Hz rhythm in the PFC has been shown to be sufficient for the generation of freezing1. The origin of this rhythm, initially referred to as the theta rhythm, is hotly debated; we propose that this oscillation comes from the olfactory bulb, itself driven by the respiratory rhythm.

Purpose: The aim of this study is to show that the fear related 4Hz rhythm in the prefrontal cortex originates in the regular breathing associated with freezing and is transmitted to the prefrontal cortex via the olfactory bulb.

Methods: We recorded breathing, LFP and single unit activity in the olfactory bulb (OB) prefrontal cortex (PFC) and hippocampus (HPC) in freely moving mice during cue fear conditioning during which a mild electric shock is associated with a sound.

Results: We observed that freezing is associated with a highly reproducible 4Hz rhythm in the olfactory bulb, entrained by regular breathing at frequencies that are highly reminiscent of this previously recorded in the fear network. These OB oscillations are strongly coherent with the prefrontal cortex whereas prefrontal-hippocampus coherence is much weaker (see Bagur et al. for disentangling OB and HPC contributions to PFC activity). Granger analysis points toward a modulation of prefrontal activity by olfactory bulb oscillations. Furthermore, prefrontal neurons are modulated by both olfactory bulb LFP and breathing, demonstrating a modulation of local activity.

To further support the role of this oscillation in cue fear conditioning, we found that the surgical removal of both OBs induced a strong decrease of the 4Hz oscillation in the PFC and a significant decrease in freezing levels.

Conclusions: Altogether, these results strongly suggest a functional role of the olfactory bulb in the genesis of the slow oscillations observed in the prefrontal cortex-amygdala network during freezing, that are required for the expression of fear behavior.

Literature Reference
ANTERIOR THALAMIC NUCLEI LESIONS ATTENUATE LATENT INHIBITION
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Objectives/Purpose: Recent evidence has revealed a critical role for the anterior thalamic nuclei in directing attention to those stimuli that are the best predictors of reward (Wright et al. 2015). The current experiments sought to assess the role of the anterior thalamic nuclei in attentional processes by examining the impact of anterior thalamic nuclei damage on latent inhibition. Latent inhibition is demonstrated when non-reinforced preexposure to the to-be-conditioned stimulus retards subsequent learning, and reflects decreased associability of, or attention to, stimuli that predict no significant outcome. The retrosplenial cortex is both anatomically interconnected with, and functionally related to, the anterior thalamic nuclei. Consequently, these experiments also examined the effect of retrosplenia damage on latent inhibition.

Methods: In Experiment 1, rats with excitotoxic lesions in the anterior thalamic nuclei, and surgical controls were tested on a within-subjects on-the-baseline appetitive latent inhibition procedure. Animals received 36 non-reinforced preexposures to an auditory conditioned stimulus (CS). Subsequently, the preexposed CS and a novel auditory CS (control) were paired with food. In Experiment 2, the impact of retrosplenial cortex lesions was assessed on the same latent inhibition procedure.

Results: Anterior thalamic nuclei, but not retrosplenia cortex, lesions attenuated latent inhibition. Anterior thalamic nuclei lesion animals acquired a conditioned response to the preexposed CS at the same rate as to the control CS. In contrast, the retrosplenia cortex lesion group showed the normal latent inhibition effect, as indexed by retarded conditioning to the preexposed CS.

Conclusions: These results provide further evidence that the anterior thalamic nuclei are vital for attending to those stimuli that are reliable predictors of reward. In their absence, attention is increased to irrelevant or poor predictors of reward.

D1/D5 RECEPTOR AGONISTS DOSE-DEPENDENTLY EXPAND AND LIMIT MEMORY CAPACITY THROUGH DIFFERENT PATTERNS OF PROTEIN KINASE A ACTIVATION IN THE FRONTO-STRIATAL CIRCUIT

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Objectives: Working memory capacity (WMC) is the limited number of elements that we can remember for a short retention interval, which is about 6 objects in mice. D1-like agonists regulate WM according to a “U-shaped” dose-response. In this study, we tested the hypothesis that D1-like agonists expand WMC in normal mice by a different pattern of activation of cAMP-dependent Protein Kinase (PKA) in the frontal cortex and in the striatum.

Purpose: This project aims at identifying the mechanism through which D1-like agonists regulate WMC.

Methods: WMC was evaluated by the different-identical objects task/DOT-IOT for mice. The effects of systemic injection of the D1-like agonists on WMC and PKA activity were evaluated through western blot analysis on striatal and frontal tissue. The role of PKA activation in mediating WMC was evaluated by focal brain injection of the agonist and the antagonist, alone or in co-administration with systemic injections of the D1 agonist.

Results: Low doses of D1-like agonists increased WMC from 6 to 8 objects. The improvement was blocked by intra-striatal injections of the PKA-inhibitor. In contrast, high doses impaired WMC. The impairment was rescued by intra-frontal cortex injections of PKA-inhibitors.

Conclusions: These findings show for the first time that pharmacological activation of striatal DA D1-PKA pathway activation expands WMC beyond its natural limit. Furthermore, they show that increasing doses of D1 agonist impairs WMC by concurrently activating PKA in the frontal cortex. These data suggest the first post-synaptic mechanism explaining why the WM improvement effects of D1 agonists follow an “inverted U-shaped” dose-response curve.

Objectives: Imagination - the ability to call to mind things not present to the senses - allows us to explore the past, the future, and the potentially possible. For most people, visual imagery is a conspicuous element of imagination, but some people report its absence. We have called this absence of visual imagery **aphantasia**.

**Purpose:** To characterise the experiences and demographics of people whose imagery is absent or extremely vivid.

**Methods:** 1,789 members of our user-group completed the Visual Imagery Questionnaire, (VVIQ, Marks 1973), a widely-accepted measure of mental imagery, and a questionnaire designed to explore their imagery experiences in more detail. Participants scoring between 16 and 24 on the VVIQ were classified as having **aphantasia**; those scoring >77 were classified as having **hyperphantasia**. Their employment was categorised using the Standard Occupational Classification (US Department of Labor, 2000).

**Results:** We focus here on individuals with aphantasia (1,671) or hyperphantasia (118). 13% of people with aphantasia worked in computer and mathematical occupations, compared to 7% of people with hyperphantasia (χ², Cramer’s V = 0.96, p = < 0.0001). In hyperphantasia, 25% worked in the creative occupations, compared to 8% of people with aphantasia (χ², Cramer’s V = 0.83, p = < 0.0001). A family history, with more than one first-degree relative affected, was seen in 15-20% of participants. The majority of participants with aphantasia (65%) experience imagery in dreams. 52% of participants with aphantasia reported the absence of imagery in other modalities. Face recognition difficulties were reported by 36% of participants with aphantasia. People with aphantasia (34%) regarded their autobiographical memory as poor, whereas only 8% did in hyperphantasia; 29% of people with hyperphantasia considered their memory good, in contrast to 8% with aphantasia.

**Conclusions:** There are substantial differences in imagery experiences between individuals, and emerging evidence that these differences associate with occupation. Many people with aphantasia experience visual images when dreaming, and a sub-set have prosopagnosia. People with aphantasia often report subjective impairment of autobiographical memory. A family history of aphantasia appears common. We are investigating whether aphantasia and hyperphantasia have distinctive neuropsychological and neural features.
GENETIC AND ENVIRONMENTAL INFLUENCES ON PERFORMANCE IN SEMANTIC VERBAL FLUENCY TEST ACROSS THE 60-SECOND SAMPLING PERIOD

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Objectives: At the conclusion of this presentation, the participants should be able to recognize the influence of genetic and environmental factors on Semantic Verbal Fluency Test during the 60s sampling period and on 15s time quartiles.

Purpose: Accurately estimate the genetic and environmental effects on Semantic Verbal Fluency

Methods: We investigated the performance of 1,375 participants from 134 extended families (mean age±SD 46±16.2, 60% female) belonging to the Baependi Heart Study, a family-based cohort study based in Minas Gerais, Brazil. Scores were the number of animals named orally in 60 seconds and in four consecutive time quartiles lasting 15-s each, because they reflect different cognitive processes along the test: automatic (beginning of the task) and controlled/executive (end of the task). To quantify the relative regressor’s contribution to the model, significant fixed effects (age, sex, schooling, time of day) were isolated from the random term of the equation (family matrix). To determine the score variance due to additive genetic factors – heritability estimates – we used the kinship2 package and, the relative contribution of fixed terms to the total variance captured by the best fitting model were calculated using the “relaimpo” package, both from R software environment.

Results: In the unadjusted model for the 60s, heritability measure was 0.32. The best-fit model contained age (beta=-0.02), sex (beta=-0.39), years of schooling (beta=0.47) and time of day (beta=0.12) added as covariates (h²= 0.21). Heritability in the same adjusted model per quartile was highest (h²=0.17) in the first quartile and decreased to 0.09, 0.12 and 0.0003 in the following ones. Years of education had the highest effect, explaining no less than 67% of the variance of any time-interval, while the other covariates had small effects.

Conclusions: Our results provided strong evidence for distinct genetic and environmental factors influencing Semantic Verbal Fluency, which could be exploited in clinical practice and genome-wide association studies.
THE EFFECT OF EARLY MATERNAL SEPARATION ON PLACE AVOIDANCE IN AN ANIMAL MODEL OF SCHIZOPHRENIA
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Objectives: As multifactorial disease, schizophrenia remains challenging both in human medicine and experimental research. Our objective is to establish animal model of psychosis based on early life stress, combining neurodevelopmental and environmental factors using valid behavioural test of cognitive coordination - the rotating arena (Carousel).

Purpose: The aim of this study is development of animal model based on the role of early life stress relevant to cognitive dysfunction in schizophrenia

Methods: Newborn rat pups were individually separated for 3 hours daily from postnatal day 1 (PD1) to PD21 randomly during light period of day. Control pups underwent early handling (the litter remains without mother for 15 min daily up to PD21 in order to decrease the stress sensitivity of pups). In PD120 rats were handled and tested in place avoidance task on rotating arena (Carousel) for 5 days followed by 3 days of reversal learning (the location of avoided place was opposite).

Results: There were no significant difference between both the stressed and control groups in basic variant of place avoidance task, but significant differences were found in several parameters of reversal task, which is more sensitive to cognitive coordination deficit.

Conclusions: Based on our preliminary results, we conclude, that early life stress induced by maternal separation could disrupt the hippocampal-specific ability of cognitive coordination, according to our preview results (Kubík et al., 2014). This study was supported by GACR 16-13399S
HUMANS TRACK FITNESS EFFECTS OF INBREEDING
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Objectives: Due to intense selection pressure, humans are thought to have psychological systems that regulate inbreeding. The difference between inbreeding situations where the self is participating and inbreeding among other relatives is only quantitative.

Purpose: Here, we examined whether human inbreeding avoidance follows inclusive fitness theory.

Methods: We gathered 27,364 pairwise forced-choices between 16 different types of inbreeding scenarios responses from a large population-based sample of 2,353 respondents online.

Results: We show that humans assess the costs of inbreeding irrespective of their self-involvement. When participants were asked to make forced-choices between different inbreeding situations, the estimated fitness costs explained 85% of the observed choices. The results were similar irrespectively of whether these costs where obtained through one self (i.e., direct inbreeding) or only through close kin (i.e., indirect inbreeding).

Conclusions: We conclude that humans perceive also the indirect fitness costs of mating decisions made by close family members, corroborating our hypothesis derived from inclusive-fitness theory. The results suggest that humans map the evolutionary effects of relative’s mate choices.
Objetives: Oxytocin (OXT) is a neuromodulator with a well-established role in social behaviour. Variation in the expression of its receptor (OXTR) contributes to inter and intra specific variability in social behaviour. Using a genetic mouse model of autism, we investigated the contribution of the OXTR system to their social deficits.

Purpose: To unravel the neuropathophysiology of autism-associated sociocognitive deficits for therapeutic research.

Methods: We previously validated mouse model based on a monogenic form of autism, knockout (KO) for the Cntnap2 gene. We also showed that Cntnap2 KO mice have lower OXT levels and that OXT administration rescues its social deficits. Here, we aimed to characterize the OXTR system in this model. OXTR distribution and quantification was performed by in vitro autoradiography using 125I-OXT followed by densitometric image analysis. Expression of OXTR-associated transcription factors was performed by RT-PCR using conventional methods.

Results: We found Cntnap2 KO mice show an abnormal distribution of OXTR compared to wildtype (WT). The major differences were found in the lateral septum, where OXTR density was strikingly 1.5 fold enriched in mutant mice. The septal region is one of the brain regions more densely innervated by oxytocin fibres and has been involved in emotional coding. It has been proposed that variation in OXTR expression arises from differential binding of transcription factors due to either genetic or epigenetic changes in the OXTR sequence. Interestingly, quantitative PCR from dissected septum showed a correlation between the expression pattern of associated transcription factors and OXTR expression.

Conclusions: There is increasing evidence of an association of dysfunction in the OXT system and autism and OXT is currently considered one of the most promising therapies for disorders of social cognition. Several autism-related animal models have been reported to have a dysregulation in either OXT or the OXTR. The findings here support the notion that investigating this system at a broader level in other forms of autism is worthwhile.

Literature References:
SWEETER THAN SUGAR? QUANTIFYING AND MANIPULATING THE VALUE OF SOCIAL INTERACTION IN A 3-CHAMBERED SOCIAL TEST
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Objectives: Social behaviour plays a large role in everyday life and is essential for many species. Social information and interactions obtain value through the process of social valuation. It is hypothesized that brain areas that execute this process largely overlap with the reward circuitry but that there are some unique contributors as well.

Purpose: The purpose of this study was to unravel the neural basis of social valuation by interfering with this process at different brain sites.

Methods: The value of social interaction was tested in a 3-chambered box with a restrained juvenile rat on one side, and different concentrations of sucrose solutions on the other side. Rats were allowed to move freely across these chambers for 10 mins. This way, a social reward was directly compared to a non-social, food reward.
In Experiment 1, the effect of 24h of social isolation on the indifference point between the two alternative rewards was tested.
Previous results from our lab found that lesioning the basolateral amygdala (BLA) abolished prosocial decisions in the Prosocial Choice Task (Hernandez-Lallement et al., 2016). Therefore, in Experiment 2, it was tested whether lesioning the BLA attenuated the value of social interaction in this paradigm.
Furthermore, Gunaydin et al., (2014) found that specific VTA-to-NAcc projections encoded social, but not non-social interaction. Therefore, in Experiment 3, an oxytocin agonist was infused into the NAcc directly before the task to see whether this affected the value of social interaction.

Results: Pilot results showed that rats readily discriminate between different concentrations of sucrose solutions. Individual indifference points were estimated in each task, within and between task conditions. It was hypothesized that the value of social interaction would increase after social isolation and oxytocin administration, whereas it would attenuate in the BLA-lesioned group relative to sham-operated controls. None of these manipulations was expected to influence valuation of the non-social reward.

Conclusions: Social behaviour is often impaired in neuropsychiatric disorders. This might be caused by a relative undervaluation of social rewards specifically, or a more general disturbance in affective processing. The results of this study will help to adjudicate between these alternative explanations.

Literature Reference
EXPLORING THE NEURAL MECHANISM BY WHICH STIMULATION OF VENTRAL TEGMENTAL AREA DOPAMINE NEURONS PREVENTS EXTINCTION OF CUED APPROACH BEHAVIORS
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Objectives: The nucleus accumbens (NAc) and its dopaminergic innervation from the ventral tegmental area (VTA) are involved in promoting reward-seeking behavior as well as strengthening cue-reward associations. Many NAc neurons exhibit cue-evoked excitations that are required for approach behavior elicited by a reward predictive cue. We hypothesized that dopamine neuronal activity at the predicted time of reward delivery is sufficient to reinforce the cued approach response by maintaining the magnitude of cue-evoked excitation of NAc neurons on subsequent trials.

Purpose: To determine whether stimulation of dopamine neurons blocks omission-induced extinction by maintaining the cue-evoked firing of NAc neurons.

Methods: Th::Cre rats were injected with a Cre-inducible AAV containing channelrhodopsin (ChR2) targeted to the VTA. After virus proliferation rats were fitted with drivable electrode arrays in the NAc and fiber optics in the VTA, allowing investigation into both behavioral and neural firing changes. Animals were trained on a conditioned stimulus task in which two distinct auditory tones were presented. One cue (CS+) predicted availability of a liquid sucrose reward while the other (CS-) was a neutral non-rewarded cue. After training, rats were subjected to an omission session followed by an omission + stimulation session. During omission sessions there was a 30 min baseline in the CS task followed by omission of the sucrose reward. Omission + stimulation sessions introduced a 20 Hz, 1s photostimulation at the predicted time of reward.

Results: During omission sessions we found a decrease in cue responding and a reduction in the magnitude of cue-evoked excitations of NAc neurons. Additionally, we found that stimulation of VTA DA during omission + stimulation sessions was sufficient to prevent extinction. Recording from NAc neurons during omission + stimulation sessions revealed short latency firing of NAc neurons during stimulation. In addition, the reduction in cue-evoked excitations during omission was attenuated by stimulation at the time of predicted reward. These results suggest a mechanism by which VTA dopamine neuronal firing influences subsequent cue-evoked excitations and thus the probability of behavioral response to the cue.

Conclusions: My current data supports the prediction that dopamine neuron stimulation is sufficient to prevent extinction of cued approach. The results suggest that this effect is due to a reduction in the decline in cue-evoked excitations that drive the approach response. In some NAc neurons, photostimulation leads to short latency firing. Further experiments are underway to investigate if this fast modulation is required for the maintenance of approach behavior.
THE EFFECTS OF EARLY LIFE STRESS AND COMPLEX HOUSING ON SOCIAL COMPETENCE IN ADOLESCENT AND ADULT WISTAR RATS

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Objectives: Early life adversity has a profound impact on brain development, which in turn results in an increased risk of developing psychiatric disorders later in life. Animal models such as maternal deprivation have provided valuable insights into the role of HPA-axis programming in the effects of early life stress on adult behaviour.

Purpose: This study aimed to investigate the effects of maternal deprivation on social competence in adolescence and adulthood and explore the potential of complex housing as an environmental enrichment intervention to diminish possible early life stress effects.

Methods: Male and female Wistar rats were either exposed to 24h maternal deprivation on postnatal day 3 or were left undisturbed. Complex housing started 5 days following weaning and consisted of housing 10 same-sex conspecifics in large, two-floor Marlau™ cages. In adolescence, social play was analysed after 3h and 24h isolation prior to testing. A pro-social task is currently being developed as a readout for social competence in adulthood.

Results: Maternal deprivation did not affect adolescent social play in males or females. However, complex housing in itself caused a large reduction in the amount of social play in both sexes after 3h isolation compared to standard housed controls. There was no interaction between maternal deprivation and complex housing. Data on social play after 24h isolation and the pro-social task is currently being analysed.

Conclusion: Previously, our lab has shown that maternal deprivation on postnatal day 3 mainly affects hippocampus dependent cognitive behaviour. We add to this by showing that maternal deprivation has no effect on adolescent social behaviour. Complex housing has strong effects on adolescent social behaviour, regardless of the early life background.
DOPAMINE ACTIVE TRANSPORTER MEDIATES LEARNING-INDUCED SHIFT IN STRIATAL PLASTICITY

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Objectives: Optimization of motor learning is mediated by practice-induced transition from phasic dopamine (DA) release action on D1 receptors in the dorsomedial (DMS) striatum, toward tonic DA action on D2 receptors in the dorsolateral striatum (DLS) (Yin et al., Nat. Neurosci 2009). However, how information acquired during initial learning is available to the DLS for optimization of motor performance remains unexplored.

Purpose: Understanding how different stages of motor learning modifies DLS synaptic plasticity.

