Mediterranean Neuroscience Society

www.mnsociety.net

MALTA NEUROSCIENCE NETWORK

6th Mediterranean Neuroscience Society Conference 2017

MALTA MNS2017

Radisson BLU, St Julian's, Malta, June 12 – 15, 2017

Organised by the Mediterranean Neuroscience Society (MNS) Hosted by Malta Neuroscience Network, University of Malta, Malta

http://www.mnsmeeting2017.com/

POSTERS

WELCOME MESSAGE

Dear Colleagues,
It is my great pleasure to welcome all delegates on behalf of the Malta Neuroscience Network of the University of Malta to the 6th Mediterranean Neuroscience Society (MNS) Conference 2017, in Malta.
This biennial MNS Conference, unlike most regional events, will bring together neuroscientists from Mediterranean regions and worldwide international experts at the forefront of basic and clinical neuroscience; moreover, it is being held in a vibrant fun location.
The President of MNS, Marc Landry, the Vice-President Liana Fattore, myself and the other members of the scientific committee have worked hard for a very successful event, both scientifically and socially. The MNS2017 programme is exceptional. It includes 8 plenary lectures, the FENS special lecture, more than 60 symposia and hundreds of poster presentations which will further stimulating interaction between participants. This 6th MNS Conference will surely be a memorable experience.
The 6th MNS Conference has been organised with the support of the University of Malta, one of Europe's oldest universities in one its most beautiful Mediterranean islands, and Malta Chamber of scientists. We also thank FENS, IBRO and all the out other partners for their support.

I very much am looking forward to seeing you at the 6th MNS Conference in Malta!

MALTA NEUROSCIENCE NETWORK

Giuseppe Di Giovanni
Coordinator of Malta Neuroscience Network
President of the Local Organizing Committee

The MNS has been created to support and help strengthen all initiatives that bring together Mediterranean neuroscientists.

The last Mediterranean Conference of Neuroscience was organized in June 2015 in Pula (Italy), four previous successful editions (Montpellier 1997**,** Marrakech 2006, Alexandria 2009**,** Istanbul 2012).
These conferences gathered scientists from all Mediterranean countries and offered a rich program with lectures, symposia poster sessions and social events.

These meetings have proved to be highly beneficial, not only for the scientific exchanges, but also in terms of training opportunities for students and young researchers.

Research on brain function in health and disease is among the priorities for today's societies, and several indicators put the Mediterranean research area among strategic issues for the European Union (EU).

Many South-North collaborations and networks have emerged in recent years through bilateral and multi-lateral actions, supported by the EU or by international and national actions, whether for setting up teaching curricula (Tempus programs), or by building human potential (Horizon programs).

Objectives of the MNS
The MNS works towards three main objectives:

- Strengthen exchanges between Mediterranean neuroscientists
- Promote education in the neurosciences and increase public awareness of progress made
- Sustain the Mediterranean Neuroscience Conference
- To reach these objectives, the MNS's policy is to work in close cooperation with existing national and international Neuroscience Societies.