Methods: In order to dissociate the effects of different learning stages on DLS neuronal plasticity, we used a rotarod incremental motor learning protocol that allowed to separate outbred mice and rats into initial learners and animals reaching plateau performance. 5-15 days after learning we applied a long-term depression protocol (LTD) to medium spiny neurons (MSN) of the DLS to study learning-induced metaplasticity. Through pharmacological manipulations of DA receptor subtypes and of the dopamine active transporter (DAT) we studied how learning induced metaplasticity was modulated by pre- and post-synaptic changes in DA transmission.

Results: The initial acquisition of motor learning on rotarod induced a DAT- and D1-, but not D2-, mediated shift from LTD to long-term potentiation (LTP) in the recorded MSNs of the DLS. The rotarod-induced shift to LTP disappeared in animals reaching performance plateau on rotarod.

Conclusions: Our findings suggest that initial learning induces D1 receptors activation, likely mediated by changes in DAT levels, not only in the DMS as previously suggested, but also within the DLS. We speculate that the activation of D1 pathway in the DLS during initial learning prevents a premature shift to habit before that performance reaches a plateau. This newly identified mechanism of cellular memory is a form of metaplasticity relevant for striatal pathologies, such as Parkinson disease and drug abuse.

Literature Reference
THE CRITICAL ROLE OF MICRONUTRIENTS IN NEURODEVELOPMENT: SHORT- AND LONG-TERM BEHAVIORAL OUTCOME IN A SELENIUM-DEFICIENT RAT MODEL

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Objectives: Research in animal models and human population shows that some essential elements such as selenium (Se) are particularly important during early stages of life to support rapidly maturation of cognitive functions. Conversely, at high concentrations essential micronutrients might also negatively influence brain development. Studies with animal birth cohorts might help to elucidate both protective and adverse effects of nutritional factors.

Purpose: Our main aim was to characterize the neurobehavioral effects of three diets with different Se content administered since the pre-conception stage up to adulthood. We performed a longitudinal assessment (since the very early neonatal stage to adulthood), by selecting different behavioral domains to evidence even subtle functional changes attributable to Se deficiency.

Methods: Adult females were assigned to one of three experimental groups based on different Se content of diet given (Se-deficient diet, Se-suboptimal diet, and Se-optimal diet) one month prior to mating through pregnancy and lactation. At weaning, offspring were fed the same diet as their respective dams until adulthood and completion of the behavioral assessment.

Offspring of both sexes were assessed for somatic growth, spontaneous movements, ultrasonic vocalizations and nest-odour recognition from postnatal day 4 to 12. At the juvenile stage rats underwent the Open Field test for locomotor/explorative activity, Dark/Light test for anxiety and Y-maze for working memory. At the adult stage rats were subjected to the novel object recognition test to assess more complex cognitive domains.

Results: Preliminary data indicate early somatic and behavioral changes, including hyperactivity in both neonatal and adolescent rats at the sub-optimal Se dose, which may be predictive of later deficits in different behavioral domains. Effects on neuroinflammatory biomarkers will be also presented.

Conclusions: The results of our research will be of potential high significance to elucidate the possible outcomes due to an unbalanced diet, to promote optimal brain development and possible intervention under adverse environmental challenges.
Subjective memory complaints (SMC) have been associated to the incidence of mild cognitive impairment, to smaller hippocampal volumes and to perceived stress. In older adults, chronic stress can lead to dysfunction of the Hypothalamic-Pituitary-Adrenal (HPA) axis and to an increased release of cortisol, the main glucocorticoid in humans. High levels of glucocorticoids are known to affect the structure and function of brain regions involved in learning and memory processes, including the hippocampus. In this study, we enrolled older people (over 65) with and without SMC to investigate associations between SMC cortisol levels and hippocampal volume. They all underwent a neuropsychological assessment consisting on several memory, attention, executive function, visuospatial ability, and language cognitive tests. In addition, we conducted a 3D T1 high-resolution structural brain MRI. Scans were acquired using a general electric 1,5 Tesla MRI scanner. T1-weighted MRI images were processed with Freesurfer software package in order to obtain the hippocampal volumes. These volumes were also normalized considering the estimated total intracranial volume for each subject. Subsequently, all participants carried out different cognitive tasks that lasted around 75 min and 4 measures of salivary cortisol levels were analyzed. Controls and SMC did not differ in initial cortisol levels, total cortisol released during the cognitive task (area under the curve), or hippocampal volume. However, the total amount of cortisol released during the cognitive task was negatively correlated with hippocampal volume in both groups. Our results suggest that cortisol release during cognitive challenging tasks can reflect subtle changes in hippocampal structure and functioning in older adults.
WHEN PREGNANT RAT FEMALE BECOMES ILL: EFFECT ON OFFSPRING BEHAVIOUR
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Objectives: Environmental factors including infection during pregnancy could play an important role in development of mental diseases. According to the hypothesis, an activation of maternal immune system disrupts maturation of foetal brain. As a consequence, some behavioural changes could appear in the offspring.

Purpose: The goal of our study was to create a model of maternal immune activation in the rat by application of bacterial lipopolysaccharide (LPS) during pregnancy and test the offspring in several behavioural tasks during development and in adulthood.

Methods: Pregnant rat females (Wistar) received subcutaneous injection of LPS (1 mg/kg) or saline (control) from gestational day 7, and every other day to delivery. The offspring of both sexes was exposed to tasks testing various aspects of behaviour: beam walking (motor coordination), elevated plus maze (anxiety), open field (locomotion, exploration, anxiety), Morris water maze (spatial navigation, working memory) and Carousel maze (cognitive coordination, long-term memory). The animals were tested behaviourally in the age of 1.5 month (development) and 3-4.5 months (adulthood).

Results: All tested rats had problem with neither motor coordination, nor the water maze. Rat males and also females prenatally exposed to LPS (but not to saline) showed hyperlocomotion and lower anxiety in several tasks in adulthood. Subtle differences in locomotion and anxiety between experimental and control animals were obvious also in 1.5 month of age. Neither group was successful in the Carousel maze.

Conclusions: We observed alterations in behaviour of experimental rats in adulthood with some signs of these changes also during development. Both sexes were affected but the effect was task-specific for males and females. We conclude that prenatal exposure to maternal immune activation led to behavioural changes which were probably caused by disruption of brain development.

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HIPPOCAMPAL LESIONS IMPAIR LEARNING AND PERFORMANCE ON A NONNAVIGATIONAL SPATIAL TASK IN MACAQUES
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Objectives: Previously we demonstrated that transient inactivation of the hippocampus disrupted performance on a self-ordered spatial memory task, the Hamilton Search Task (Forcelli et al., 2014). This was the first time a robust impairment was found in a nonnavigational spatial task in nonhuman primates after disruption of hippocampal function as other studies using similar spatial tasks in nonhuman primates have found little or no effect of hippocampal lesions. Our result raised questions whether the impairment was due to the acute nature of the inactivation technique or whether similar impairment would be found after permanent hippocampal lesions due to the demands of the task.

Purpose: We aimed to determine the effects of excitotoxic hippocampal lesions on the same task. In addition, we assessed the effects of transient bilateral inactivation of the parahippocampal cortex in another group of monkeys.

Methods: Animals are presented with an array of eight boxes, each containing a food reinforcer; one box may be opened per trial, with trials separated by a delay. Only the spatial location of the boxes serves as a cue to solve the task. The optimal strategy is to open each box once without returning to previously visited locations. Five macaques with bilateral excitotoxic lesions of the hippocampus and three controls were trained on the task to criterion with 1sec delays between trials, followed by a test with 10 and 30sec delays. Another group of three control monkeys were trained to criterion; bilateral inactivation of the parahippocampal cortex was conducted by infusions of kynurenate via a chronic infusion implant and the animals were tested with 1 and 30sec delays.

Results: Hippocampal lesions significantly impaired performance on 30 sec delays compared with controls (ANOVA; p<0.05), with the animals’ performance dropping to chance levels. Parahippocampal inactivation resulted in a significant impairment on 30sec delays compared with 1sec delays and vehicle infusions (ANOVA; p<0.05).

Conclusions:
- Hippocampal lesions resulted in an impairment similar to that described after acute transient inactivation, indicating that the task demands require intact hippocampus for an optimal performance.
- Parahippocampal inactivation impaired performance on the longer delays to a similar degree as hippocampal inactivation, indicating that this temporal cortex also contributes to performance on the nonnavigational task.
HIGH FAT HIGH SUGAR DIET INCREASES IMPULSIVITY
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Objectives: To examine if high fat high sugar diet is associated with obesity.
Purpose: There is evidence of correlations between obesity, a high fat, high sugar (HFHS) diet, and low self-control. It is commonly assumed that highly impulsive individuals choose a HFHS diet, and therefore become obese. We tested an alternative hypothesis: That a HFHS diet causes individuals to become highly impulsive.
Methods: Baseline impulsivity was assessed in laboratory rats with a delay discounting task, and were then randomised to either a control diet or a 6 week diet of sweetened condensed milk (SCM; Experiment 1) or a Western cafeteria diet (WCD; Experiment 2). They were then reassessed for impulsivity on the delay discounting task. Memory was also assessed in the novel location recognition task. Neural tissue was collected at the end of the study and assessed histologically.
Results: Initial impulsivity did not predict SCM or WCD consumption. However, SCM or the WCD consumption caused the rats to become more impulsive compared to control rats. The HFHS diets also caused the rats to display poorer spatial memory. The HFHS diets also upregulated the expression of microglial Iba-1 antigens in the prefrontal cortices.
Conclusions: These experiments show that daily consumption of a HFHS diet cause laboratory rats to become more impulsive, and that this diet also causes neuroinflammatory changes within the prefrontal regions of the brain associated with impulsive choice. We argue that there is a dynamic relationship between diet and self-control: Individuals who consume HFHS diets become more impulsive, and therefore may become more obese as a consequence of the effects of the HFHS diets on the brain.
Creative Boost: Enhancing Creativity using tDCS
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Recent studies show that damage to the left inferior frontal gyrus (lIFG) may have a ‘releasing effect’ of creativity, suggesting that these areas may ‘inhibit creativity’. Based on these findings and on the twofold model of creativity, a novel neurocognitive model is suggested according to which creativity involves two recursive stages: a generation phase that is mediated by a fronto-parietal network and an evaluation phase, mediated by the lIFG. Our aim was to explore cultural differences in creativity by examining the role of the lIFG using tDCS. Since in East-Asian cultures uniqueness is discouraged, original ideas are more likely to be inhibited during the ‘evaluation phase’. Thus, we hypothesized that inhibition of the lIFG using cathodal stimulation will enhance creativity by decreasing the evaluation stringency.

First, we compared Israeli and Japanese students on their creativity level, in both phases. Creativity was measured by the ‘Alternate Uses Task’ (AUT; Guilford, 1978). Evaluation was measured by a new task; evaluating the appropriateness of ideas generated by others. Israelis were more creative and evaluated others’ ideas as more appropriate compared to Japanese.

Then, we recruited 30 Japanese students and divided them into two groups (Anodal/Cathodal). Each participant underwent the experiment twice: under stimulation and under sham.

Significant differences were found between the groups in both tasks: Anodal stimulation decreased creativity and the rating of appropriateness compared to sham, while Cathodal stimulation increased both, indicating less stringent evaluation.

Thus, temporary inhibition of the evaluation network may influence creativity, even in a culture that is perceived as less creative.
ENHANCEMENT OF SLOW WAVES WITH CLOSE-LOOP AUDITORY STIMULATIONS
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Slow-wave-sleep is a critical phase for recovery. More precisely, slow oscillations coming from the rhythmic occurrence of delta waves – broad oscillations (~1Hz) observed in mammals - seem to provide the temporal window necessary for neural plasticity and memory consolidation. It is possible to induce them with sensory stimulations, such as sounds, a method which is adapted to a regular use in humans. This process has been used in a human study to increase the duration of a train of delta waves, with EEG-synchronized auditory stimulations.

Our project aims at understanding the neural mechanisms involved in the auditory induction of delta waves and quantify the effect on sleep parameters. We therefore investigated the impact of the auditory closed-loop stimulation periods, by multi-site recordings on mice in vivo. We also compared our results to human data on a similar protocol.

The probability for a tone of inducing a delta waves depends on several parameters: sleep stage, the moment of the night and the occurrence of the last delta wave. Sounds have a short-term effect, it can densify or sparse delta waves occurrence, and a more global effect on sleep architecture, it increases the ratio of slow-wave-sleep without increasing the ratio of wakefulness.

In conclusion, we found optimal parameters for the auditory induction of delta waves, which could help increasing the ratio of slow-wave-sleep without increasing arousals. We need then to assess the effect of such a protocol on sustained attention, which is correlated to the amount of slow waves. This process could then be adapted to a human use, to enhance slow-wave sleep and recovery.
REDUCED DIETARY OMEGA-6 TO OMEGA-3 FATTY ACID RATIO IN EARLY LIFE PROTECTS AGAINST THE EARLY-LIFE STRESS INDUCED COGNITIVE IMPAIRMENTS THROUGH ALTERATIONS ON HIPPOCAMPAL NEUROGENESIS AND MICROGLIAL PROCESSES

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Early-life stress (ES) is associated with cognitive deficits in adulthood. Mechanisms underlying such programming remain elusive and the role of nutrition has largely been ignored in this context. Importantly, a delicate balance of the essential fatty acids (EFA) precursors of omega-6 (linoleic acid: LA) and omega-3 (α-linolenic acid: ALA) are key for brain development. Indeed, omega-6:omega-3 imbalances during early developmental periods are linked to cognitive impairments later in life. We therefore studied if; i) ES affects central and peripheral fatty acid profiles ii) early dietary intervention with a reduced LA/ALA ratio prevents the ES-induced cognitive impairments, and if iii) alterations on hippocampal neurogenesis and microglia underlie the effects of this diet.

We used a chronic ES mouse model in which C57/BL6j dams are housed with limited nesting/bedding material from postnatal day (P) P2-P9, resulting in cognitive decline in adulthood. The diets were equal in total FAs, but either containing a low (1) or high (15) LA/ALA ratio between P2-P46.

Chronic ES; i) lastingly reduced the omega-6:3 ratio in the liver. Interestingly, levels of docosahexaenoic acid, the main omega-3 fatty acid, were increased in the hippocampus in adulthood. In addition, ii) low LA/ALA diet early in life prevented the ES-induced cognitive impairments as assessed by the object recognition, object location and morris water maze tasks. Moreover, iii) this diet prevented the ES-induced reduction of adult born neuron survival and the increased CD68 expression in the hippocampus, suggesting that the beneficial effects of the diet may, at least partly, be mediated by preserving the neurogenic capacity and reducing the phagocytic microglial activity in ES-exposed offspring.

These results highlight for the first time the relevance of dietary LA/ALA in programming the effects of ES and suggest that early life dietary lipids have great potential for early nutritional interventions.
LOSING MEMORIES WITH TARGETED MEMORY REACTIVATION
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Objectives: Targeting memories during sleep opens powerful and innovative ways to influence the mind. This presentation will describe a study using targeted memory reactivation aimed at inducing forgetting during sleep.

Purpose: To determine if specific memories can be weakened during sleep.

Methods: Targeting memories during sleep opens powerful and innovative ways to influence the mind. We modified targeted memory reactivation (TMR), which to date has been used to strengthen learned episodes, to instead induce forgetting (TMR-forget). Participants were first trained to associate the act of forgetting with an auditory tone cue. In a second, separate, task they learned object-sound-location pairings. Shortly thereafter, some of the object sounds were played during slow wave sleep, paired with the forget tone cue to induce forgetting. One week later, participants were tested for recall.

Results: At recall, participants demonstrated lower recall of reactivated versus non-reactivated objects and impaired recognition memory and lowered confidence for the spatial location of the reactivated objects they failed to spontaneously recall.

Conclusions: We show that it is possible to target memories during sleep for selective weakening. The ability to induce forgetting during sleep has implications for developing novel therapeutic techniques for psychological disorders such as PTSD and phobias.
GABA/SOMATOSTATIN NEURONS IN HIPPOCAMPUS ARE TARGETED BY ASCENDING RELAXIN-3 NEURONS: FUNCTIONAL EFFECTS OF CHRONIC RELAXIN-3 RECEPTOR MODULATION

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Objectives: Relaxin-3/RXFP3 (neuropeptide/receptor) signalling is implicated in the control of arousal, stress-related responses, innate anxiety, and learning and memory. The goal of our studies is to examine the regulation of limbic neural networks by relaxin-3/RXFP3 signalling and identify the specific neuron populations targeted in the septohippocampal system, to inform the underlying mechanisms and assist in the design of further functional studies.

Purpose: Studies were designed to: (i) identify the neurochemical content of hippocampal neurons in rats and mice that receive a relaxin-3 innervation and express RXFP3 mRNA; and (ii) use different methods to chronically activate or deplete RXFP3 within the hippocampus and assess behavioural effects and the impact on the identified target neurons.

Methods: Relaxin-3 and neurochemical markers for putative target neurons were detected using fluorescence immunohistochemistry and RXFP3 and marker mRNAs were detected by RNAscope™ fluorescent in situ hybridisation histochemistry. Chronic RXFP3 activation in ventral hippocampus was produced by an AAV1/2-vector that produces local secretion of the RXFP3 agonist, R3/I5 [1] and affective/social behaviours were assessed; and depletion of RXFP3 was produced by AAV1/2-Cre-mediated deletion of RXFP3 in dorsal dentate gyrus (DG) hilus in a ‘floxed-RXFP3’ mouse line [2] and aspects of spatial memory were assessed.

Results: In both rats and mice, relaxin-3-positive nerve terminals make close contact with GABA/somatostatin neurons in hippocampus, and RXFP3 mRNA is present in vGAT- and somatostatin mRNA-positive (GABA) neurons in CA1, CA3 and DG hilus, suggesting that RXFP3 signalling can modulate hippocampal neuron/network activity. Chronic activation of RXFP3 in ventral hippocampus of adult male rats produced significantly elevated anxiety-like behaviour in the light-dark box and elevated-plus maze tests, and reduced social interaction with a conspecific stranger. Chronic activation of RXFP3 also produced a marked reduction in hippocampal neuronal somatostatin immunoreactivity levels, suggesting inhibition of their activity. Depletion of RXFP3 in the DG hilus of adult mice impaired spatial reference memory in an appetitive T-maze task, reflected by a reduced % correct choices and increased time to meet criteria, relative to control. In a continuous spontaneous alternation Y-maze task, RXFP3-depleted mice made fewer alternations in the first minute, suggesting impairment of spatial working memory. However, RXFP3-depleted and control mice displayed similar locomotor activity, anxiety-like behaviour, and learning and long-term memory retention in the Morris water maze.

Conclusions: Our novel data have identified a specific interaction between relaxin-3/RXFP3 signalling and key GABA/somatostatin-positive neurons in CA1/CA3 and DG hilus of rodent hippocampus, and revealed that regional alterations (increased/reduced) in RXFP3 signalling produce region-specific changes in anxiety-like and social behaviour, and in spatial memory. These findings improve our understanding of the ascending neural networks that modulate behaviour and identify novel signalling processes involved in hippocampal regulation.

References
THE ROLE OF H2AX PROTEIN IN CENTRAL NERVOUS SYSTEM FUNCTION

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Recently some studies demonstrate that adult neuronal genome is a genetic mosaic but the role of this mosaicism and how can be generated are not well known. Some evidences of alterations in central nervous system development found in knock-out (KO) mice for proteins related with DNA repair processes, suggest that neuronal genome mosaicism may be related with the generation of neuronal diversity during central nervous system development. However, if these processes take place in the adult nervous system during neuronal plasticity events are not yet established.

The main objective of this work was to determinate the role of H2AX protein, the main DNA breaks sensor, in the nervous system function.