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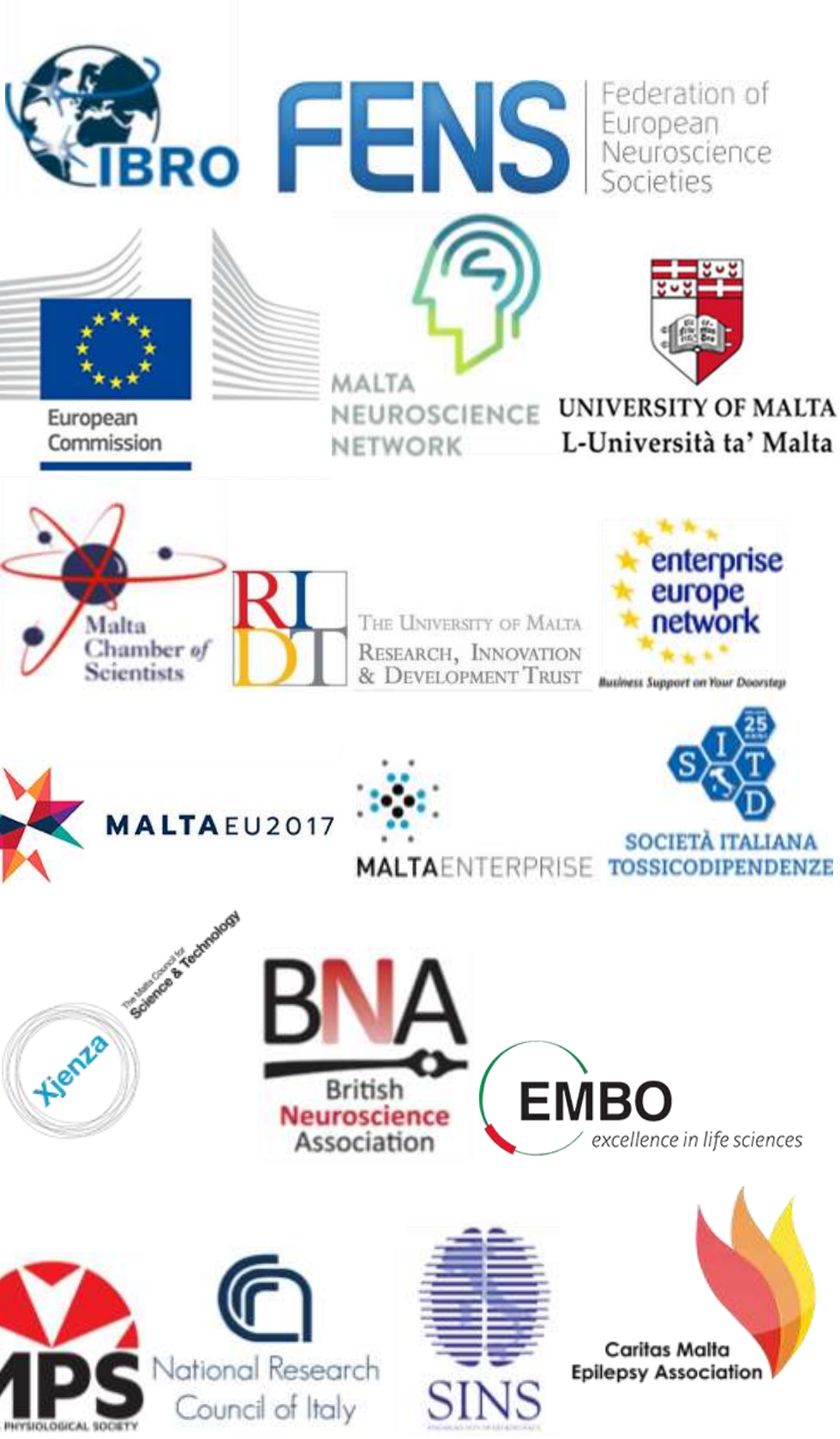

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Secretariat of the 6th MNS Meeting 2017
Sandra Brincat
ECMeetings
sandra@ecmeetings.com

INFORMATION FOR SPEAKERS AND CHAIRPERSONS

The role of the chairpersons is to monitor speaking and discussion times and to lead the discussions. Chairpersons control the switch between presentations.

Use a presentation in the 4:3 format. All speakers must submit their presentations in the Secretary Room, on the ground level of the venue in the Ballroom, at least 2 hours before the start of their session in order to check their slides with the technical staff and upload the presentation onto the network.

Multimedia Considerations and Slide Preparation
Presenters: Make your presentations compatible with on-site audio/visual specifications.

All screens in Malta will be 4:3 widescreen format.

...Before Traveling (Recommended)…

It is highly recommended to send your presentation by email from the 5th to the 11th of June to: malta.neuroscience@gmail.com SPECIFYING IN THE SUBJECT Symposium number and Symposium presentation (e.g. S33.2 Symposium n 32 presentation n 2).

Speakers can upload their presentations at any time from the beginning of the Conference and do not need to wait until the day of presentation. Speakers in morning sessions are strongly advised to pre-load their presentation the day before.

Data presentation:

If using a PowerPoint presentation (or any other PC based application), please note you need to bring it on a USB Memory stick and load it on one of the Conference computers in the Secretary Room at least 2 hour before the start of the session.

Please note that the conference computers in the session halls are being supplied with Office 2013.
If combining video films with PowerPoint, please make sure to check it in the session hall where your lecture is taking place during a coffee or lunch break prior to your session, at least 30 minutes before the start of the session - even after checking it in the Speakers' Ready Room.
Alternatively you may supply your own laptop computer. In such a case please confirm that it has a VGA socket for external signal and **come to check it first in** Secretary Room as soon as you arrive and later on in the session hall where your lecture is taking place during the coffee or lunch break prior to your session, at least 30 minutes before the start of the session.