Using H2AX KO as a mice model, we performed anatomical brain approaches by Nissl, immunohistochemistry against Calbindin and immunofluorescence against PSD95 and Gephyrin as postsynaptic markers. Furthermore, we evaluated motor function with electromyography recordings and muscle strength measures and, we carried out a complete characterization of behaviour at different levels: motor learning, coordination, anxiety, depression, social interaction, learning and memory.

Our results showed that H2AX KO mice presented alterations in some areas of limbic system: an increase amygdale area, a decrease at the granular and molecular layers in hippocampus and an imbalance in the excitation/inhibition synaptic ratio at the Stratum radiatum. In addition, at behavioural level, these mice presented impairment in cognition, depression and social interaction.

In conclusion, our results show that the depletion of H2AX in the germinal line provokes alteration in central nervous system function.
ACCUMBAL DOPAMINE RELEASE DURING SOCIAL INTERACTION IN A MOUSE MODEL OF AUTISM

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Impaired social behaviour is the main hallmark of autism spectrum disorder (ASD). The nucleus accumbens (NAcc) within the mesolimbic reward circuitry has been proposed as a central integrator of social information. In fact, it has been recently reported that release of the neurotransmitter dopamine (DA) in the NAcc plays a key role in social behavior1, but whether such system is disrupted in animal models of ASD remains still obscure.

Our aim was to investigate the modulation of DA release in the NAcc during social interaction, using a genetic mouse model of ASD. 

Cntnap2 gene knockout (Cntnap2-KO) mouse has been thoroughly validated as a mouse model of autism2. In the present work, 8-week male mice were subjected to in vivo freely-moving brain microdialysis assays at basal conditions before, during and after social interaction. DA concentrations were continuously monitored in the NAcc of wild-type and Cntnap2-KO mice, and quantified by Ultra Performance Liquid Chromatography (UPLC) coupled with an electrochemical detector.

We found that DA basal concentrations in the NAcc of Cntnap2-KO mice were strikingly lower compared to its wild-type counterparts. Conversely, the short exposure to an unfamiliar conspecific significantly increased DA release in the NAcc of mutant mice, whereas it exerted a much weaker effect in control mice.

There is increasing interest in understanding the neural circuits and molecular mechanisms that guide social behaviour, and which brain circuits are affected in animals with disruptions of social behaviour. Results from this study point out differences in DA basal concentrations and distinct pattern of DA release during social interaction in mice with an autism-like phenotype, which may explain some features of social behaviour deficits in these mice.

References:
USING THE VALPROATE-INDUCED AUTISTIC SPECTRUM DISORDER RAT MODEL TO STUDY THE MICROGLIA ACTIVATION AND SOCIAL EMOTIONAL BEHAVIOR

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Objectives: Recent evidences suggest neuroinflammatory and immunological dysregulation is important in the pathogenesis of autistic spectrum disorder (ASD). Prominent microglia activation in certain brain regions has been discovered in ASD patients.

Purpose: However, the underlying mechanism of abnormal neuroinflammation response and its effect on the pathogenesis of ASD remain unclear.

Methods: Sprague Dawley rats are mated, with pregnancy confirmed as embryonic day 0.5 (E0.5). On E12.5, dams received a subcutaneous injection of sodium valproic acid (VPA, 500 mg/kg) and control dams receive an equal volume of saline. Behavioral experiments were conducted on 4, 6, and 8-week-old, which are open field test, elevated plus-maze, 3-chambered social preference. Collecting rat brains for microglia immunohistology study on P7, 14, 21, 28, 42, 56.

Results: Precocious development with shorter self-righting latency, earlier of eye opening and the teratogenic effect of crooked shorten tails in VPA-exposed offspring. VPA-exposed male offspring shown more frequently and longer duration of self-grooming in open field test. 4-week-old rats spent more time in center area of open field box than 8-week-old, but VPA males were not, even thought they had more moved distance in the box. In the elevated plus maze test, 4-week-old animals spent more time in open arms than 8-week-old but not related to VPA-exposed. In the 3-chambered social preference tests 6-week-old VPA-exposed offspring shown the autism-related behavioral deficits. VPA-exposed offspring have increased microglia area in the brain sections, especially in the substantia nigra and amygdala.

Conclusions: The results suggested the possible role of emotion brain neuroinflammation in the pathogenesis and the intervention of ASD. This work may shed light on our understanding of ASD and ultimately pave the way for developing safe and effective therapeutic strategies.
Objective
Social complex behavior, like empathy, emerge over phylogeny from various precursors. One of the simplest is emotional contagion, i.e. sharing emotional states between individuals. Receiving signals of a potential danger may increase chances of survival, thus emotional contagion plays an important role in learning about external environment. The phenomenon is well described at the behavioral level, but the neural circuits necessary for sharing emotions are unknown. We designed a rat model of fear contagion and showed that a brief social interaction with a fearful cage mate promotes risk assessment behavior and activates the central amygdala (CeA) in an otherwise naïve rat.

Purpose
The purpose of this project was to elucidate the role of the CeA circuits involved in socially shared fear.

Methods
To investigate the functional outputs of the activated CeA neurons we mapped neural circuits downstream from the CeA combining anterograde tracing with an imaging of activated neurons in transgenic “Venus” rats. To test the function of CeA “social fear” neurons we optogenetically stimulated or inhibited subpopulation of CeA neurons activated by social interaction using c-fos-driven targeting of channelrhodopsin and halorhodopsin.

Results
In rats that socially shared fear of their partners, we observed strong activation of structures involved in anxiety and motor functions. Most of the activated cells received projections from the CeA. Optogenetic activation of the “social fear” neurons in a social context led to behavioral pattern resembling the one observed during social interaction with a fearful partner. Activation of neurons in non-social context induced exploration and risk assessment behavior (active fear). Inhibition of them had the opposite effects.

Conclusions
The results suggest that the CeA neurons involved in socially transferred fear mediate active fear responses and anxiety-related behaviors in both social and non-social conditions.
ESCULETIN ALLEVIATES RESTRAINT STRESS-INDUCED ANXIETY-AND DEPRESSIVE-LIKE BEHAVIOURS, AND COGNITIVE IMPAIRMENTS IN MICE

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Objectives: Stressful events are implicated in the pathogenesis of neuropsychiatric disorders and cognitive impairments which induces neuroinflammation, oxido-nitrosative stress and alters plasticity of the brain. Esculetin (ESC) possesses antioxidant, anti-inflammatory and neuroprotective potential and showed attenuating effect against acute restraint stress (ARS)-induced behavioural and biochemical changes in mice.

Purpose: To investigate the alleviating effect of esculetin against ARS-induced behavioural and biochemical changes in mice.

Methods: Mice (n=10) were pre-treated with esculetin (50 mg/kg) or fluoxetine (FLU; 10 mg/kg) orally for 14 days and subjected to ARS for 6 h to induce behavioural and biochemical changes. After 40 min of ARS procedure, mice were subjected to Elevated Zero maze (EZM) test, Tail suspension test (TST) and Novel object recognition test (NORT) to assess anxiety- and depressive-like behaviors, and cognitive impairments. Following behavioral studies, mice were sacrificed to isolate hippocampus (HC) for the analysis of IL-1β, TNF-α, BDNF, MDA, GSH and nitrite level.

Results: Acute ARS significantly decreased both open arms entries and duration in EZM (P<0.01), increased immobility time in TST (P<0.001) and decreased recognition index in NORT (P<0.001) in mice which was significantly alleviated by ESC (P<0.05) and FLU (P<0.01) pre-treatment. Hippocampal IL-1β, TNF-α, MDA & nitrite level increased significantly (P<0.001) after ARS in mice which were reversed by ESC & FLU pre-treatment. Furthermore, ESC (P<0.05) and FLU (P<0.01) pre-treatment significantly restored hippocampal GSH & BDNF level in ARS subjected mice.

Conclusions: In summary, results suggested that ESC provided alleviating effect against ARS-induced neurobehavioral and neurochemical alterations by impeding neuroinflammation and oxido-nitrosative stress. Thus, ESC may be potential therapeutic agent for the treatment of stress related psychiatric and memory disorders.

Literature Reference
OPIATE WITHDRAWAL CONDITIONING ALTERS OSCILLATORY STATES IN THE NUCLEUS ACCUMBENS

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Opiate withdrawal is a key feature of opiate dependence and this negative emotional state is crucial in the addictive process. Several studies support the existence of conditioned withdrawal effects, which can act to influence drug-seeking and drug-taking behaviors. The nucleus accumbens (NAC) is a key structure underlying addictive processes, and is crucial for both acute withdrawal and reactivation of withdrawal memories following conditioning. Moreover, NAC gamma oscillations are modified during morphine dependence and acute naloxone-precipitated withdrawal. The objective here was to characterize NAC oscillatory state during opiate withdrawal conditioning and conditioned withdrawal.

NAC local field potentials (LFPs) were recorded in morphine-dependent rats which were conditioned to naloxone-precipitated withdrawal (or saline injection) in a specific context. Electrophysiological recordings were performed daily at each conditioning (5 sessions) or test session. Behavioral signs of withdrawal were scored at each step of the protocol. Data processing includes LFP time-frequency analyses (power spectral densities, wavelet transform, Z-score, PCA,) locked on the occurrence of the various behavioral events.

We found that the gamma oscillatory states are deeply modified along with withdrawal conditioning with a highly specific interplay between low (60 Hz, G60) and high (80 Hz, G80) gamma rhythms. Indeed the G60/G80 frequency variations are strongly correlated both with the intensity of the withdrawal score, and the various behavioral signs of withdrawal. These variations tended to increase with the number of conditioning sessions. This suggests that G60/G80 interplay established through the conditioning process could underlie the coding of opiate withdrawal aversive memory.
OBJECTIVES: Several studies have shown that the emotional state of a conspecific subject can influence one’s stress response. The attenuation of fear responses by the presence of a conspecific is called social buffering of fear (SBF), but the neural mechanisms underlying SBF are not yet fully understood. One molecular candidate believed to mediate SBF is oxytocin (OT), a neuropeptide well known for its pro-social effects. We previously found that activation of the OT receptors in the central amygdala (CeA) can significantly reduce expression of fear. We here investigated the potential mechanisms involved in the endogenous release of OT, in particular projections from the ParaVentricular Nucleus (PVN) of the hypothalamus to the CeA.

PURPOSE: We hypothesize that the activation of the projections from the ParaVentral Nucleus (PVN) of the hypothalamus to the CeA are required for the SBF response.

METHODS: To test our hypothesis, we optogenetically or chemogenetically modulated endogenous release of OT after viral expression of the corresponding constructs under the oxytocin promoter. We pharmacologically activated or inactivated OT receptors, and we conducted electrophysiological recordings in vivo with optogenetic stimulation of the PVN-CeA pathway in rats, exposed or not exposed to SBF.

RESULTS: We found that the presence of the conspecific produced an immediate and a long-lasting decreased fear expression. These Effects were blocked by the local administration of an OT receptor antagonist. Electrophysiological recordings in vivo, in combination with optogenetic identification of OTergic neurons in the PVN, showed that these behavioral responses were accompanied by changes in the activity of OTergic neurons in the PVN as well as differential neuronal responses in the CeA depending on their sensitivity to OT.

CONCLUSIONS: These findings aim to provide a first characterization of the OTergic circuits involved in SBF.
HIPP NEURONS IN THE DENTATE GYRUS MEDIATE THE CHOLINERGIC MODULATION OF BACKGROUND CONTEXT MEMORY SALIENCE

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Objectives: Background context memory is acquired together with memory for the elemental cues during auditory fear conditioning. The context salience is critically controlled by cholinergic neuromodulation in the hippocampus, but the local hippocampal circuits that mediate this salience control have not been identified so far.

Purpose: We set out to examine the putative role of hilar perforant path-associated (HIPP) cells of the dentate gyrus in the control of background context memory salience and to identify the molecular components involved.

Methods: We employed fear conditioning in combination with pharmacogenetics and pharmacological intervention in mice to dissect the local circuitry and its molecular components. We analyzed genes expression by laser dissection and qPCR and resolved the local circuit activity regulation with anatomical and electrophysiological tools (patch clamp and field potential recordings).

Results: With selective pharmacogenetic inhibition through DREADD receptors we demonstrate that HIPP cells of the dentate gyrus mediate the devaluation of background context memory during Pavlovian fear conditioning. The salience adjustment is sensitive to reduction of hilar neuropeptide Y (NPY) expression via dominant negative CREB expression in HIPP cells and to acute blockage of NPY-Y1 receptors in the dentate gyrus during conditioning. We show that NPY transmission and HIPP cell activity contribute to inhibitory effects of acetylcholine in the dentate gyrus and that M1 muscarinic receptors mediate the cholinergic activation of HIPP cells as well as their control of background context salience.

Conclusion: Our data provide evidence for an adaptive peptidergic local circuit in the dentate gyrus that utilizes NPY to mediate the cholinergic encoding of background context salience during fear memory acquisition.

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DEFICITS IN EPISODIC MEMORY FORMATION AND MENTAL TIME TRAVEL IN PATIENTS WITH POST-TRAUMATIC STRESS DISORDER

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Objectives: Post-traumatic stress disorder (PTSD) is characterized by impairments in mnestic functions, especially in the domain of episodic memory. These alterations might affect different aspects of episodic memory functioning.

Purpose: We used a novel reverse translational approach to investigate episodic memory formation and the capacity for “mental time travel” (MTT) in patients with PTSD.

Methods: We tested PTSD patients and healthy controls (matched for age, sex and education) in a newly developed virtual reality episodic memory test (VR-EMT), a test for mental time travel, episodic future thinking, and prospective memory (M3xT). In a cross-validation experiment, their performance was further evaluated in the Rivermead Behavioural Memory Test (RBMT).

Results: PTSD patients demonstrated impairments in episodic memory formation and mental time travel and showed difficulties in utilizing information from episodic memory to solve problems. Diminished attention and concentration in PTSD did not account for performance deficits in these tasks but higher levels of negative arousal were found in PTSD patients. Furthermore, performance in the VR-EMT and RBMT in PTSD patients correlated negatively with self-reported measures of stress and depression.

Conclusions: Our results suggest that deficits in episodic memory formation and mental time travel in PTSD lead to difficulties in utilizing the content of episodic memories for solving problems in the present or to plan future behavior. Clinical implications of these findings and suggestions for cognitive-behavioral treatment of PTSD are discussed.
AN OPERANT DELAYED MATCH TO POSITION (DMTP) TASK FOR COGNITIVE ENHANCING DRUGS DISCOVERY
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Objectives: The majority of daily-life activities rely on an efficient working memory (WM) processing. For example, WM functions closely impact on several cognitive domains including cognitive flexibility, attentional set-shifting, response inhibition, reversal learning (RL) as well as long-term memories. WM deficits are observed in several psychiatric and neurodegenerative conditions, and to date represent a significant unmet medical need. Hence, the development of pre-clinical models for the profiling of potential pro-cognitive drugs able to improve WM is of substantial relevance.

Purpose: The present study aimed at validating an operant WM task in rodents with the purpose of testing new drug entities enhancing WM in unimpaired rats. Given the clinical relevance for psychiatric ailments, RL was also measured as delayed non-matched to position (DNMTP) response type, whereby rats were requested to reverse their response by pressing the non-matched lever.

Methods: In an operant-based Delayed-Match-To-Position (DMTP) task, male Lister hooded rats (n=30-32) learned to press the Match-to-Sample lever to obtain food reward as described in Smith et al., 2011. Drug treatments were performed once rats reached a stable performance of 80% accuracy at 1-5s delay for 3 consecutive sessions or (in a separate rat’s cohort) when rats reached 70% accuracy at 2s delay for 2 consecutive sessions. This study was performed to observe possible drug effects on non-overtrained-trained subjects. Effects of the 5-HT₆ antagonist SB742457 (1, 3, 6mg/kg, sc), the D₁R partial agonist SKF38393 (2, 4, 6mg/kg, ip) or the α7nAChR partial agonist Encenicline (0.1, 0.3, 1mg/kg, po) were evaluated in terms of DMTP performance or RL (SB742457). In a separate cohort, effects of the NMDAR antagonist MK-801 (0.03 and 0.06mg/kg; sc) on DMTP performance were also evaluated.

Results: Rats acquired the DMTP task within 20 sessions showing a typical delay-dependent performance, suggesting that in this task a form of WM was indeed engaged. None of the tested drugs improved the performance of unimpaired rats, while SB742457 (3mg/kg) improved RL in a DNMTP reversal paradigm. Confirming previous literature, MK-801 (0.06mg/kg) impaired WM selectively at 2s delay.

Conclusions: The operant DMTP represents a valuable behavioural task to investigate WM performance in rodents. Results obtained so far, suggest that possible ceiling effects due to subjective maximal performance might render the screening of WM enhancers unfeasible in unimpaired subjects. On the other hand, an impairment of cognitive performance via pharmacological, genetic, developmental or environmental manipulations, might enable the investigation of WM enhancers. Further studies are needed to validate the DMTP task as a tool to assess potential pro-cognitive effects of new drug entities.

THE IMPACT OF LOW-PRESSURE BLAST WAVE EXPOSURE ON THE AGING BRAIN

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Objectives:
While posttraumatic stress disorder (PTSD) and mild traumatic brain injury (mTBI) are both well-described in the general population, the literature concerning PTSD and/or mTBI in the elderly is scanty and patchy. Longitudinal and cross-sectional imaging studies have reported smaller global brain volumes, reduced cortical thickness, and expansion of the ventricular system in the brains of older adults. In addition, many brain functions are also affected by aging. Therefore, age at injury is likely to influence the way the brain is able to respond and repair itself as a result of developmental status, extent of anatomical, morphological and cellular senescence.

Purpose:
The overall objective of this study was to explore the question of how age at the time of BLAST exposure (age at injury) effects behavioural and cognitive responses in multiple neurological, behavioral, molecular, morphological and imaging domains over an extended time course.

Methods:
We employed a controlled experimental blast-wave paradigm in which non-anesthetized middle aged male rats (12-13 month) were exposed to visual, auditory, olfactory, and tactile effects of an explosive blast-wave produced by exploding a thin copper wire. Validated cognitive-behavioural paradigms were used to assess both mTBI-, PTSD- and depressive-phenotypes on days 7–14 following the blast.

Results:
The results demonstrate a degree of heterogeneity in individual responses, which was different than the patterns of younger animals. At old age, exposure to the experimental blast wave did elicit mTBI-like phenotype, PTSD-like phenotype and combined mTBI-PTSD-like symptoms and also elicit a high percentage of depressive-like phenotype, which not observed in younger rats.

Conclusions:
The behavioural and cognitive response to low-pressure blast wave displays significant age-dependent differences. A better understanding of the mechanisms of age-related compromise may inform the development of therapeutic interventions to mitigate age-related risk.
MODULATION OF THE REPRODUCTIVE BEHAVIOURS IN A POLYPHAGOUS PEST MOTH BY NON-HOST PLANT VOLATILES
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Objectives: For finding mate, host, and mating and oviposition sites, insects are dependent mainly on volatiles compound released from their mate partners and host and non-host plants. The main objective of current study was to evaluate the potential of non-host plant volatiles in modulating the reproductive behaviours of a herbivorous insect pest.

Purpose: Identification of non-host plant sources and their associated chemical compounds to be used in insect pest management.

Methods: Modulation in reproductive behaviours of a polyphagous pest moth species, *Spodoptera litura*, were observed in oviposition bioassays, where the delay in onset of 1st calling, calling duration, delay in onset of 1st mating, mating duration, fecundity and longevity of newly emerged moths were observed in the presence of host plant, Cotton, while giving freshly detached leaves (as a background odour source) of four different non-host plant species; [Neem, Citrus, Eucalyptus, and Moringa. Furthermore, the effect of all non-host plants leaves as larval diet on larval survival, their relative growth rate and larval diet consumption by adding leaf dry powder in artificial standard diet were observed. The addition of Neem and Moringa leaf powder compared to the control showed 100% mortality within first 24 hrs. Neem and Moringa leaf powder were further used for dose response assays at 5 different concentrations.