Important note for Macintosh users

In order to use MAC presentations on a PC compatible computer please note that you need to prepare it according to the instructions below, before bringing it to the Secretary Room:
» Use a common font, such as Arial, Times New Roman, Verdana etc.
(special fonts might be changed to a default font on a PowerPoint based PC).
» Insert pictures as JPG files (and not TIF, PNG or PICT - these images will not be visible on a PowerPoint based PC).
Alternatively you may use your own Macintosh laptop computer. In such a case please confirm you provide it with a **VGA adaptor** for external signal, advise the operators in the Secretary Room about it as soon as you arrive and later on test it in the session hall where your lecture is taking place during the coffee or lunch break prior to your session, at least 30 minutes before the start of the session.

POSTER INFORMATION

Poster Presentations

Whole-day poster presentations take place in the Poster Area of the exhibition hall in front to the main restaurant from Monday through Thursday, June 12-15. Authors are requested to be in attendance at their poster for discussion, as scheduled below:

Monday, June 12 – Thursday, June 15
08:00 - 16:15 **Poster session**
12:30 - 14:00 **All poster authors in attendance**

Please find your board number by locating your abstract on the programme book.
You should display your poster on the board number assigned to you.

Poster boards are 2 meters high and 1 meter wide (portrait format).

Posters can be affixed by double-sided adhesive tape, available at the Poster Assistance desk onsite.
Posters should be mounted at 08:00 am.
Removal: Posters from the day sessions must be removed imperatively at the end of the day of presentation. Please respect this removal so that the following poster presenters can mount their material.
The organisers cannot be responsible for posters not removed by the above stated time.

POSTERS

Monday, June 12th 2017

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Department of Peripheral Nervous System Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Japan.

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P12.1

ANTI-INFLAMMATORY DRUGS EXERT ANTIDEPRESSANT-LIKE EFFECTS AND REDUCE BRAIN LEVELS OF IL-6 IN RATS

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A large body of data suggests that inflammation plays a role in the pathophysiology and treatment of mood disorders. Consistently, anti-inflammatory drugs were found to exert mood-stabilizing effects in randomized clinical trials of mood disorders patients.
This study was undertaken to: *i*) Examine the anti-depressive-like effects of the anti-inflammatory drugs dexamethasone (DXM, a potent anti-inflammatory corticosteroid) and pentoxifylline (PTF, a tumor necrosis factor-α inhibitor) in rats subjected to a depression-inducing protocol; and, *ii*) determine the effects of DXM and PTF on interleukin (IL)-6 levels in hypothalamus (HT) and hippocampus (HC) of the "depressed" rats.
Rats were subjected to an unpredictable chronic mild stress (UCMS) protocol for 6 week during the last 2 weeks of which they were treated (intraperitoneally) daily with DXM (1 or 2 mg/kg) or PTF (10 or 50 mg/kg). Rats were subjected to a sucrose consumption test at different time-points. Moreover, at the end of DXM and PTF treatment rats were subjected to a forced swim test (FST). One day after FST rats were sacrificed, their brains were ousted and HT and HC were extracted. HT and HC were homogenized, centrifuged and supernatants were separated for determination of IL-6 levels by ELISA.
Sucrose consumption was significantly lower in UCMS rats. PTF but not DXM significantly increased sucrose consumption in UCMS rats, suggesting an antidepressant-like effect of PTF. Consistently, PTF significantly reduced immobility time in the FST. Moreover, PTF significantly decreased IL-6 levels in HT and HC while DXM (2 mg) reduced IL-6 levels only in HC. These results suggest that PTF exhibits anti-depressive-like effects which may be associated with its inhibitory effect on IL-6 production in the brain.

P12.2

NEURONAL AND BEHAVIORAL CORRELATES OF PHASIC AND SUSTAINED FEAR IN FREELY BEHAVING MICE

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Sustained fear paradigms in rodents have been developed to model clinical situations in patients suffering from long-lasting anxiety disorders. The bed nucleus of the stria terminalis (BNST), as part of the extended amygdala, has been shown to be critically involved in processing of sustained fear responses to more diffuse and unpredictable than discrete and predictable threats. We used a recently established fear conditioning paradigm, which allows the distinction between phasic and

sustained states of conditioned fear in non-restrained mice to investigate neuronal and behavioral correlates of phasic/sustained fear.
Thus, we examined different states of conditioned fear (fear-potentiated startle, freezing), induced by predictable or unpredictable training (CS-US timing), on single unit activities in the BNST and on anxiety-like behavior in the elevated plus-maze during fear memory retrieval.
Electrophysiological data, based on intra-BNST unit recordings and a non-biased cluster-analysis, revealed 3 distinct neuronal subpopulations: biphasic-, sustained fear on- and sustained fear off-neurons in the anterolateral BNST. Biphasic- and sustained fear on-neurons indicated the shift from phasic to sustained components of fear, with sustained fear on-cells being activated during sustainment of fear. Behavioral data, based on the elevated plus-maze test, revealed that phasic and sustained states of fear can differentially affect anxiety-like behavior: induction of sustained fear increased anxiety and, induction of phasic fear lead to reduction of anxiety during fear memory retrieval. Our data provide evidence of i) the existence of sustained fear on- and biphasic-neurons confirming the pivotal role of the BNST in processing of sustained fear on the neuronal level, and ii) altered anxiety states using the phasic/sustained fear paradigm in freely behaving mice after predictable or unpredictable CS-US timing.
With this study, we advise the phasic/sustained fear model in rodents to investigate molecular and neuronal mechanisms of phasic and sustained fear with particular focus on the BNST as a target for the development of novel therapeutic strategies. Finally, we want to promote this animal model as an appropriate translational model for human anxiety disorders.

P12.3

ALTERATIONS OF ULTRASONIC VOCALIZATION (USV) IN PURKINJE CELL SPECIFIC TSC1 KNOCKOUT MOUSE

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Mice, and other rodents, are able to communicate using sounds in the ultrasonic range called ultrasonic vocalizations (USV). Quantitative and qualitative analysis of this activity gives information about the social interactions, for example in animal models of autistic spectrum disorders (ASD). USV was analyzed in a mouse model of tuberous sclerosis complex (TSC), where progressive degeneration of Purkinje cells (PC) occurs. TSC is an inherited human disorder with autistic like behavioral manifestations.
To evaluate the influence of PC insufficiency on USV activity, recordings of USV were made in transgenic mouse line lacking expression of hamartin (TSC1) in PC. USV was recorded in newborns from 2 – 14 postnatal day (PND) with use of the isolation test protocol. Transgenic mouse line used for the experiments was established by PC-specific knockout of the *TSC1* gene. All animal used in that

experiment were bred in the animal facility of the Department of Experimental Medicine at the Medical University of Silesia in Katowice. All experimental procedures were planned and performed according to the permission obtained from the Local Committee for Animal Experiments and Welfare.
This approach resulted in a progressive generation of PC in the cerebellar cortex. Analysis of obtained data revealed developmental changes in the USV activity of the pups with some traits characteristic only for the TSC1 knockout animals.
We concluded, that the progressing impairment of PC physiology resulted in disturbance of motor functions of the vocal apparatus and cerebellum dependent alterations of the social behavior.

P12.4

THE FAVORABLE IMPACT OF TIANEPTINE ON THE EVOKED BY PRENATAL STRESS DYSREGULATION OF CHEMOKINE-CHEMOKINE RECEPTOR AXIS IN BRAIN OF ADULT OFFSPRING RATS

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The impact of stress during pregnancy has received increasing attention. In the CNS the role of chemokines seems to be very intriguing. They are involved not only in neuro-immuno-modulation but also regulation of neurodevelopmental processes. Disturbances in chemokine and their receptors axis may be involved in the pathogenesis of depression.
The aim of present study was to examine whether prenatal stress influence on the CX3CL1 and CXCL12 level in the frontal cortex (Cx) and hippocampus (Hp) of adult rats offspring. The impact of chronic tianeptine administration on this system were evaluated.
Pregnant rats were subjected to restraint stress. At 3 months of age, control and prenatally stressed rats were tested for behavioral changes in Porsolt test. After that male offspring were administered i.p. for 21 days with tianeptine. The animals' behaviour was tested again. The mRNA expression of all analysed chemokines and their receptors was measured by qRT-PCR assay. The protein level was determined by ELISA assay.
Prenatal stress causes long-lasting behavioral alterations expressed as an increase in immobility and a decrease in swimming and climbing time measured in the Porsolt test. Chronic treatment of tianeptine normalized all above-mentioned changes in prenatally stressed offspring. Prenatal stress diminished mRNA and protein of CX3CL1 and CX3CR1 in the Cx and Hp. In brain of prenatally stressed rats expression of CXCR4 was decreased and levels of CXCL12 and its receptor CXCR7 were elevated. The chronic tianeptine administration attenuated all evoked by stress changes in chemokine- chemokine receptor axis.
Prenatal stress procedure leads not only to persistent behavioral disturbances but also malfunction in brain chemokine-chemokine receptors network. Brain chemokines systems can be indicate as a potential attractive target for antidepressant drug action.
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P12.5