Results: The results showed that non-host volatiles (NHV) of Neem, Moringa, and Citrus caused significant delay in 1st calling, while Eucalyptus had no effect as compared to the control (cotton alone). Similarly, delay in 1st mating was significantly higher in the presence of Neem and Moringa as compared to the control. Moreover, female fecundity was reduced significantly in the presence of volatiles emitted by Neem, Moringa and Citrus leaves. Interestingly, insect longevity was not affected by any non-host plant leaves as compared to the host alone. Results from feeding assay showed that larval survival, larval weight and diet consumption were lower at all different diets contaminations of both Neem and Moringa leaves powders as compared to the control (diet without non-host contamination).

Conclusions: Results will be helpful in understanding the host plant range and diet breadth of a polyphagous herbivore, which may lead to develop a better crop protection strategy against this serious pest of economically important crops and vegetables. Moreover, it is evident from the results that non-host sources or their associated chemicals have the potential to be used in insect pest management.
A QTLS ON CHROMOSOME 1 MODULATES INTERMALE AGGRESSION IN MICE
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Introduction: Intermale aggression is a complex social behaviour that is likely regulated by multiple genes. In this study the BXD recombinant inbred mouse strains (RIS) were used to map quantitative trait loci (QTLs) underlying behaviours associated with intermale aggression.

Methods: Four hundred and fifty-seven males from 55 strains (including the parentals) were observed at an age of 13 +/- 1 week in a resident-intruder test following 10 days of isolation. Attack latency was measured directly within a 10 minute time period and the test was repeated 24 hours later. The variables analysed were the percentage of attacking males in a given strain (on days 1 and 2, and both days combined), as well as the attack latency on days 1 and 2.

Results: On day 1, 29% of the mice attacked, which increased to 37% on day 2. Strain differences were highly significant for all variables measured, indicating significant heritability. From these data, we identified a significant QTL on chromosome 1 for attack variables and suggestive QTLs on mouse chromosomes 7, 11, 12, and 13 for both attack and latency variables. The chromosome 1 QTL interval maps to a gene sparse region.

Discussion: The most likely candidate gene modulating this trait is Htr2b which encodes the serotonin 2B receptor and has been implicated in aggressive and impulsive behaviour in both mice and humans. mRNA expression data and phenotype correlation analyses show significant relationships with the amygdala and striatum, and with fear and anxiety.
DIFFERENTIAL ENCODING OF FEAR AND REWARD IN BNST CIRCUITS
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Objectives: The ability to discriminate environmental stimuli predicting positive and negative outcomes is critical for survival. The limbic system plays a central role in the encoding of stimulus values. However, how the same limbic regions differentially encode emotions of opposite valence remains poorly understood.

Purpose: We aimed to delineate neuronal circuits of fear and reward-related emotional states within key emotional hotspots.

Methods: We developed a combined fear and reward Pavlovian conditioning paradigm during which a sound (Reward-CS) is followed by the delivery of sucrose reward, whereas a different sound (Fear-CS) is followed by a footshock. During the test session, the mice expressed specifically either reward-seeking or freezing responses during Reward-CS and Fear-CS, respectively. We combined this behavioral protocol with c-Fos brain-wide mapping, intracerebral muscimol injection and optogenetic manipulations during CSs re-exposure.

Results: Using c-Fos as an activity marker, we first identified the bed nucleus of the stria terminalis (BNST) as a key emotional hotspot activated by both Fear-CS and Reward-CS. We found similar activity in a main BNST input and output, the basolateral amygdala (BLA) and the paraventricular hypothalamus (PVH), respectively. Pharmacological inactivation during CSs re-exposure demonstrated that BNST is necessary for both fear and reward expression. Optogenetic experiments revealed that BLA-BNST neurons gates both fear and reward expression. However, BNST neurons control specifically reward-seeking or freezing responses depending on their projecting target, i.e. PVH or ventral tegmental area (VTA), respectively.

Conclusions: These findings suggest that BNST acts as a neural hub in integrating positive and negative information from the BLA to control the expression of fear and reward responses by projecting to different brain targets.
TRAMADOL AND CYCLING PERFORMANCE: A DOUBLE BLIND RANDOMIZED PLACEBO-CONTROLLED CLINICAL TRIAL
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The use of tramadol, an analgesic medication, in cycling is generating particular interest and concern. Tramadol might enhance cycling performance at the cost of reducing the ability to stay focused.

This study aimed to test the hypothesis that acute oral administration of tramadol improves exercise performance during a 20-min cycling Time-Trial (TT) (Experiment 1) in a group of cyclists and whether sustained attention would be compromised during exercise (Experiment 2).

This study used a placebo-controlled, double blind methodology. We administered a single oral dose of Tramadol (100mg), or placebo 120min before starting the TT. Electroencephalography measures (EEG) were recorded throughout the cycling exercise and at rest. In Experiment 2, the methods were the same as in Experiment 1 except that participants performed an Oddball (cognitive) sustained attention task during exercise.

We recruited 56 cyclists in total. In Experiment 1, overall power output was higher in the tramadol condition than in the placebo condition. This result was partially replicated in Experiment 2, as the power output during the second half of the TT was higher under tramadol, while no differences were observed in the first part of the TT. Effects of substance intake on the EEG signal elicited by the oddball stimuli during the exercise performance were also found. No effects of tramadol were shown on the behavioral outcome of the oddball task.

We conclude that tramadol may improve performance, but it may be mediated by fatigue (Experiment 2). Regarding brain electrocortical activity, tramadol does not seem to impair behavioural (cognitive) performance during exercise in a sustained attention task. However, EEG data showed a significant effect at the neural-related activity.
THE IMPACT OF COGNITIVE REGULATION STRATEGIES ON EXTINCTION-BASED TREATMENT OUTCOME
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Objectives: Cognitive regulation strategies (CRS) are important for controlling negative emotional responses. CRS have been shown to directly modulate fear extinction. Applying CRS might hence bear an enormous clinical potential to augment the efficacy of extinction-based treatment for anxiety disorders.

Purpose: The present study explored the effects of CRS on extinction-based treatment outcome in patients with height phobia.

Methods: Patients with height phobia underwent a single session of virtual reality exposure to heights. After exposure, participants either received a cognitive regulation intervention (i.e. self-efficacy enhancement), control intervention, or no intervention (i.e. treatment as usual). The cognitive regulation and the control intervention involved the retrieval of the exposure session with or without a focus on personal mastery experiences during exposure, respectively. The effects of CRS on therapy-induced fear reduction and symptom improvement were measured on the behavioral level (i.e. in-vivo Behavioral Approach Tests, BATs) and subjective level (fear during the BATs and height phobia-related questionnaires).

Results: A substantial increase in perceived self-efficacy was observed in participants receiving the cognitive regulation intervention. Most importantly, participants with enhanced self-efficacy showed a more pronounced increase in approach behavior and greater fear reduction during the in-vivo BAT from pre-to post-treatment.

Conclusions: Our preliminary data suggests that CRS (i.e. self-efficacy enhancement) can boost the efficacy of extinction-based therapy in height phobia. Further studies are needed to elucidate whether increased self-efficacy is responsible for enhanced consolidation of extinction memories during exposure. Nevertheless, our findings might represent a new treatment option for anxiety disorders with a learning-based mechanism of action.
GENERALIZED ANXIETY DISORDER IN ELDERLY AND ASSOCIATION WITH COGNITIVE PERFORMANCE

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Objectives: Evaluate the presence of the generalized anxiety disorder in elderly and association with cognitive performance. Purpose: Evaluate the relationship between aging, anxiety and cognitive performance. Methods: This was a cross-sectional study. The research population consisted with elderly of age ≥80 of the public health. We included every elderly who agreed to participate and according with the inclusion criteria. The interviews were accomplished out by household survey; the instruments were the questionnaire socio-demographic and health, beyond of the Mini-Mental State Examination and GAD-7. Categorical variables were being used as frequency and percentage. The comparison of the Test Mini-Mental State Examination was initially performed using the chi-square test. This study is part of a Macro-Project which was submitted to the Research Ethics Committee of University of the Extremo Sul Catarinense (UNESC) and approved under number 1.032.742.

Results: 165 elderlies were interviewed. The participants were older (mean 84.8±3.6 years), predominantly female (63%) with the mean of education in years of 2.9 ± 1.8. A cognitive performance poor was found in 35.2% of the elderly; 68 (41.2%) have trouble sleeping; 75 (45.5%) living with family (sons). There was association between GAD and cognitive performance (p=0.044).

Conclusions: These results indicated that the GAD in elderly can be associated with the impairment cognitive. Difficulty sleeping can contribute for the increase symptoms of the anxiety. The most of the elderly was female sex, which may explain a percentile high of anxiety on this population.
THE ROLE OF VALENCE IN JUDGMENTS OF LEARNING AND RECOGNITION USING TWO DIFFERENT INTERNAL SOURCE MEMORY TASKS

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Objectives: The role of emotional events in source memory monitoring - the ability to correctly attribute something we remember to its source – remains unclear. The current study aimed to investigate how stimulus valence influences judgements of learning (JOL) and internal source memory recognition.

Purpose: It is important to understand which conditions might enhance, impair or exert no influence in source memory operations. To this end, this study examined behavioral performance in two specific internal source memory tasks (read aloud vs. read in silence; common vs. self-reference judgments) and associated JOLs, while stimulus valence (negative/neutral/positive) was manipulated.

Methods: In experiment 1 (E1), 28 healthy university students (Mage = 20.25, SD = 3.62; 23 females) performed three study-test cycles in which they had to read aloud or in silent a list of words and do JOLs for each stimulus. This was followed by a test phase in which they had to perform old-new judgments by selecting one of the following options: 1) read in silent; 2) read aloud; 3) old, but do not remember if read aloud or silently; 4) new. The procedure was similar for experiment 2 (E2), but participants (n = 32; Mage = 22.59, SD = 5.89; 30 females) performed two study-test cycles and made common or self-reference judgments across learning and test phases. Stimuli were controlled for arousal, frequency, number of letters, and number of syllables.

Results: Regarding item memory, we observed that negative words were better recognized than both positive and neutral words in E1, but in E2 neutral words were better recognized than negative words. Even though no valence effect was observed in the case of source memory in E1, a differential pattern was found for E2; in the self-reference condition, the source memory accuracy was higher for both positive and neutral words than for negative words, whereas in the common condition neutral words were better recognized than both positive and negative words. Additionally, in the metamemory judgments, while positive and negative words were regarded as more memorable than neutral words in E1, positive words in the self-reference condition were considered more memorable compared to both neutral and negative words in E2, with no valence effect in the common condition.

Conclusions: The pattern of results obtained here supports the notion that different factors might account for the mixed findings concerning valence effects in source memory monitoring. In this study, we showed that distinct cognitive elaborations during the encoding (read aloud vs. read in silence; common vs. self-reference judgments) might interact in a different manner with the valence properties of the material, leading to different outcomes in terms of item and source memory. Differential patterns were also reflected in the metamemory judgments for source memory. Overall, this study shows how important it is to understand which conditions might support the success of internal source memory, especially considering that our results show that not always emotional events (positive and/or negative) result in a better episodic memory recognition. Indeed, this study suggests that positive and neutral stimuli encoded in a self-referential manner result in a better internal source memory functioning, which can have implications, for example, in the development of internal compensatory strategies targeted for both content and qualitative features of episodic memory.
DIFFERENTIAL EFFECTS OF EXERCISE DURING ADOLESCENCE AND ADULTHOOD ON COGNITION AND PLASTICITY

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Objectives: Adolescence is a critical period for postnatal brain maturation and thus a time for increased susceptibility to developing emotional and cognitive-related disorders. Exercise during adulthood has been shown to increase hippocampal neurogenesis and enhance cognition. However, the impact of exercise during adolescence on the brain and behaviour in adulthood remains to be fully elucidated.

Purpose: The objective of this study was to determine the impact of exercise during adolescence on neural plasticity and cognitive performance in hippocampal neurogenesis-dependant and independent tasks.

Methods: Adolescent (4 week) and adult (8 week) male Sprague Dawley rats were divided into sedentary control (n = 40) and exercise (n = 40) groups. All rats were pair housed in either standard housing or with continuous access to a running wheel. Following four weeks of exercise, rats performed a location discrimination and reversal learning task in a touchscreen operant chamber or non-touchscreen hippocampal-dependent behavioural tasks; spontaneous alternation in the y-maze, contextual fear conditioning and novel object recognition. Tissue was collected for analysis of neural plasticity.

Results: The results indicate that exercise during adolescence and adulthood enhanced reversal learning in the location discrimination task. Interestingly, acquisition of the location discrimination was unaffected by exercise. In addition, adolescent exercise impaired contextual fear recall, while exercise during adulthood enhanced contextual fear recall. Similarly, spontaneous alternation was impaired following adolescent exercise, but was unaffected by adult exercise while novel object recognition was unaffected by adolescent and adulthood exercise. Adolescent exercise also increased mRNA expression of the plasticity markers PSD-95, synaptophysin, BDNF, TLX and DCX in the hippocampus.

Conclusions: These findings suggest that exercise enhanced reversal learning regardless of when exercise occurred, but had a differential effect on hippocampal associated behaviours. Investigations into the impact of exercise during adulthood on neural plasticity are ongoing.
SOCIAL-COGNITIVE PROFILES IN VIOLENT GROUPS
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Introduction. Terrorism has devastating consequences for its victims and governments. In Colombia, terrorism by paramilitary groups had a shocking effect on society in the last few decades. Researchers in the cognitive sciences are called upon to study the nature of this phenomenon since a better understanding of will allow to take preventive actions so that it does not recur and to appropriately react to such atrocious practices. Purpose this study is examine the social-cognitive profiles in terrorist paramilitary groups. Methods. We assessed the social-cognitive profiles of 66 ex-combatants from a paramilitary terrorist group, relative to a control group matched in age, gender, years of education, and verbal and fluid intellectual capacities. To assess the performance in relevant cognitive-affective domains (moral judgment, intellectual level, Executive functions and emotion recognition) we ask for the participants to resolve Moral Judgment Task, the Raven’s Progressive Matrices and the INECO Frontal Screening and the Awareness of Social Inference Test (TASIT). Results. We found that moral judgment in terrorists was abnormally guided by outcomes rather than by the integration of intentions and outcomes. Such a pattern was partially related to emotion recognition abilities but independent from other cognitive domains such as fluid intelligence and executive functions. In addition, moral judgment was the measure that best discriminated between groups, even when compared with other cognitive-affective variables in which terrorists exhibited atypical or impaired performance. Conclusions. The unprecedented evidence that we found about the social-cognitive profiles of terrorists from paramilitary groups, suggest that moral judgment is the measure that best distinguished between terrorists and controls. Finally, the sensitive instruments could eventually contribute to characterize terrorist behaviour.
DO ACOUSTIC FEATURES MODULATE OUR PERCEPTION OF EMOTIONAL STIMULI?

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Objectives: The voice has a crucial role by providing identity and affective cues, ensuring an effective emotional communication. Understanding how non-verbal vocalizations’ acoustical properties are related with their perception is of great relevance in auditory processing studies, and it remains unclear.

Purpose: The present study aimed to identify vocalizations emotion through a two-alternative forced choice task (2-AFCT).

Methods: Six volunteers with normal hearing took part in the task (3 females and 3 males, mean age = 31 ± 3.69). Eighteen vocalizations were chosen from the Montreal Affective Voices (Belin et al., 2008), corresponding to 2 actors (male and female) emotional interjections using the vowel /a/, expressing happiness, sadness, fear, anger, pleasure, pain, surprise, disgust and neutral. The vocalizations were normalised in energy (RMS) at an intensity of 70 dB SPL. Each stimulus was emitted, and two possible emotions were simultaneously displayed on the computer screen. Participants were instructed to answer, as soon as possible, which was the perceived emotion in the vocalization presented, using one of two mouse buttons. The task consisted of 720 trials per participant: all possible combinations between the 9 emotions (72 combinations) x 2 actors x 5 repetitions.

Results: The acoustical properties of the eighteen non-verbal vocalizations were analysed. Some variations were registered in their duration, which mean was 976 ± 480ms, and in pitch, with a mean $F0$ of 298 ± 78Hz and mean $F0$ amplitude of 193 ± 104Hz. The best recognized emotions were the happiness, sadness, disgust and pleasure (accuracy of ≈ 97%). Fear was the less well identified (accuracy of ≈ 90%). The highest pitch amplitudes showed an increased accuracy rate. Also, the stimulus with larger durations were identified more quickly. Additionally, the female voice (mean $F0 = 327 ± 68$Hz; mean $F0$ amplitude = $161 ± 92$Hz) was better recognized than male’s one (mean $F0 = 269 ± 78$Hz; mean $F0$ amplitude = $225 ± 10$Hz).

Conclusions: Although there were no significant correlations between the different affective categories recognition and their acoustic cues, the results suggested that $F0$, and pitch variation in stimulus time course, may contribute to the modulation of the perception of the emotional content in non-verbal expressions. Complementary studies based on pitch contour variations should be performed to clarify pitch effect on perception.

Literature Reference
URANIUM, AN ENVIRONMENTAL FACTOR THAT WORSEN THE ALZHEIMER DISEASE?
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Purpose: Alzheimer’s disease is associated with genetic risk factors, of which the apolipoprotein E (ApoE) is the most prevalent, and is affected by environmental factors that include exposure to metals. The natural and anthropogenic origins of uranium resulted in an increase of its deposition in some areas and led to a possible environmental factor.

Methods: The present study aims to ascertain the effects on the behaviour, the metabolism of cholesterol and acetylcholine and the oxidative stress on adult male ApoE-/- mice exposed to natural uranium (20 mg.L⁻¹) for 9 months.

Results: Uranium exposure induced a significant effect on cholesterol metabolism and oxidative stress and leads an increase of the depression and a decrease of the short-term memory to the wild mice. After 9 months of uranium exposure, any significant effect has been found at behavioural and molecular levels on ApoE-/- mice compared to control ApoE-/- mice.

Conclusions: In conclusion, these results demonstrate that uranium exposure not worsen the development of the Alzheimer disease. In order to conclude more definitively on the effects of uranium on the development of the disease, it appears necessary to launch further experiments on female.
THE EFFECTS OF STRESS HORMONES ON A MEMORY ENGRAM
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Objectives: Emotional and stressful memories are usually remembered very well. This is, in part, attributed to the release of stress hormones (glucocorticoids) after exposure to a stressful event. How glucocorticoids (GCs) facilitate memory remains largely elusive, as it is not clear which exact cells contribute to a specific memory engram. Characterizing the neurons that are recruited into a memory engram upon a stressful learning experience might be key towards understanding the mechanisms and the role of stress hormones on memory formation.

Purpose: To identify the number and properties of the neurons which are recruited into a memory engram upon a stressful learning experience.

Methods: Mice were exposed to a mild (0.2 mA) repeated fear conditioning paradigm, acutely followed by a CORT treatment (2 mg/kg). Using a genetic mouse line with a fluorescent Arc reporter, we visualised neurons that are activated upon the formation of this memory engram. This allowed us to investigate the number and properties of the neurons in the network which are recruited into a memory engram.

Results: We show that GCs enhance tone-evoked freezing behaviour in mice, 24-hours after auditory fear conditioning. In parallel, we found that the number of Arc-dVenus+ neurons in the dentate gyrus of the hippocampus was enhanced. This effect was not yet present 5 hours after training.