EFFECT OF CO-TREATMENT WITH ARIPIPRAZOLE AND ANTIDEPRESSANTS ON THE MK-801-INDICED CHANGES IN THE OBJECT RECOGNITION TEST IN RATS

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Schizophrenia is a devastating psychiatric disorder that impairs mental and social functioning and affects approximately 1% of the world's population. It is known that in contrast to pharmacotherapy with typical antipsychotics, atypical antipsychotic agents alleviate not only the positive symptoms of schizophrenia but also the negative ones, but those effects are small and mechanisms of this action are still unknown. A few clinical reports have suggested that antidepressant drugs are able to augment the activity of atypical antipsychotic drugs, thus effectively improving treatment of the negative and some cognitive symptoms of schizophrenia.

In the present study, we aimed to evaluate the effect of antidepressants (escitalopram or mirtazapine) and aripiprazole (an atypical antipsychotic drug) given separately or jointly, on the behavioral deficits induced by MK-801 (a NMDA receptor antagonist) given prior to the first introductory session, in the object recognition memory test. The experiments were conduced in a black polyvinyl chloride box (57×67×30 cm). Male Sprague-Dawley rats (230-250 g) were tested for the ability to discriminate between an old, familiar and a novel object. Antidepressants and aripiprazole were given 30 min before MK-801, and MK-801 was administered 30 min before the first introductory session. Memory retention was evaluated for 5 min, starting 60 min after the introductory session.

The present results showed that MK-801 (0.1 mg/kg) decreased memory retention when given before the introductory session. Aripiprazole (0.3 and 1 mg/kg) reversed that effect. Co-treatment with an inactive dose of aripiprazole (0.1 mg/kg) and escitalopram or mirtazapine (5 mg/kg, but not 2.5 mg/kg) abolished the deficit of object recognition memory induced by MK-801.

The obtained results suggest that antidepressants may enhance the antipsychotic-like effect of aripiprazole in the animal test used for evaluation of some cognitive symptoms of schizophrenia.

This study was financially supported by statutory funds of the Institute of Pharmacology, Polish Academy of Sciences, Kraków, Poland.

P12.6

THE ANTIDEPRESSANT EFFECTS OF KETAMINE ON THE LATERAL HABENULA AND THE BEHAVIOUR OF NORMAL, RESTRAINT STRESS AND MATERNALLY DEPRIVED RATS

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Depression accounts for around 800,000 deaths globally every year, therefore there is a need to produce an antidepressant with a rapid onset of action and sustained effects, which is shown with ketamine. Ketamine, a NMDA antagonist, has been

linked with the decrease of neuronal activity in the lateral habenula (LHb), which is an important structure in modulating the midbrain's monoaminergic system, and is typically hyperactive in depressed patients. The aim of this study is to investigate the antidepressant effects of ketamine and citalopram in normal rats and in animal models of depression by using a behavioural and electrophysiological approach.
Control rats, randomly assorted into 3 groups received either ketamine 10 mg/kg, citalopram 10 mg/kg or saline 1 ml/kg (n = 10 for each group) and underwent to forced swim test (FST) and elevated plus maze (EPM) test. Following the behavioural study, cells-per-track experiments were performed in the same rats to investigate the effects of these treatments on the LHb basal neuronal activity, by using standard *in vivo* single unit electrophysiology. Moreover, the effect of intravenous ketamine (0.25-8 mg/kg; n = 20) on the LHb neuronal activity was investigated in control and chronically-stressed rats (an animal model of depression) by using extracellular *in vivo* recording technique.
Preliminary results in normal rats show that ketamine and citalopram induced an antidepressant-like effect in the FST, as well as a decrease in anxiogenic behaviour in the EPM test. In chronically-stressed rats, ketamine produced a reduction of LHb basal firing rate by greater than 50%.
These results show that ketamine potentially has an antidepressant effect, as well as causing inhibition of the LHb neuronal activity of the depressed rats. Future studies need to be conducted in order to understand if these two phenomena are mere epiphenomena or causally correlated to be involved in the antidepressant mechanism of ketamine.