Conclusions: These results indicate that CORT has an effect on neuronal consolidation, possibly increasing the time window in which neurons can get recruited into a memory engram.
VISUAL TWO-ARMED BANDIT REINFORCEMENT LEARNING IN RODENTS
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Reinforcement learning (RL) is the behavioral process of learning to make choices to gather rewards and avoid losses. RL is often studied in the context of two-armed bandit tasks, in which subjects have to make choices between a pair of options which lead to different outcomes. By integrating the outcomes over trials they can learn which choice is most rewarding, and choose that option in the future. In rodents, choices in such tasks are often between levers or ports in different locations within an operant box. The neural circuitry underlying learning about which port or lever is most rewarding has been examined. In studies using primates and humans, choices are often between visual objects whose location varies trial-by-trial. Recent evidence suggests that the neural circuitry that underlies learning to select rewarding actions is different than circuitry underlying selection of rewarding objects. Therefore, we developed a rodent two-armed bandit task using a touchscreen platform in which rodents (n = 12 rats) initiated a trial by nose-poking a food magazine located opposite the visual display. Two different geometric objects were presented on the left and right side of the touchscreen. The animals subsequently approached the touchscreen and made a choice by nose-poking one of the two visual objects. A response to the correct object was rewarded with 10% sucrose liquid reward. A response to the incorrect object was not rewarded. On average, the animals acquired the stimulus-reward association within 5 days, selecting the rewarded object more than 80% of the time in two consecutive days. We subsequently reversed the stimulus-reward contingencies such that the animal had to reverse their preference. The animals successfully reversed their preference within an average of 9 days and switched to selecting the newly rewarded object. Future experiments will examine the neural circuitry underlying these behaviors.
Objectives: Orbitofrontal cortex lesion may direct attention allocation to task-relevant emotion and diminished attention to task-irrelevant emotion (1, 2). We investigated the role of the orbitofrontal cortex (OFC) in regulating emotion – attention interaction and executive functions.

Purpose: To study the role of the OFC in involuntary attention allocation to threat-related emotional distractors and assess the objective and subjective executive function performance of patients with lesion in the OFC.

Methods: 12 patients with lesion in the OFC and 12 controls completed a visual Go/NoGo task engaging executive functions and embedded with threat-related emotional and emotionally neutral distractors. Electroencephalogram was recorded simultaneously. The performance in the executive function test was assessed with reaction times and the number of errors made. N2P3 peak-to-peak amplitude of event related potentials (ERPs) was used as a general measure of attention allocation. Behavior Rating Inventory of Executive Functions (BRIEF) was used to evaluate participants’ subjective assessment of their executive functions.

Results: The OFC group reported more executive function difficulties in BRIEF compared to the control group (61.27±13.6 points vs 49.17±9.68 points, p = 0.026). In the Go/NoGo task the OFC group missed responding more frequently than the controls (Main effect of Group, OR = 0.19 (95% CI = 0.043-0.809), 0.9% (OFC) vs 0.2% (controls). The reaction times did not differ between the groups. The N2P3 peak-to-peak amplitude in Go situation showed a Group by Emotion interaction (F(1,22) = 7.74, p = 0.011) with a tendency of healthy subjects allocating more attention to emotional distractors as opposed to neutral distractors (Controls N2P3 Emotion (7.93 µV ) vs Neutral (7.61 µV), F(1,11) = 4.55, p = 0.056) and OF patients failing to do so.

Conclusions: The OFC group reported more challenges in executive functions and their performance in Go/NoGo task was slightly compromised, thus both subjective and objective deficits in executive functions were observed. The control group allocated more attention to emotional distractors whereas the OFC group failed to do so in Go situation, reflecting possible deficits in involuntary attention allocation to emotional distractors due to OFC lesion. In conclusion, OFC has a role in guiding attention to task-irrelevant emotional information. Deficits in social and emotional behaviors reported in patients with OFC lesion may relate to the inability to pay attention to subtle emotional cues that are not directly linked with one’s own behavioral goals.

Literature Reference:
THE EFFECT OF SLEEP DEPRIVATION ON MEMORY

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Objectives: This study was undertaken to examine the effect of chronic sleep deprivation on memory and to assess if the memory deficit could be modulated by co-administration of the phosphodiesterase-4 inhibitor, Rolipram.

Purpose: Given the effect sleep deprivation elicits on our lives, understanding the cellular and molecular pathways impacted by sleep is of profound clinical and social significance.

Methods: This study included three groups of 8-10 age-matched male mice. Two groups were deprived of REM sleep for 12 hours / day for 5 consecutive days using the multiple platform over water technique (platform diameter = 3.5 cm). Mice were then subjected to daily post-sleep deprivation behavioural tests in the Morris Water Maze (MWM). This test evaluates learning and memory by measuring mean escape latencies (MEL) to find a hidden platform and time spent in platform quadrant, respectively. One of the sleep-deprived (SD) groups was injected with the phosphodiesterase 4 inhibitor, rolipram. The drug was administered at a dose of 1mg/kg/day for the length of the experiment. At the end of the 5 days, the mice were sacrificed and all the brains were tested for cAMP and Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) levels by ELISA technique. A control group was subjected to the same experimental conditions but on larger platforms that allowed sleep.

Results: SD mice showed a significantly lower MEL and higher time spent in platform than control and rolipram groups. Moreover, SD mice had significantly lower levels of brain cAMP. Rolipram significantly elevated MEL, cAMP and Nrf2 and reduced time spent in platform.

Conclusions: Sleep deprivation caused a deficit in encoding and consolidation of memory. This deficit in memory can be attributed to the decrease in levels of cAMP. Administration of rolipram resulted in reversal of the deficit in learning and memory which could be linked to the increase in levels of cAMP and Nrf2.
THE EFFECT OF MULTITASKING ON VISUOSPATIAL PROCESSING IN STROKE AND MCI PATIENTS
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Objectives: Spatial awareness depends on the complex interplay between spatial and non-spatial cognitive processes; our previous studies on stroke patients have shown that it is dramatically hampered by increased attentional load (Bonato et al., 2011; Blini et al., 2016). Here we assessed the effect of multitasking on visuospatial monitoring in a larger sample of stroke patients with unilateral (either left or right) brain damage, as well as in patients with mild cognitive impairment (MCI) and elderly controls.

Purpose: Compare left and right stroke patients, as well as MCI patients, in terms of spatial bias under multitasking.

Methods: Chronic stroke patients with unilateral lesions (n=37) but no clinical signs of neglect, MCI patients (n=22), and healthy elderly controls (n=17) completed a computerized spatial monitoring test with and without a concurrent secondary task). There were three conditions: single task, visual dual task, auditory dual task; sensory stimulation was identical across conditions.

Results: Contralesional spatial awareness deficits emerged in stroke patients independently of lesion side. For left stroke patients, a population in which spatial deficits are thought to be uncommon (Blini et al., 2016), size of deficit was similar to that observed in right stroke patients. Intra- and cross-modal load were equally disruptive for most patients. Performance of MCI patients was affected by multitasking but did not show consistent lateralized bias.

Conclusions: A paradigm exploiting both lateralized and non lateralized (i.e. attentional load) factors is much more sensitive than standard clinical tests in detecting spatial disorders. Our multitasking paradigm mimics complex everyday life requirements, maximally triggers competitive mechanisms, and selectively exacerbates contralesional spatial deficits after brain damage.

Literature Reference
METFORMIN IMPROVES LEARNING AND MEMORY IN STREPTOZOTOCIN-INDUCED DIABETIC RATS
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Objectives: Alzheimer's disease (AD) is a neurodegenerative disease characterized by cognitive impairment, and characterized by the accumulation of extracellular amyloid-β (Aβ) plaques, and intracellular hyperphosphorylated Tau protein in the brain. Increasing evidence has indicated that AD is closely associated with impaired insulin signaling in brain. It has been shown that diabetic mice had increased tau phosphorylated proteins and Aβ levels in their brains and treatment with Metformin (Met) attenuates the increase of tau phosphorylated proteins.

Purpose: we aimed to investigate the therapeutic efficacy of Met on learning and memory, in streptozotocin (STZ) -induced diabetic rats.

Methods: Animals were divided into 4 groups randomly: (1) Control group (n = 8), which was the normal rats and received saline intraperitoneally (0.1 ml/100 g), (2) Vehicle group (DM), which was the diabetic rats and received saline as Vehicle of Met intraperitoneally (0.1 ml/100 g), (3) DM+ Met groups, which were diabetic rats and treated with Met (100, and 200mg/kg per d) for 20 days. All rates were trained in the Morris water maze (MWM) and in shuttle-box apparatus respectively.

Results: Met groups found platform in less time and with less distance traveled, in comparison with DM group. Met also increased the percentage of time elapsed and the distance swum in the target quadrant in STZ-induced diabetic rats, in probe test. In the Passive avoidance test, Met also dose-dependently increased the step-through latency and total time spent in the light area in STZ-induced diabetic rats.

Conclusion: An ip injection of STZ resulted in a significant decline in spatial learning and memory and treatment with Met can enhance learning and memory. Met dose dependently improved spatial learning and memory and also enhanced retention performance in STZ-induced diabetic rats. The results show that Met as an anti-diabetic drug and K-ATP channel blocker through, blocking of K-ATP channels or by sensitizing insulin in the brain improves learning and memory storage in a dose-dependent manner and so is useful for AD treatment.
Novel Methods and Technology Development
INNOVATIVE PROTOCOLS TO ASSESS SEX DIFFERENCES IN FRAILITY IN MOUSE MODELS OF AGEING
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The ageing process is often characterized by frailty, a state of increased vulnerability to stressors and diseases, which includes a decline of physical conditions, muscle strength, motor coordination, metabolic alterations and impairment of cognitive functions. In this context, it is a well-described clinical phenomenon that though females live longer than males they tend to experience greater levels of co-morbidity and disability (Gordon et al. 2017). Standardized systems to assess frailty in the ageing population, as well as in animal models of ageing, still need to be developed. In the framework of the European project “Ageing with Elegans”, we sought to establish a comprehensive protocol to assess frailty in both male and female mice. A specific phenotyping battery was developed to allow testing 20/24-month-old male and female C57Bl/6N mice. A frailty index was adapted from the protocol of Whitehead et al. (2014). Motor coordination and balance were assessed by means of the accelerating rotarod and beam walking tests, while muscle strength was measured using the grip strength test. Specific protocols developed to measure cognitive performance, emotionality and motivation in the automated apparatus IntelliCage (TSE, Germany) allowed to test mice in their home-cage and to avoid social isolation and the experimenter’s manipulation, markedly reducing the stress imposed by testing, a condition to which old animals are highly sensitive. Using this testing battery, we found that, despite females appeared in worst physical condition than males, they showed better performance in most of the above-described tasks, in agreement with the gender differences described in the human population. In conclusion, this protocol can be applied to better understand the pathophysiology of frailty and to devise specific interventions. Support: H2020 AwE (grant N. 633589).

ADMINISTRATION OF THE ANTIOXIDANT N-ACETYL-CYSTEINE (NAC) IN PREGNANT MICE PROTECTS THE OFFSPRING FROM THE NEGATIVE EFFECTS OF PRENATAL HIGH-FAT DIET IN A SEX-DEPENDENT FASHION

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Objectives: Early life experiences can shape a developing organism affecting foetal programming and the offspring’s health outcome throughout life. A growing body of evidence suggests that maternal obesity, the consumption of high-fat diet (HFD) during pregnancy and the associated increase in oxidative stress (OS) might act as powerful prenatal stressors, leading to adult metabolic or stress-related disorders.

Purpose: We hypothesized that administration of antioxidants throughout gestation might counteract the negative effects of prenatal exposure to metabolic challenges on foetal programming leading to a reduced short- and long-term metabolic and emotional vulnerability in the offspring.

Methods: Thus, female C57BL/6J mice were fed HFD for 13 weeks (from 5-weeks of age until delivery) and were exposed to the N-acetyl-cysteine (NAC) antioxidant from 10-weeks of age until right before delivery. Adult offspring were tested at 3-months of age for its metabolic, neuroendocrine and emotional profile.

Results: Results showed that NAC led to improved glucose tolerance and insulin sensitivity particularly in adult male offspring. In this same sex NAC resulted in increased adiponectin levels while counteracting the HFD-dependent rise in leptin levels only in females. In addition, all NAC treated subjects showed reduced emotionality and increased exploration respectively in the elevated-plus-maze and in the open field; these effects were associated to reduced neuroendocrine activation in response to a restraint stress only in male subjects.

Conclusions: Overall, prenatal NAC administration was able to mimic a condition of reduced OS during pregnancy, at least from the metabolic point of view, strengthening the strict relationship between OS and metabolic regulations. These effects were long-lasting and sex-dependent.

A NOVEL APPROACH TO ANALYSE SPONTANEOUS ACTIVITY OF RATS IN GROUP HOUSING CONDITION USING RADIO FREQUENCY IDENTIFICATION SYSTEMS
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Objectives: It is well known that spontaneous physical activity influence the physiological and psychological health benefits. In animal studies, spontaneous wheel running is a common experimental model to investigate the beneficial effects of physical activity. Rodents used in these studies are conventionally housed individually in cages with running wheel in order to correctly record the amount of physical exercise, while laboratory rodents are usually housed in small groups in cage because of social animals in the wild. It is thus possible that individual housing condition for laboratory rodents have a negative impact in physiological and psychological outcomes induced by physical exercise.

Purpose: In the present study, we tried to analyse the spontaneous physical activity in group housed- rats using our original novel technique using radio frequency identification systems (RFID).

Methods: Male Wistar rats were implanted with microchips subcutaneously providing each animal with a unique identification number. Animals, 4 weeks old at the beginning the experiment, were single or group-housed in plastic cages with running wheel for 4 weeks. Each cage was equipped to monitor an individual animal’s access to running wheel using microchip-scale system. Daily wheel revolutions in each cage were recorded digitally from counters attached to the running wheel, and individual running distance estimated to be calculated by multiplying wheel circumference by the number of revolutions based sequential data of individual access behaviour.

Results: The result from our original calculation showed no significant difference in average daily running distance between individual and group housing conditions. Additionally, individual and group housing did not significantly differ in physiological measurements indicating the growth rates and stress level of these rats.

Conclusions: These results indicate that we can analyze spontaneous physical activity correctly in group housed- rats without stress response using RFID system. We assume that our RFID system may extent the role for analyze another types of behavioral in rodents, such as enriched environment test.
ECOCAPTURE: PATIENTS’ BEHAVIOR TRACKING USING SENSOR DATA TO IMPROVE VIDEO-BASED ASSESSMENT OF APATHY
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Objectives:
Apathy can be defined by a quantitative reduction of goal-directed behavior (Levy and Dubois, 2006). ECOCAPTURE is a behaviorist method providing quantitative and qualitative evaluation of apathy in a short-time, near real-life situation to track subjects’ behavior.

Purpose:
Our purpose is to demonstrate how sensor data can provide useful insights and improve video-based assessment of apathy.

Methods:
ECOCAPTURE method consists in a short scenario taking place in a common room of the ICM’s functional exploration platform equipped with video and sensor based-system. From video analysis, we focus on several discrete behavior-specific variables.

ECOCAPTURE was applied to a group of fronto-temporal lobar degeneration (bvFTLD) patients (n = 6) matched to healthy participants. We reported that these behavior-specific variables strongly differentiate bvFTLD patients from controls (Lecouturier and al., 2017).

The sensor (Move II, ®MOVISENS) records data such as 3D movement acceleration, body inclinations, barometric pressure and temperature. From these data, secondary parameters like activity class, body position, steps, energy expenditure, metabolic equivalents (MET) are calculated.

Based on the sensor metrics acquired during the whole 45 minutes experimental session, only trends have been revealed to differentiate the two groups.

The method consists in:
- describing precisely the sensor metrics, confronting their consistence to video metrics
- exploiting sensor data on short-time windows.

Results:
First results show that:
Understanding the way sensor data are evaluated is crucial to avoid any misinterpretation
Parameters reveal their best when sorting them out by sensibility and specificity: specific activity patterns can be then easily identified on a timeframe
Exploiting data on short time windows can prove to be a great strategy to get useful statistics

Conclusion:
After analysis of results, what is the opinion or judgment of the author(s)?
The good exploitation of the sensor data acquired during the short-time real-life situation contributes to distinguish apathetic patients from controls.

Has the project achieved its objective(s)?
Yes, as sensor data allowed to support video-based assessment of apathy.

What new knowledge was gained from the project and what change(s) happened as a result?
The sensor metrics can be categorized by their sensibility and specificity and we are eager to apply the method on short-time windows.

What are the implications of the study?
To diagnose apathy, video and sensors can therefore be used and since sensors are transposable systems, they can be easily placed remotely to track patients’ behavior.

EFFECTS OF NUCLEUS REUNIENS DEEP-BRAIN STIMULATION ON RAT MEMORY USING A WATERPROOF STIMULATOR

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Objectives: 1. Gain an insight into the design of robust waterproof active implants, for animal use. 2. Observe behavioural and memory changes from deep-brain stimulation of the nucleus reuniens.

Purpose: The nucleus reuniens connects reciprocally to the medial prefrontal cortex and the hippocampus (see [1] for a review), yet its role in learning and long-term memory is unclear. This study investigates the behavioural effects of deep-brain stimulation (DBS) of this structure, for animals trained in a Morris Water Maze task. To accomplish this, a novel device was developed that can allow for DBS inside the water maze.

Methods: A portable, programmable deep-brain stimulator was developed (2.11g including battery and housing) using ultra-small components and 3D-printing. The device features 2 charge-balanced biphasic channels with a 12V compliance, and is waterproof. Rats were trained in a reference memory variant of the Morris Water Maze, whereby they had received DBS in the nucleus reuniens, using either theta-bursting (n=12), high-frequency (n=11), or sham (n=20) stimulation parameters.

Results: The devices had functioned in all rats without complications, including when rats swam underwater. Rats with theta-burst stimulation had shown a significantly increased platform latency and path length during acquisition, when compared to the sham group. Also, significant reductions in Wishaw’s Index and target quadrant time were observed during both acquisition and probe trials. No significant effects were observed in high-frequency stimulated rats, when compared with the sham controls.

Conclusions: This project demonstrates the feasibility of water-maze DBS studies using a novel approach, and can help to expand on the range of possible modalities for DBS research. Marked behavioural changes during acquisition were observed for theta-bursting parameters, thus highlighting the importance of stimulus parameter selection on animal behaviour. Furthermore this provides insights into the workings of the nucleus reuniens during tasks that employ spatial reference memory.

Literature Reference
A VIRTUAL STIMULI BASED APPARATUS TO MEASURE EMPATHY-LIKE BEHAVIOUR IN RATS: TOWARDS THE 3Rs

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Current animal models to study empathy-like behaviour in rodents rely on stressed animals to drive said behaviour. Here, we describe the development of an apparatus which replicates original conspecific emotional states via reproduction of natural stimuli using movement tracking, audio-visual playback systems applied to studying empathy-like behaviour in rats.

The apparatus consists of two spatially distinguishable white and black compartments, joined by a single door. Under neutral conditions, animals allowed free exploration of the environment show a place preference for the ‘safer’ black compartment. At testing, distress stimuli from conspecifics are presented in the black compartment, whereas neutral conspecific stimuli are presented in the white compartment. Control subjects were presented with the same neutral stimuli but mock stimuli, mimicking distress audio-visual, were presented in the black compartment. The amount of time a subject spends in either compartment is assessed as a response to conspecific condition. Accordingly, empathy-like behavior is interpreted as increased time spent in the white environment as it is animals’ less favored compartment but their presence there reduces the appearance of audio-visual signs of conspecific distress.

Subjects were 2-month-old male Wistar rats handled over a 10-day period, then given a ‘place preference assessment’. Afterwards, they were given a 3-day ‘training’ in which forced exposure to specific environments helped them associate each compartment to respective conspecific condition (i.e., neutral or test/control stimuli). Subsequently, animals were subjected to a ‘stimuli test’ where they were given free access to both compartments with audio-visual stimuli activated depending on animals’ position.

Results in the place preference test revealed the expected bias towards the black compartment for all animals. Whereas the results of the stimuli test showed that test subjects spent more time in the non-preferred compartment, control subjects did not. In conclusion, such an apparatus controls the variability involved by using the same natural stimuli as trigger, in lieu of changing demonstrator-observer relations with each test. It offers promising possibilities to investigate animals’ empathy-like behavior without exposing empathy-triggering animals to stress or pain and, thus, also help advance implementation of the 3R principles.
EXPLORING BEHAVIORAL TAGGING: A RECENT MODEL FOR LTM FORMATION
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Objective & Purpose To explore BT as a novel mechanism thought to be involved in the complex interaction of events leading to LTM formation in object recognition paradigm and the timeframes of LTM formation. To investigate the role of glutamatergic NMDA receptors in BT employing object recognition paradigm.

Materials & Methods To demonstrate the phenomena of BT, novel object recognition task and open-field were used to assess LTM formation within different timeframes. For Plasticity Related Proteins assessment western blot was used. Dopamine ad GABA levels were assessed using HPLC-ECD. NMDA receptor antagonist MK-801 and partial agonist D-cycloserine were used to assess the role of NMDA receptors in BT.

Results Results show that 1h is the critical time window within which NOR-LTM consolidation takes place in response to a weak NOR training. Previous exposure to an open-field 1 h before and after and not 2 h before and after training promotes LTM formation of the novel object recognition task. Dopamine levels were significantly higher in BT group while a significant decrease in GABA levels was observed. Activation of NMDA Receptors and role of BDNF was found to be critical in object recognition LTM via open-field exposure.

Conclusions This model provides an important platform to study and analyze memory, offering a consistent structure able to define promotion, modulation, and interference in the formation of lasting memories. This model could also serve as a novel therapeutic tool for the treatment of psychiatric disorders in humans as the persistence of maladaptive memory components is a common feature in many psychiatric disorders.

Keywords: Glutamate · Behavior · Tagging · MK-801 · D-cycloserine · Dopamine · NMDA
REPEATED SESSIONS OF BIFRONTAL TRANSCRANIAL DIRECT CURRENT STIMULATION FOR TREATMENT OF INTRACTABLE TINNITUS: A RANDOMIZED CONTROLLED TRIAL

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Objectives: To investigate the therapeutic effects of multi-session bifrontal transcranial direct current stimulation (tDCS) in patients with chronic intractable tinnitus.

Purpose: To investigate the effects of repeated sessions of tDCS on the Tinnitus handicap inventory (THI), tinnitus loudness and distress, Beck anxiety (BAI) and Beck depression inventory (BDI) scores.

Methods: In a single-blinded randomized controlled trial, 44 patients were assigned to groups of real (F=11, M=18, age: 47.67±7.96 years, disease duration: 8.7±3.72 years), and sham tDCS (F=8, M=7, age: 45.17±9.33 years, disease duration: 7.8±3.14 years). Real tDCS consisted of a daily single tDCS session (2 mA, 20 minutes, 35 cm\(^2\) carbon electrodes) over 5 consecutive days per week for 2 consecutive weeks. The anode was placed over the left dorsolateral prefrontal cortex (DLPFC, F3), and the cathode over the right DLPFC (F4). In the sham group, the electrode montage was identical, but the device was turned off after 30 s. The THI was obtained before and after intervention, and at one month follow-up. Tinnitus loudness and distress were assessed using a numerical visual analogue 0-10 rating scale before stimulation, and immediately, one hour, the night after stimulation, one week and one month follow-ups. BAI and BDI-II scores were determined before the first session, immediately after, and one month after the last stimulation.

Results: Repeated-measures ANOVA showed a significant treatment effect in the THI score (significant interaction between time and stimulation). Similar patterns were observed for the secondary outcome measures BDI, BAI, tinnitus loudness and distress. Post-hoc comparisons revealed significant between-group differences for THI, BDI, and BAI, after the last session, which remained significant for one month after intervention.

Conclusions: Repeated sessions of bifrontal tDCS effectively suppress tinnitus intensity and tinnitus-related distress over a prolonged time course. Bifrontal tDCS may be a potential therapeutic modality for treatment of chronic tinnitus.
TRACE EYEBLINK CONDITIONING IN HEAD FIXED MICE
PAIRING VIBRISSAE STIMULATION AND CORNEAL AIRPUFF
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Objectives: Trace eyeblink conditioning (tEBC) has been used as a declarative memory task across species (e.g. humans, rabbits, rats and mice). The purpose of this study is to establish this paradigm in head fixed mice to allow refined electrophysiological, imaging and molecular genetic approaches combined with a well-controlled behavioural paradigm.

Purpose: We have used vibration of the mystacial vibrissae and corneal airpuff to establish a hippocampal-dependent learning paradigm in head-fixed C57BL6 mice to allow for a more in-depth analysis of the neural circuitry involved.

Methods: In tEBC, a neutral conditioned stimulus (CS), such as vibration of the whiskers, is repeatedly paired with an aversive unconditioned stimulus (US), such as a corneal airpuff, which elicits a reflexive eyeblink response which we detect with subdermal microwires to record electromyographic (EMG) activity from the upper eyelid. The two stimuli are separated by a stimulus free “trace” interval.

Results: Acquisition of the tEBC task is evidenced by conditioned responses (CRs), defined as blinks elicited by the CS before onset of the US. Our results indicate that conditioned animals show a higher percentage of CRs compared to those of control animals which received in random order unpaired CS and US trials. Our results also indicate that the whisker vibration conditioning stimulus (CS) evoked a minimal number of short latency startle responses. This paradigm allows us to set and monitor in real time the amplitude of the vibration CS with a Micro-Epsilon laser-optical displacement sensor. Additionally, the mice are monitored with a webcam to ensure trial presentation only when the animals are not moving (e.g. running, grooming and whisking).

Conclusions: The use of whisker vibration and airpuff stimuli will permit the study of learning and memory in aging animals, as other sensory modalities such as vision and audition deteriorate with aging. In addition, these stimuli will allow for in vivo recordings during training and following memory consolidation. This mouse based paradigm is ideal for molecular genetic techniques, such as Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) and optogenetics, to be used in future experiments to investigate the role of brain regions including the somatosensory cortex and limbic regions in learning and memory.

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Topic 8

Others
IMPACT OF PAIN PATIENT’S CANCER ON THEIR CAREGIVERS
ASBAYO Fatima
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The suffering of patients and caregivers is real in Oncology today, is a global suffering given
the complexity and the multiplicity of aspects involving games during the trajectory of cancer
and requires a holistic support of patients. That's suffering dislodges the world of care and is
only an opportunity to interview the previous relationship.
Imaging by functional magnetic resonance techniques were used to identify today a network
of brain areas activated in phenomena painful and had shown the close link between proven
pain and pain experienced, live the pain and see the pain, seeing someone who has active
regions similar in those who observes it, these activated areas are the emotional pain
component and are all enabled by Visual means; However, the caregiver uses his body
mirrored the body of the patient, his emotions and his suffering in an emotional space.
The present study makes new contributions to our understanding of this emotional share
experienced by caregivers in Oncology at the Morocco. To our knowledge it is the only study
devoted exclusively to this type of suffering caused by the confrontation with physical pain
and psychic patients with cancer and so far no research has not quite centered on the idea that
suffering is contagious and that the individual suffering repercussions on the environment also
the effects of the pain of the patient on caregivers in Oncology.
EVOLUTIONARY SHAPED BRAIN FUNCTIONS, UNDERLYING MOTIVATIONAL SYSTEMS, ARE RESPONSIBLE FOR GENDER DIFFERENCES IN INFEDELTY BEHAVIOUR

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Objectives: Gender differences in the brain is typically assumed to prove that humans belong to two distinct categories and thus ‘justify’ differential behaviours of males and females, like differences in mating behaviour. Although human brains cannot be categorized into two a male and female brain, some evolutionary shaped brain functions have a greater impact on males, than on females. For example, sex drive. Sex drive inherently motivates a person to engage in specific partner related sexual behaviour.

Purpose: In this study it was investigated to what extend sex drive is responsible for infidelity behaviour, keeping in mind that, in general, males, as compared to women, have a higher sex drive and report more incidents of infidelity.

Methods: It was expected that males more often report infidelity, because they have a higher sex drive. This was investigated in a group of 245 adult subjects, all in a steady relationship (215 females; mean age 36.9 years (SD=12.7); range 18-63 years and 88 males; mean age 37.8 years (SD=13.0); range 18-67 years). Sex drive was assessed by using the Sex Drive Scale. Infidelity was assessed by asking how many times one had sex with someone else than their partner, for last month.

Results: It was found that, males, as compared to women have a higher sex drive en reported a higher incidence of infidelity. Furthermore, mediation analysis showed that the gender difference for reported infidelity was completely mediated by sex drive.

Conclusions: It is concluded that sex drive, as an evolutionary shaped brain function, contributes strongly to infidelity behaviour, stronger for males as compared to females, because of a gender differences in sex drive.
Global seizures of methamphetamine (METH), a psychostimulant drug of abuse, have increased 158% between 2010 and 2015 (UNODC 2015), indicating a dramatic increase in their abuse. However, no pharmacological treatments are available for METH use disorders. Lobeline, a natural product isolated from “Lobelia inflata”, reduced METH self-administration (SA) in rats via inhibiting the function of the vesicular monoamine transporter-2 (VMAT2). Lobeline completed Phase 1b clinical trials as a treatment for psychostimulant abuse, however, this natural product is not selective for the VMAT2 target protein, also acting at nicotinic receptors. We hypothesized that analogs of lobeline which exhibit improved selectivity and potency at VMAT2 will inhibit the neurochemical and behavioral response to METH more efficiently, and will be effective pharmacological treatments for METH use disorders. Based on series of structure activity relationship studies, (S)-GZ-11608 exhibited high potency at VMAT2 (Ki = 25.5 ± 3.57 nM), and selectivity at VMAT2 over the hERG channel, dopamine transporter, serotonin transporter, and nicotinic acetylcholine receptors (163-fold, 241-fold, 94-fold, and >1180-fold, respectively). (S)-GZ-11608 injection (30 mg/kg, s.c.) specifically decreased METH-SA, and tolerance did not develop to this effect following repeated (S)-GZ-11608. Importantly, (S)-GZ-11608 (0.01, 0.05, 0.1, and 0.5 mg/kg/infusion, i.v.) did not substitute for METH (0.05 mg/kg infusion, i.v.) in METH self-administering rats, indicating it likely has low abuse liability. In conclusion, the potent and selective VMAT2 inhibitor, (S)-GZ-11608, specifically inhibited the behavioral response to METH. Supported by NIH U01 DA013519.
EFAVIRENZ INDUCES ACTIVATIONAL DEFICITS POTENTIALLY RELATED TO DEPRESSION: STUDIES IN ANIMAL MODELS.

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Background: Efavirenz (EFV) is an antiretroviral drug with high efficacy and favorable pharmacokinetics, prescribed for HIV-infected patients. However, this drug has adverse effects on the CNS, and it has been associated with neuropsychiatric dysfunctions including depressive symptoms. In addition to depressed mood, depressed people display motivational symptoms related to behavioral activation, such as psychomotor retardation, fatigue and loss of energy. These symptoms are thought to involve nucleus accumbens dopamine (DA). In previous studies we demonstrated that tetrabenazine (TBZ), a vesicular monoamine transport (VMAT-2) inhibitor that depletes accumbens DA, altered behavioral activation in measures of voluntary running wheel (RW) activity and effort-based choice in rodents. EFV also binds to VMAT-2, and thus potentially can induce depression-like effects in rodents.

Objectives: We analyzed the impact of EFV on a measure of behavioral activation (voluntary running wheel activity, (RW)) and a classical paradigm for the study of depressive-like behaviors (the Forced Swim Test (FST)). In addition, the effect of this drug was also assessed on anxiety and social interaction paradigms to evaluate mood parameters involved in depression.

Methods: EFV was administered intraperitoneally (IP) to CD1 male mice tested in seven behavioral paradigms: FST to assess depressive-like behaviors, RW to assess behavioral activation, Dark and Light box (DL box) and Elevated Plus Maze (EPM) to evaluate anxiety-like behavior, Open Field (OF) to assess locomotion, and Social Interaction (SI) to evaluate social preference. Bupropion (DA transport blocker) was coadministered to reverse the effects of EFV on the RW.

Results: EFV dose-dependently reduced immobility and swimming time in the FST, and voluntary RW activity. The suppressive effect of EFV on voluntary RW activity was reversed by the antidepressant bupropion. None of the doses had an effect on anxiety and social parameters evaluated in the DL box, the EPM, and the SI.

Conclusions: EFV produces depressive-like behaviors as assessed in the FST, and also affected behavioral activation as assessed in the RW, an effect that was reversed by the antidepressant bupropion, which potentiates effort-based performance in animal models of anergia and appears to improve energy-related symptoms in humans. These results suggest that EFV may affect mesolimbic DA. These results have implications for understanding the depressive symptoms observed in HIV patients exposed to EFV.
Fear behavior is known to depend on the interaction between the prefrontal cortex (PFC) and the basolateral amygdala (BLA), and the expression of fear involves synchronized activity in Theta (4–12 Hz) and Gamma (30–120 Hz) frequency oscillations. Recent studies showed that freezing, a behavioral expression of fear, temporally coincides with the development of sustained 4-Hz oscillations in prefrontal–amygdala circuits. During fearful state, rats emit 22-kHz ultrasonic vocalizations (USV, 22kHz) time-locked to freezing behavior. Interestingly USV emission strongly alters the animal’s respiratory rate (3-8 Hz), thus potentially affecting respiration-locked rhythm that has been recently suggested to play a role in the organization of prefrontal network activity.

The present study was aimed at assessing the impact of the emission of 22-kHz ultrasonic vocalizations (USV) on oscillatory activities in the gamma and theta bands within the neural network involved in fear expression and memory. For this, rats were implanted with four electrodes respectively in the PFC, BLA, dorso-medial striatum and olfactory cortex, for chronic recording of local field potentials. The animals were then trained in an odor fear conditioning paradigm in which an odor was repeatedly paired with a mild footshock. During the training session, local field potentials were recorded together with three behavioral parameters: Freezing, USV and respiration. Three periods were compared: before odor onset, during odor, after shock delivery.

The data show that USV emission induces significant changes in Theta and Gamma frequency power in the recorded structures. The amplitude of the changes is correlated with the intensity of the USV calls and their impact on the respiratory signal parameters (volume, peak amplitude) which were maximal after shock delivery.

The present data suggest that part of the changes in Theta and Gamma frequency oscillatory activities described during fear expression might be ascribed to the emission of USV.
ASSOCIATION BETWEEN ANK3 POLYMORPHISMS AND BIPOLAR DISORDER IN KOREAN POPULATION
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Objectives: Bipolar disorder (BD) is a major psychiatric disorder characterized by alternating mood episodes. Previous genetic studies of BD have reported several genes, such as ANK3, BCR, CACNA1C, BDNF, and DGKH, as potentially associated with BD. The ANK3 gene, encodes the linker protein ankyrin-G, has been identified as a possible BD susceptibility gene in previous genome-wide association analyses.

Purpose: The goal of the present study was to evaluate the association between ANK3 polymorphisms and BD in the Korean population.

Methods: According to previous reported results, we selected two single nucleotide polymorphisms (SNPs), rs1938526 and rs10994336, in the ANK3 gene. The study included 287 BD patients and 340 healthy controls. We performed case-control association and case-control haplotype analyses of the two ANK3 polymorphisms.

Results: No significant association of either single SNP with BD was found by case-control association analysis. However, rs1938526 and rs10994336 showed significant association (overall P = 3.6 × 10^-11; permutation P = 0) in a case-control haplotype analysis.

Conclusions: We conclude from our haplotype analysis results that ANK3 polymorphisms rs1938526 and rs10994336 may confer susceptibility for BD in the Korean population. Association analysis revealed a probable genetic difference between Korean and Caucasian populations in the degree of ANK3 involvement in BD pathogenesis.

Literature Reference
Objectives: The participants should be able to understand the importance of microglia in satiety and the feeding regulatory system. Microglia are the resident immune cells of the brain. Previous work has shown that microglia become activated acutely and long-term in the presence of dietary interventions such as a high-fat diet or early life overfeeding.

Purpose: Here we use a novel rat model of acute conditional microglial knockout to investigate if microglia have a direct role in regulating satiety and feeding.

Methods: We used transgenic rats with a diphtheria toxin receptor (DTR) incorporated into the promoter region of the CX3CR1, expressed on microglia and monocytes. Diphtheria toxin (DT) thus selectively ablates microglia and monocytes, with at least 50% ablation of microglia in the brain by 24 hr after DT administration and full restoration of normal microglia after 7-14 days. Microglia in wildtype rats are not affected.

Results: Acute ablation of microglia caused a dramatic reduction in weight gain in the week following DT that was at least partially accounted for by a short-term reduction in food intake. If microglia were chronically ablated, food intake and weight remained suppressed. Acute microglial ablation caused an increase in circulating satiety hormones to signal feeding, however, the responses to exogenous ghrelin were normal. This reduction in weight loss and food intake did not affect the gene expression of the orexigenic peptides NPY or AGRP.

Conclusions: These findings suggest that microglia are critical in weight and normal feeding behaviours. An increased metabolism may be responsible for this acute weight loss and anorexia after ablation of microglia, but this remains to be tested.
INDIVIDUAL DIFFERENCES IN RUNNING WHEEL PERFORMANCE ARE RELATED TO DIFFERENCES IN PREFERENCE FOR EFFORT-REQUIRING REINFORCERS AND DA LEVELS
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Background: Motivation is characterized by high levels of behavioral activation, vigor, persistence and goal directed behavior. These functions are impaired in pathologies such as depression or Parkinson disease. Dopamine (DA) in striatum, mainly in nucleus accumbens (Nacb), plays an important role in the regulation of speed or perseverance in goal motivated behavior. Studies in animals show that DA depletions in Nacb produce a shift in relative preference between reinforcers that require different levels of behavioral activation, decreasing time spent on a running wheel (RW), and increasing time spent eating. Therefore, differences in basal DA levels could underline individual differences in the vulnerability to suffer motivational impairments.

Objectives: These studies were conducted to explore a potential relationship between individual differences in voluntary wheel running, striatal (ventral and dorsal) DA activity, and selection of reinforcers with different levels of behavioral activation and effort requirement. In addition, social interaction, anxiety, and exploration activity levels were compared between different groups of runners.

Methods: CD1 male mice were used in these experiments. All animals were assessed in a Dark and Light box to evaluate anxiety-like behavior, in an Open Field (OF) to assess exploration, and in a Social Interaction paradigm to evaluate social preference. After these tests, and during 4 weeks of testing (2 hours a day/5days a week), animals were allowed to train on a RW placed in a Plexiglas box that also had straw to build a nest. Different activity groups were determined using first and 4th quartiles of the average running counts. Two behavioral tasks to evaluate effort-related decision-making were used: The three choice T-maze task, and the T-maze barrier choice task. After these tests, brains were collected and expression of DARPP-32 phosphorylated at the threonine (Thr) 34 and 75 residues was assessed immunohistochemically to provide a marker of DA-related signal transduction.

Results: There were no significant differences in anxiety, OF exploration and social interaction, although the high runners showed indifference in the exploration of the conspecific versus the object. In the three-choice T-maze task, the high runners spent significantly more time in the RW, and less time in contact with the food than the low runners. In the T-maze barrier choice task the high runners tended to engage more in the effortful alternative. Finally, pDARPP32-Thr34 was lower among the high runners in the 4 areas of striatum studied, and also in the anterior cingulate cortex.

Conclusions: These results suggest that differences in basal levels of voluntary exercise are related to preferences for reinforcers that require high levels of activation and effort, and those could be mediated by an increase in DA D2 receptor stimulation in striatal encephalin-positive neurons. The present results have implications for understanding and treating symptoms such as fatigue, anergia and psychomotor slowing seen in pathologies with a clear motivational component.
NUTRITIONAL INTERVENTION WITH ESSENTIAL MICRONUTRIENTS DIMINISHES THE LASTING CONSEQUENCES OF EARLY-LIFE STRESS ON COGNITIVE FUNCTION

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Objectives: Early-life stress (ES) is associated with lasting cognitive impairments later in life. Because prevention of ES is often not possible, intervention strategies are highly needed. Our aim is to elucidate the underlying mechanisms, with a specific focus on the role of early nutrition, which has been largely ignored so far.

Purpose: Here we investigated the possible role of early nutrition in programming later cognition after ES, as this might open new avenues for nutritional intervention strategies, which are non-invasive and easily applicable.

Methods: We focused on essential one-carbon metabolism associated micronutrients (1-CMAM; i.e. methionine and B-vitamins), important for development and epigenetic modifications. We studied in an established ES animal model if ES alters micronutrient availability in milk, plasma and brain and investigated the epigenetic, structural and behavioral effects of ES. Subsequently we tested if early 1-CMAM-supplementation can reverse ES-induced changes in the offspring.

ES was induced in C57Bl/6 mice from postnatal day (P) 2-9, while dams received either control or 1-CMAM enriched diet. Nutrient content was measured at P9 in offspring’s stomach milk, plasma and brain. Next, we studied effects of 1-CMAM supplementation on ES-induced alterations in maternal behavior, the offspring’s HPA-axis activity, neurogenesis, DNA methylation levels (global and Nr3C1 specific) and DNA methyltransferase expression in the hippocampus.

Results: ES reduced methionine levels in offspring’s plasma and brain. Importantly, 1-CMAM supplementation ameliorated ES-induced cognitive impairments in adulthood, abolishing deficits in spatial learning and memory. 1-CMAM supplementation restored methionine levels in the offspring and also prevented ES-induced stress axis hyperactivity.

Conclusion: A short and early nutritional intervention can prevent lasting ES-effects on hippocampal function. To take these findings from bench to bedside we are currently setting up a human cohort to assess whether stress affects the nutritional composition of breastmilk as well, and how this relates to food intake.
EFFECTS OF JUVENILE ALCOHOL CONSUMPTION IN LEARNING: CHANGES IN HIPPOCAMPAL PHOSPHOPROTEOME

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A new way of ethanol intake consisting in excessive and intermittent alcohol consumption over a very short period of time, known as binge drinking, has recently emerged in juvenile population. Several results provide strong evidence for ethanol-associated alterations in memory processes related to hippocampus. However, the neural mechanisms that contribute to changes in hippocampal signaling in ethanol users remain unknown.

This study aimed, first, to investigate age-related changes in the hippocampal phosphoproteome after acute alcohol administration and, afterwards, to study the lasting effects of juvenile ethanol binge drinking in cognitive plasticity for hippocampal dependent spatial learning and memory.

We have compared the hippocampal phosphoprotein expression of adult and adolescent Wistar rats treated with a single dose of ethanol. Our proteomic analysis revealed that 13 proteins involved in neuroprotection were differentially affected by age, ethanol administration or both. On the other hand, we carried out experiments with adolescent male Wistar rats that self-administered ethanol following two protocols differing on the pattern of intake percentage and chronicity to compare binge and chronic/moderate intake of alcohol. Spatial and reversal learning was impaired in both binge and chronic ethanol groups.

Moreover, the analysis of genetic expression of the proteins differently expressed in the phosphoproteomic approach showed an up-regulated expression of some of these proteins after chronic and moderate ethanol intake.

Our data demonstrate that juvenile ethanol exposure might increase the risk of hippocampal spoilage, due to the alterations of some neuroprotective proteins, and the consequent alterations in memory and spatial abilities. Furthermore, those proteins might be used as biomarkers for addiction.
THE “RAM EFFECT”: A MODEL TO UNDERSTAND THE ROLE OF KISSPEPTIN AS A RELAY BETWEEN SOCIO-SEXUAL INTERACTIONS AND THE GONADOTROPIC AXIS

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Reproduction depends on the interactions between hypothalamus, hypophysis and gonads, the HPG axis, but can be modulated by environmental factors such as socio-sexual interactions. Sheep are seasonal breeders but reproduction can be stimulated in sexually quiescent ewes by exposure to an active ram (the “ram effect”). We previously showed that this effect partly depends on olfaction but many brain structures are activated, sexual experience is necessary and noradrenaline is implicated (Fabre-Nys et al 2015). Kisspeptins (Kiss) present in the arcuate nucleus (ARC) and the preoptic area (POA) are potent stimulators of LH secretion. Our aim was to understand the role of Kiss neurons on LH secretion during the “ram effect”.

With a double immunofluorescent detection we identified Kiss neurons (Kiss IR) activated (Fos IR) by exposure to a ram for 2h (M2), 12h (M12) or to ewes for 2h (C) and showed that activation (Kiss IR also Fos IR cells) was higher in M2 and M12 than in C in ARC (p<0.002) and POA (p<0.02). In ARC activation was also higher in M12 than in M2 (p<0.02 and p<0.05).

Kiss antagonist (P234 10^{-6}M) administered in the POA at the time of ram introduction greatly reduced the amplitude of the male-induced LH increase compared to solvent (p<0.02), the effect was more limited in ARC (p<0.038 1h after P234). In contrast Kiss antagonist (P271 10^{-4}M) infused in ARC but not in POA 6 to 18 h after ram introduction prevented the ewe to have an LH surge (0/6 versus 4/5 and 4/6 in C).

These results show that both populations of Kiss neurons are implicated in the ram induced pulsatile LH secretion and in the LH surge and suggest that they play a role in adapting the activity of the gonadotropic axis to sociosexual interactions possibly partly via noradrenaline.


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NEURAL ACTIVITY IN THE MEDIODORSAL THALAMUS AROUND HIPPOCAMPAL RIPPLES

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Objectives: Highly synchronized population bursts, or ripples (~150Hz), in hippocampus (HPC) promote replay of recently acquired memories and facilitate information transfer to cortex for long term storage. Aside hippocampal-cortical interactions, the activity within a larger scale neural network supporting declarative memory consolidation is essentially unknown. Mapping of the whole brain activity around the times of ripple occurrence revealed a very characteristic pattern of positive BOLD responses in many cortical and limbic structures and negative BOLD responses in a number of subcortical regions, including sensory and association thalamus (Logothetis, 2012). Mediodorsal thalamus (MD) has been long implicated to play a role in mnemonic functions. The MD receives input from the entorhinal cortex and has dense reciprocal connection with the medial prefrontal cortex (mPFC). We would like to characterize how thalamic neural activity contributes to hippocampal-cortical dialogue underlying memory consolidation.

Purpose: In the present study, we sought to characterize in detail the ripple-associated neural activity in the MD.

Methods: We recorded broad-band (0.1Hz – 8kHz) extracellular activity in the MD, HPC, and mPFC in behaving rats.

Results: The MD firing rate was suppressed ± 2.34 sec around ripple peaks (63% compared to the baseline). The modulation profiles differed for the ripples occurring during awake or sleep. The temporal window of modulation was much narrower during ‘awake’-ripples (± 1.74 sec compared to ± 2.43 sec during sleep). We further subdivided ripples depending on the presence or absence of co-occurring sleep spindles in the mPFC. Notably, the MD activity was not suppressed when ripples were coupled with sleep spindles.

Conclusions: Our results support the hypothesis that thalamic suppression during ripples may reduce interference for hippocampal-cortical interaction, yet suggest that there may be temporal windows when thalamic activity plays a functional role for cross-regional communication underlying memory.

Literature Reference
EFFECTS OF DIFFERENT SCHEDULE OF COCAINE ADMINISTRATION ON ACQUISITION AND EXTINCTION CONDITIONED PLACE PREFERENCE IN MICE
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Background: Previous studies have demonstrated that fixed daily doses of cocaine resulted in low magnitude and rapid extinction of conditioned place preference (CPP) in B6;129S F2 and C57BL/6J mice. However, administration of ascending doses of cocaine induced strong and enduring conditioned memories in these strains of mice.

Objectives: The present study was undertaken to examine whether a fixed vs. ascending schedule of cocaine administration would induce differential levels of acquisition and extinction of CPP in CD-1 mice. Additionally, we investigated c-Fos expression during CPP extinction in animals exposed to both cocaine schedules.

Purpose: To compare the effects of fixed vs. escalating doses of cocaine on the acquisition and extinction of CPP in outbred mice.

Methods: Male CD-1 mice were trained using a fixed or an escalating conditioning procedure, achieved by varying the cocaine conditioning dose (fixed 11.25 vs. 3, 6, 12, 24 g/kg respectively). After 8 (4 x saline; 4 x drug) conditioning sessions, animals were given a 30-min preference test (T1). Following T1, mice received 27 additional 30-min choice extinction tests. Brains were collected at the end of the last extinction test.

Results: Animals conditioned with ascending doses of cocaine showed the same level of preference on the acquisition test (T1) than animals on the fixed group. However, while animals on the fix group extinguished preference along sessions, the ascending dose group maintained the same levels of high preference during 28 sessions. Resistance to extinction correlated with increased activity in the prelimbic prefrontal (PL) cortex compared to the infralimbic part (IL) of the same region.

Conclusions: These data indicate that escalating drug use could induce perseverant and long-lasting pathological memories difficult to extinguish. As previously reported, the PL cortex has an important role in controlling perseverance in contextually dependent behavior.
CNS STIMULANT-INDUCED PSYCHIATRIC DISORDER
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Objectives: Several stimulants abuse has been rarely reported. Phentermine and phendimetrazine are amphetamine analogues. Methylphenidate is indirectly acting sympathomimetics. Overuse of phentermine and phendimetrazine as an appetite suppressant can induce psychotic symptoms. Overuse of methylphenidate as a treatment of concentration difficulty can develop psychotic symptoms. These cases presentation will be cautious to overuse of several stimulants.

Purpose: Physicians should be aware that they observe carefully side effects of stimulants and monitor psychotic symptoms and mood symptoms develop in patients.

Methods: Cases presentation

Results: 1st case, 36-year-old, unmarried female had heavy drinking history for 3 years. She started to take phentermine of 75mg daily as a diet pill prescribed by a doctor. Her dosage increased to 150mg and then psychotic symptoms developed. 2nd case, 28-year-old, unmarried female was alcoholics for 8 years. She began to use phendimetrazine 70mg daily as a diet pill by prescription. The dosage increased to 140mg daily and then psychotic symptoms and elevated mood developed. 3rd case, 33-year-old, unmarried male had depressed mood and anhedonia. He took methylphenidate for improving anhedonia and concentration difficulty by prescription. The dosage increased to 100mg daily and then psychotic symptoms and mood elevation developed. These three patients have been admitted to psychiatric institution from once to several times.

Conclusions: Overuse of CNS stimulants have potential danger of developing psychotic symptoms and mood symptoms in patients. Three patients mentioned above have taken antipsychotic drugs for treatment of their psychotic and mood symptoms to the latest day. Especially, the effectiveness of these diet pills has never been validated. Physicians should monitor carefully patient’s stimulant overuse and major psychiatric symptoms develop.
THE ROLE OF HYPOTHALAMIC FKBP51 IN ENERGY HOMEOSTASIS
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Objectives: Metabolic disorders, including type 2 diabetes and obesity, affect millions of people worldwide and are considered an immense burden for western societies. The FK506 binding protein (FKBP51), encoded by the FKBP5 gene, is known for its ability to regulate signaling cascades through direct protein-protein interactions. Interestingly, recent animal studies revealed that the global loss and the pharmacological inhibition of FKBP51 lead to resistance against obesity and improved glucose sensitivity.

Purpose: The aim of the current study is to investigate the regulatory function of hypothalamic FKBP51 in neuronal circuits controlling nutrient sensing, glucose homeostasis and thermoregulation.

Methods: To entangle the function of hypothalamic FKBP51 in metabolic control we injected an adeno-associated virus targeting the ventromedial hypothalamic nucleus (VMH) to overexpress FKBP51. The FKBP51 overexpressing animals were screened for glucose tolerance, insulin tolerance, energy expenditure and hormonal changes. Additionally, different metabolically relevant tissues like WAT, BAT, liver and hypothalamus were analysed for molecular alterations.

Results: We show that overexpression of FKBP51 in the VMH reduces body weight gain on chow and under high fat diet conditions. Interestingly, no significant changes in food intake were observed. Additionally, FKBP51 OE animals showed an improved glucose metabolism and insulin resistance under high fat conditions.

Conclusions: Our results demonstrate that changes in central FKBP51 levels differently regulate metabolic pathways and are the starting point to unravel the detailed function of peripheral and central FKBP51 in energy homeostasis. This is essential to further evaluate FKBP51 as a potential therapeutic candidate for metabolic disorders.
Several findings suggest that 5HT2A receptors (5HT2AR) may be involved in the molecular mechanisms responsible for psychotic symptoms. Hallucinogenic drugs acting as 5HT2AR agonists, such as psilocybin, lysergic acid diethylamide (LSD) and dimethoxyiodoamphetamine (DOI) produce psychosis-like symptoms in healthy subjects. On the other hand, cannabis intoxication induces in healthy subjects cognitive alterations similar to those seen in schizophrenia and worsens the symptoms in schizophrenic patients. These data suggest a link between cannabis and psychosis. Our aim was to evaluate sensorimotor gating in adolescent mice chronically treated with Δ⁹-THC, at basal conditions and after acute (±)DOI exposure, as well as the status and functionality of 5HT2AR in brain cortex of these mice.

Mice were treated during adolescent period with Δ⁹-THC (10 mg/kg daily, 30 days, i.p.) or vehicle. Prepulse inhibition (PPI) test was performed in both groups at basal conditions and after acute DOI injection (0.5 mg/kg, i.p.). Displacement curves of specific [3H]ketanserin binding (2 nM) by DOI were also carried out in brain cortex membranes. Moreover, specific stimulation of different Gα proteins by DOI (10⁻⁵M) following a [35S]GTPγS binding assay combined with immunoprecipitation was determined.

Chronic Δ⁹-THC did not affect PPI at basal levels, nevertheless it significantly potentiated (p<0.05) the DOI-induced reduction in the PPI. Additionally, a significant increase (p<0.01) in DOI affinity for G-protein pre-coupled population of 5HT2AR was observed in brain cortex of Δ⁹-THC-treated mice. Moreover, a significant increase (p<0.05) in the 5HT2AR-mediated stimulation of Gαi1, Gαi3, Gαo and Gαz protein subtypes but not of Gαs or Gαq/11 subunits was found in Δ⁹-THC-treated mice compared to controls.

Our results show that chronic Δ⁹-THC exposure induces a pro-hallucinogenic 5HT2AR conformation that may facilitate the development of psychosis-like states and enhances the 5HT2AR ability to activate specific pathways of inhibitory Gα protein subtypes in brain cortex.
FROM SAFETY BEHAVIORS TO SAFETY SIGNALS
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At the face fear provoking stimuli, individuals tend to escape. However, when that is not possible, they tend to resort to Safety Behaviors, such as calling a therapist or carrying medicine with themselves. Several studies have reported a fear reduction effect after the use of Safety Behaviors (Rachman, Shafran, Radomsky, & Zysk, 2011). Nevertheless, the mechanism responsible for such decrease is not clear. A recent study proposed that Safety Behaviors lead to Safety Signals, which in turn, alter the informational value regarding the occurrence of aversive outcomes, thus reducing fear responses (Restrepo-Castro, Castro-Camacho, Labrador, 2017). In other words, calling a therapist (Safety Behavior) may not itself reduce fear; the reassurance provided by the therapist (Safety Signal) may be responsible for such effect.

Objectives: The aim of the present work was to compare fear reduction associated to an instrumental process (analogue to Safety Behaviors) versus fear reduction associated to an informative process (analogue to Safety Signals).

Purpose: Contribute to the understanding of the mechanisms responsible for fear reduction after the use of Safety Behaviors.

Methods: A series of single research studies (N = 4) were conducted to address the aforementioned objective. Individuals who reported high levels of Public Speaking Anxiety were requested to provide a 5 minute speech in front of a video camera, while electrodermal activity and pulse were recorded. Two of the participants were presented reassuring words on a screen (e.g., good work, keep going) throughout the experiment. The other two participants were given the option to press a key, which prompted the same words displayed to the other participants (good work, keep going).

Results: Psychophysiological measures indicate fear reduction throughout the experiment in all participants. Subjective reports were consistent with this trend. The results support the idea that Safety Behaviors lead to Safety Signals.

Conclusions: The results suggest that instrumental behaviors are not necessary for fear reduction. The latter points to the potential advantage to emphasize on informational processes, rather than exclusively preventing avoidance (instrumental processes) during exposure-based interventions.

Literature Reference
N-ACETYLCISTEINE AND ETHANOL RELAPSE-LIKE DRINKING BEHAVIOUR: A PRECLINICAL STUDY
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There is increasing evidence that addiction to different drugs of abuse (such as cocaine, nicotine or ethanol) is related to alterations of glutamate homeostasis within the corticostriatal circuitry. The normalization of glutamate homeostasis by N-acetylcysteine (NAC), a precursor of cystine, has been suggested to decrease cocaine seeking and promote abstinence in preclinical and clinical studies. In the case of ethanol, the reported data with NAC are scarce and recent studies have shown that this drug is able to reduce voluntary ethanol intake in the rat. Nevertheless it should be remembered that one of the major concerns in the clinical treatment of alcohol-dependent patients is the prevention of relapse during periods of abstinence. In recent years, the alcohol deprivation effect (ADE) model has become a widely used paradigm in examining the efficacy of possible pharmacological agents to prevent relapse drinking. The fact that the clinically effective anti-relapse drugs naltrexone and acamprosate reduce or even abolish the ADE lends predictive validity to this model for the development of new and better drugs as treatment for relapse. For these reasons, the main goal of the present study is to evaluate whether NAC is able to prevent ethanol relapse-like drinking behavior using the ADE model under a four-bottle home cage paradigm. This long-term voluntary alcohol drinking procedure, including all deprivation phases, lasts around 40 weeks. The effects of NAC treatment have been studied along the fourth abstinence period and after the implantation of a mini-osmotic pump delivering either saline or NAC (1 mg per hour) during two weeks. In conclusion, and according to our preliminary results NAC seems to modify the ADE behaviour under the aforementioned experimental conditions.
REINFORCEMENT LEARNING OF SOCIAL VALUE IN RATS
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Objectives: Reinforcement learning theory states that when stimuli are added to stimulus that fully predicts reward, learning about those additional stimuli will be blocked (Kamin, 1969). Learning about added stimuli can become unblocked by an increase in reward value that is then associated to these additional stimuli (Holland, 1984). Here, we intend to show that unblocking could occur when the additional reward is delivered to a social partner.

Purpose: This project is aimed at demonstrating that rats can learn the social value of cues through observation of the benefit of rewards to others.

Methods: N=32 rats were trained in a novel social reinforcement learning task. First the rats learned a pavlovian discrimination task, where one was exposed to an auditory CS+ vs CS- and the other group to a visual CS+ vs CS-. When this discrimination was learned, rats went through compound conditioning. Now, rats of the different groups are trained together in pairs and are subjected to three compound stimuli. Compound 1 consists of both the visual CS+ and the auditory CS+, and both actor and partner rat are rewarded (Both reward/unblocked). Compound 2 consists of the CS+ for the actor rat paired with the CS- of the partner, and only actor is rewarded (Own Reward(blocked)). Compound 3 consists of previously learned CS- stimuli. After compound conditioning, rats went through a probe session in extinction. In this session, the original CS+ and CS- and the unblocked and blocked cue are presented to assess learned associative value through conditioned responding. Throughout the task, responding is quantified by recording the time spent in the nosepoke and the total number of nosepokes.

Results: Pilot results indicate good discrimination between both pairs of stimuli. We tested conditioned responding in an extinction session to the initially conditioned cues and blocked vs unblocked cues added in the compound phase. We hypothesised that responding to the socially unblocked cue would exceed responding to the blocked cue.

Conclusions: Learning about things that have value for others is a prerequisite for successful social navigation. If we find that rats are learning the value of cues by ways of observation of the benefit of others this will strengthen the body of evidence pointing to the existence of social other-regarding motivations in rodents.

Literature Reference
EMOTIONAL EMPATHY AND FACIAL MIMICRY FOR FEAR AND DISGUST
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Objectives: Empathy is a process that comprises affective sharing, imagining, and understanding the emotions and mental states of others. One aspect of empathy is the ability to react emotionally to the emotional expressions of other persons. Until recently, the impact of empathic traits on facial mimicry for other than happiness and anger displays has received little attention. In the light of published studies regarding a link between empathy and facial mimicry, we assumed that high compared to low-scoring empathic subjects would elicit stronger facial muscle responses, especially for dynamic displays, since real-life faces are dynamic by nature, particularly when expressing emotion.

Purpose: In present studies, we tested whether emotional empathy modulated facial mimicry for biologically relevant emotions, i.e., fear and disgust facial expressions.

Methods: Thirty-six healthy volunteers (18 females) participated in the study. EMG responses were recorded in the corrugator supercilii, levator labii, and lateral frontalis muscles, while participants viewed static (photos) and dynamic (videos) displays.

Results: In accordance with our predictions, the highly empathic group responded with larger activity in the corrugator supercilii and levator labii muscles. Moreover, dynamic compared to static facial expressions of fear revealed enhanced mimicry in the high-empathic group in the frontalis and corrugator supercilii muscles. In the low-empathic group the facial reactions were not differentiated between fear and disgust for both dynamic and static facial expressions.

Conclusions: We conclude that highly empathic subjects are more sensitive in their facial reactions to the facial expressions of fear and disgust compared to low empathetic counterparts. Our data confirms that personal characteristics, i.e., empathy traits as well as modality of the presented stimuli, modulate the strength of facial mimicry. In addition, measures of EMG activity of the levator labii and frontalis muscles may be a useful index of empathic responses of fear and disgust.

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Literature Reference
Patients with cocaine use disorder, a pilot clinical trial of the efficacy of an inhibitor of ALDH2

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Objectives: Soy beans contain different isoflavones, on of them is daidzein that is an inhibitor of aldehyde deshidrogenada-2. Inhibitors of aldehyde deshidrogenada-2 has been associated with a reduction of cocaine use in animals (ALDH2). It is interesting to know whether daidzein can be effective in cocaine use disorder.

Purpose: To carry out an exploratory clinical trial to evaluate the possible efficacy of a natural inhibitor of ALDH2 (daidzein) in patients with cocaine use disorder.

Methods: The design is unicentric, open, uncontrolled. During 12 weeks of treatment and 4 weeks more of tracking, urine analysis, Severity Dependence Scale(SDS), Brief Substance Craving Scale (BSCS) and Cocaine Selective Severity Assessment (CSSA) were conducted. An intention to treat analysis was performed and the data were analyzed with SPSS 18.0 statistical package.

Results: 9 human subjects participated with Cocaine Use Disorder (mean age of 48±9.2 and 88.9% were male). The 77.8%(7) of subjects end the study, no one was abstinence from cocaine during the last three weeks of the treatment, but SDS had a significant decrease between weeks 0-12(p=0.024), and weeks 0-16 (p=0.002). BSCS and CSSA decreased their values but not significant.

Conclusions: These preliminary results show a decrease of the severity and a high retention in treatment although patients did not reach abstinence. For these findings, we considered daidzein could be a potential therapeutic value for cocaine use disorder.

Literature Reference
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INFLAMMATORY CYTOKINES AND FUNCTIONAL IMPAIRMENT IN DRUG-FREE SUBJECTS WITH MOOD DISORDER


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Objectives: The aim of this study was to assess peripheral levels of inflammatory cytokines and functional impairment in subjects with BD and MDD compared to the population control. We also assessed the correlation between inflammatory cytokines and functional impairment.

Purpose: Evaluate the serum IL-6 and IL-10 levels and functional impairment in subjects with BD and MDD compared to the population control.

Methods: This was a cross-sectional study with a matched sample of drug-free young adults with BD (n = 48), MDD (n = 48) and population controls (n = 48). Mood disorder was confirmed by a certified psychologist using the Structured Clinical Interview for DSM-IV (SCID-I). Functional impairment was assessed using the Functional Assessment Short Test (FAST). Serum levels of IL-6 and IL-10 were measured by ELISA.

Results: Peripheral levels of IL-6 and IL-10 were not significantly different between subjects with BD, MDD compared to controls. Higher levels of functional impairment were verified in subjects with BD and MDD compared to population controls (p ≤ 0.001). In addition, IL-6 and IL-10 levels were positively correlated with functional impairment in subjects with BD (IL-6: r = 0.349, p = 0.016; and IL-10: r = 0.351, p = 0.016).

Conclusions: Inflammatory dysregulation was associated with functional impairment among drug-free subjects with BD. This finding suggests that inflammatory dysregulation may be involved in the neuroprogression of BD.
Objectives: The aim of this study was to investigate the changes in serum levels of BDNF, GDNF and NGF with suicidal behavior (including suicidal ideation (SI), suicide attempted (SA) and risk suicide (SR), as well as clinical characteristics, in sample adults with MDD.

Purpose: Evaluate the serum levels of neurotrophic factors in MDD suicidal patients.

Methods: This is a paired cross-sectional study nested in a population-based study. Individuals were rated for MDD and suicide behavior by a diagnostic interview – Mini International Neuropsychiatric Interview (M.I.N.I). The total population of the sample was comprised of 219 subjects distributed into the groups: subjects with current depressive episode without suicide behavior (MDD); subjects with current depressive episode and with SI (MDD+SI); subjects with current depressive episode and with SR (MDD+SR); and subjects with current depressive episode and with SA (MDD+SA). Serum levels of BDNF, NGF and GDNF were measured by ELISA.

Results: NGF serum levels were significantly reduced in the MDD+SA groups when compared with group MDD (p=0.0285). However, there were no differences in NGF levels between the MDD and MDD+SI and MDD and MDD+SR groups (p >0.005). Furthermore, there were no differences in BDNF and GDNF levels MDD, MDD+SI, MDD+SA and MDD+SR.

Conclusions: In our study, we highlighted the recent and ongoing studies on neurotrophic factors role, particularly NGF, in psychiatric diseases and we observed that NGF levels may be a marker of suicide behavior in relation of the attempted suicide. The development of new therapeutic strategies that augment the production of NGF can be an important adjunctive treatment option in patients with SB. Moreover, neurotrophins may serve as biomarkers, making possible understanding of the pathophysiology of MDD and SB, acting a tool in its diagnosis, treatment and clinical evaluation.
RESTING STATE FUNCTIONAL CONNECTIVITY OF THE NUCLEUS ACCUMBENS IN RECENTLY DETOXIFIED ALCOHOL DEPENDENT PATIENTS
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Objectives: The human brain is organised in specific networks composed of structurally separated regions that communicate continuously. While much is known of the health damages in alcohol dependence (AD), there is not enough known about its impact on functional connectivity within the neuronal reward system. In the current project (LeAD study, DFG FOR 1617) the nucleus accumbens (NAcc) has been chosen as representative seed region for this specific network.

Purpose: The aim of this project was to evaluate how the detection of potential functional changes in the resting brain of abstinent alcohol patients can be related to specific behaviour, such as future relapse.

Methods: Resting state fMRI (rsfMRI) data were acquired from 93 AD patients (14 females, age: M = 44.2, SD = 10.46) and 84 healthy controls (HC, 13 females, age: M = 43.59, SD = 11.23). Furthermore, AD patients were classified as prospective relapers (N = 49, 6 female, age: M = 44.22, SD = 9.44) or abstainers (N = 28, 6 female, age: M = 46.10, SD = 12.79) based on interviews within a 48 week follow up period after detoxification. For group comparisons between AD patients versus HC and relapers versus abstainers a permutation tests (5000 iterations) was generated and a significance threshold of p <.05 was used, threshold-free cluster enhancement (TFCE) was corrected for multiple comparisons across the brain.

Results: AD patients and HC did not differ in their resting state functional connectivity (RSFC), neither for the left NAcc nor for the right NAcc as seed region. Relapers and abstainers showed no difference in right or left NAcc RSFC either. In this project, AD protracted over three years or more did not modify the NAcc RSFC with any brain region.

Conclusions: Attempts were made to replicate seminal findings in the field of rsfMRI in addiction with an improved and clean design as well as a large clinical sample of AD patients. Furthermore, a wide pre-processing and robust rsfMRI analyses were applied. However, null-findings from this project must be taken seriously in view of existing findings in RSFC.
PILOT PROJECTS OF REGULATED ACCESS TO CANNABIS IN SWITZERLAND: MOTIVES OF POTENTIAL PARTICIPANTS

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We are witnessing an increasing awareness concerning the failure of the war on drugs, supported among others by position papers of the Global Commission on Drug Policy and the UNODC. This progressive change of vision resulted in marijuana law or jurisdiction changes in various countries. In Switzerland, the cities of Geneva, Zurich, Bern and Basel have formed a working group to conceive pilot projects of regulated access to cannabis.

Method
A research group representing the Universities of the four concerned cities has realized an online survey (December 2016 – January 2017) to estimate the number of potential participants for such pilot projects and to question them about their consumption motives. To assess the association between the consumption motives and self-assignment to one of the proposed consumer categories (Recreational, Self-Care or Problematic Use) a multinomial logistic regression was performed with Recreational as the reference category.

Results
Among the 3454 participants included into the analyses, the following consumption motives predicted self-assignment to the Self-Care group: to enhance concentration (p<0.001), to reduce sadness (p<0.001), to improve sleep (p<0.001), to alleviate worries (p<0.05), to ease pain (p<0.001), to reduce cramps (p<0.001), and to reduce fears (p<0.01). The probability of self-assignment to the Self-Care group was, however, reduced by following motives: to enhance fun being together (p<0.001), to have fun at parties (p<0.001), to get high (p<0.05), and because it is fun (p<0.001).

The probability of self-assignment to the Problematic Use group was increased by: to reduce sadness (p<0.001), to improve sleep (p<0.05), to alleviate worries (p<0.001), to have fun at parties (p<0.05), to get high (p<0.001); and reduced by: to facilitate new experiences (p<0.01), to enhance fun being together (p<0.01), to enhance pleasant feelings (p<0.01), and because it is fun (p<0.05).

Conclusions
Self-assignment to a Self-Care group was consistently predicted by self-care motives and the probability reduced by hedonic motives. Self-assignment to the problematic Use group was correlated to mixed motives.
IS AN HABITUATION TRAINING PROGRAM IN A FORCED RUNNING WHEEL AN STRESSING CONDITION?
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Habituation training protocols are determinant to enhance the locomotor performance in forced exercise conditions. The habituated rats exposed to exercise programs reach higher speeds and cover longer distances compared to the non-habituated ones. This improvement is progressively decreased over time without a permanent training. Several mechanism could contribute to support a higher exercise load following a progressive habituation protocol. Physical activity produces biochemical changes that upgrade muscular aerobic metabolism. However, evidence using treadmill suggests that higher charges of exercise than used during the habituation are necessary to induce muscular endurance. On the other hand, plasmatic lactate and glucose levels are increased during acute running; and can be related with stress responses and the running improvement. The aim of our work was to evaluate the plasmatic lactate and glucose fluctuations during the habituation protocol in a forced running-wheel system. Sprague Dawley rats were randomly assigned to either a group that received an exercise training habituation protocol, or a control group. The habituation protocol was developed during 8 days followed by 10 sessions that increased progressively the speed and the time spent running. Plasmatic lactate and glucose concentrations were determined previous to start (5 min -A-), after finish each session (5 min -B-), and 30 min once finished each session (30 min -C-). The mean value of lactate for each extraction was 3,4 ±1,55 mmol/l (A), 3,2 ±1,67 mmol/l (B) and 3,2 ±1,67 mmol/l (C), without any statistically significant difference between experimental and control (p>0,10). The mean value of glucose for each extraction was 164,3 ±16,99 mg/dl (A), 167 ±18,62 mg/dl (B) and 170,4 ±19,77 mg/dl (C), without any statistically significant difference between experimental and control (p>0,10). These data suggest that the forced running wheel is not stressful during the habituation training.
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TEMPORAL SIGNATURES OF VOCAL EMOTIONAL RECOGNITION

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Objectives: The current study adds to emotional prosody research by shedding light on the time required to identify emotions from nonverbal vocalizations. We demonstrated that the amount of vocal information that is necessary to decode the emotional meaning of nonverbal emotional vocalizations varies as a function of emotion type.

Purpose: The main purpose of the current study was to probe the minimum stimulus duration for accurate recognition of different vocal emotions selected from the Montreal Affective Voices (MAV; Belin et al. 2008) battery.

Methods: 52 European Portuguese individuals (mean age = 23.42, SD = 7.80 years, ranging from 18 to 49 years; 27 females) participated in the current study. 58 MAV nonverbal vocalizations conveying anger (n = 10), disgust (n = 10), fear (n = 8), happiness (n = 10), sadness (n = 10) and neutral (n = 10) states were selected. An auditory gating paradigm, in which listeners were presented with increasing (cumulative frequency) amounts of vocal emotional nonverbal information, was used. Stimulus duration was equally shortened to encompass seven distinct temporal intervals (100-700 ms), yielding a total of 406 vocalizations.

Participants were asked to complete a forced-choice recognition task.

Results: To control for listeners’ response biases, unbiased recognition accuracy rates (Ha score; Wagner, 1993) were computed for each discrete emotion and time interval. Listeners needed less time to accurately recognize happiness, sadness and disgust (400 ms) than anger and fear (700 ms) vocalizations. Differences between each emotion type were also observed within each gate duration: happiness and anger vocalizations were, respectively, the most accurately and the most poorly recognized.

Conclusions: These findings suggest that the amount of information necessary to decode emotional meaning from nonverbal vocalizations varies as a function of emotion type. Further, they add to existing research by shedding light on the critical role of stimulus duration in vocal emotional perception and recognition. The time course underlying accurate recognition of vocal emotions has received little attention so far. This study provides the starting point for further research aiming to unveil temporal effects in vocal emotional perception.

Literature Reference:
EFFECTS OF THREAT IN INDIVIDUAL AND SOCIAL SPACE: AN ERP STUDY
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We measured the electrical brain response during the visual processing of threat in individual (Near/Far) and social (Near the other) space. Using an experimental set-up from previous studies [1,2] participants had to indicate whether the objects (threatening/non-threatening insects) were near enough to be reached. Stimuli were presented at nine positions displayed on a 52”inch-long screen placed orthogonally to participants’ location. In one block, participants performed the task alone while in the other the experimenter sat at the opposite side of the screen. We replicated previous effects showing faster responses to objects presented in Near space than in Far-space and found a significant interaction of threat, space and social context. When performing the experiment on their own, affective modulations were observed in Near-space but not in Far-space. However, when the experimenter was seating at opposite side of screen, the same effect of threat was observed in Far-space (Near the other). Analyses of ERPs replicated previous results of faster latencies and greater amplitudes in N1 occipital component for objects presented in near space. Additionally, we found centro-parietal (CP) negative modulation sensitive to threat at around 500ms. As in RT measures, this modulation was only for objects in Near-space when completing the task alone. When the experimenter was located at the opposite side of the screen, the (CP) modulations disappeared and new effects of threat were found at frontal electrode sites in a Negative component peaking around 400ms. Our results suggest the action of different brain systems involved in the processing of threat to us and threat to others. A centro-parietal system for the individual space, and a frontal system for the space of others. The slower modulation of individual space may be due to the interaction between affective features and the spatial location when we have to react to a potential threat.

INFLUENCE OF EMOTIONAL CONTEXTS ON FACIAL EMOTION ATTRIBUTION IN SCHIZOPHRENIA
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Objectives: One of the most consistent results in emotion recognition studies in schizophrenia is the misattribution of emotional content to neutral faces (e.g., Romero-Ferreiro, 2016). These studies have been carried out by presenting faces in absence of any other sources of information. However, in daily life, facial expressions are usually perceived within a certain situational context.

Purpose: The main goal of the present work was to study whether or not emotional contexts bias perception of emotionally neutral faces leading to a misattribution of emotionality.

Methods: Participants performed an emotion categorization task with neutral faces that were superimposed on pictures showing affectively positive, negative or neutral scenes. They were asked to categorize neutral faces by choosing one label among six options. Second, they were also asked to rate the valence of the faces on a 1 to 9 Likert scale (ranging from “very unpleasant” to “very pleasant”).

Results: In the presence of positive and negative contexts, patients tended to categorize neutral faces as fearful more frequently than controls (p = .004; p = .003, respectively). However, this effect was not found with neutral contexts. On the other hand, affective ratings were biased by the valence of the context (e.g., neutral faces were rated as more negative after negative than after positive contexts) to the same extent in both groups.

Conclusions:
- The presence of emotional contexts (positive or negative) triggers a bias towards misattributions of negative emotions to neutral faces in patients with schizophrenia. However, in the presence of neutral contexts patients' responses do not differ from the controls.
- These results provide new evidence on the role of contextual modulation of emotion recognition in schizophrenia that might be used to inform improved intervention programs in the domain of social cognition in this pathology.

HEIGHTENED SENSITIVITY TO ENVIRONMENTAL INFLUENCES HAS A GENETIC BASIS: HERITABILITY TO MOLECULAR GENETIC RESULTS
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Objectives: According to the differential susceptibility theory (Belsky & Pluess, 2009) individuals differ in the extent to which they are impacted by the context of their environment and that individual differences in heightened sensitivity to context have a genetic basis. Our main objective was to address an empirical gap in research by identifying the genetic factors that are associated with trait-like environmental sensitivity using genome-wide data.

Purpose: The main purpose of the project was to identify the genetic variants that are associated with heightened sensitivity to environmental influences.

Methods: We used the Highly Sensitive Child scale to index trait-like environmental sensitivity, in a large sample of adolescent twins (N = 2,868) from the Twins Early Development Study in the United Kingdom. Heritability of environmental sensitivity and its genetic overlap with the big-five personality traits were estimated using twin design methodology. Next, we conducted genome-wide association study, polygenic scoring and gene-based analyses to identify the genetic variants associated with environmental sensitivity, using summary statistics from large GWAS data from the Social Science Genetic Association Consortium on personality (N = 170,911) and subjective well-being (N = 298,420) in our sample of 650 individuals.

Results: Highly sensitive personality was found to be 47% (CI = 30-53) heritable. High environmental sensitivity was significantly correlated with neuroticism (r = .34) and extraversion (r = -.18), and these phenotypic correlations were mainly due to the effect of overlapping genetic influence. Polygenic scores of neuroticism and subjective well-being significantly predicted our phenotypic measure of environmental sensitivity in the TEDS sample (up to 2%). We did not find significant associations from the GWAS or gene-based analyses.

Conclusions: The results supported theoretical predictions that trait-like environmental sensitivity is heritable. The proportion of variance explained by the polygenic score from common genetic variants was small, indicating that, similar to other complex traits, individual differences in environmental sensitivity is a function of many genetic variants of small effect sizes.