P12.7

A NEUROIMAGING STUDY ABOUT EMOTIONAL PERSPECTIVE-TAKING: AN FMRI STUDY

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Perspective-taking is one of social cognitive function, and the ability of taking either one's own perspective or the perspective of others is very important for people to live in social community. This study aimed to investigate the difference of brain activity in viewing common emotional situation according to perspective-taking.
Using fMRI, brain activities were measured while performing the task viewing common emotional situation (happy, anger, sad, neutral) on either his own perspective (self-perspective) or the perspective of his mother (third-person perspective) in fourteen healthy men. The relatively activated brain areas on either self-perspective or third-person perspective were investigated, then the relationship between the activated brain region and the scores of self report about some emotion or empathic ability were explored.
The relatively activated brain area on self-perspective were bilateral paracentral lobule (BA 5), right postcentral gyrus (BA 3), right precentral gyrus (BA 4), left superior temporal gyrus (BA 22), left medial frontal gyrus (BA 6), whereas on third-person perspective were right inferior frontal gyrus (BA 47), left caudate body and tail, right superior temporal gyrus (BA 38), right medial frontal gyrus (BA 8). The relative activity of left superior temporal gyrus on self-perspective was positively correlated with the score of Beck Depression Inventory.

This study demonstrated that the activated brain region according to perspective-taking were different while viewing common emotional situation. The depressive feeling would have influence on the brain activity related to perspective-taking.

P12.8

BRAIN MORPHOLOGY AND FUNCTIONAL CHANGES ASSOCIATED WITH VISUAL SEXUAL AROUSAL IN MENOPAUSAL WOMEN

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This study utilized a combined use of fMRI and voxel-based morphometry (VBM) to assess the brain morphological and functional alterations in menopausal women. Twenty premenopausal women and 20 menopausal women underwent functional and structural MRI. Brain functional activity was measured while viewing an erotic video. The activation maps were obtained from the contrast of 30 sec sexual activation period versus 30 sec neutral period. An analysis of covariance (ANCOVA) adjusting for age was used to evaluate the differential functional and morphological alterations between the two groups. Compared with premenopausal women, menopausal women showed significantly decreased activity in the precentral gyrus, orbitofrontal gyrus (OFG), superior frontal gyrus, and dorsolateral prefrontal cortex while viewing the erotic video clips ($p<0.00$). In morphometric analysis, menopausal women exhibited significantly decreased gray matter (GM) volumes of the supplementary motor area, OFG, middle temporal gyrus, and insula and decreased white matter (WM) volume of the precentral gyrus compared with premenopausal women ($p<0.005$). In addition, the GM volume changes in the OFG were positively correlated with blood-oxygen-level-dependent (BOLD) signal changes in the OFG during sexual arousal in menopausal women. This study highlights the relationship between menopause-related morphological and functional alterations in menopausal women. The decreased GM/WM volumes and reduced functional activity together are closely associated with the symptoms of menopause. This research was supported by the NRF grants funded by Korean Government, the Ministry of Education (2014R1A1A2006730) and MSIP (2015R1A2A2A01007827).

P12.9

THE LONG TERM BRAIN EFFECTS OF BINGING ON ALCOHOL AND MARIJUANA IN ADOLESCENT TOBACCO USERS: A STUDY ON MOTIVATION IN OPERANT FOOD-REINFORCED RESPONDING; "THE PACEVILLE PROJECT: II"

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This study is focused on the long term effects on motivation of nicotine administration together with binging on cannabinoid and alcohol during adolescence

in Long Evans rats. This research focuses on the effect of this combination of drugs, which is on the increase in human adolescents, on the developing brain.
P30 males (treatment and vehicle groups, n=10 each) and females (treatment and vehicle groups, n=10 each) rats were treated daily with 1 mg/kg of nicotine intraperitoneally for 28 days, together with twice weekly (Binging Days) for four weeks intraperitoneal injections of 1.2 mg/kg WIN55,212-2 mesylate and 3 g/kg ethanol via gavaging or with their vehicles respectively. At P90 these rats underwent a starvation regime and after reaching an approximately 85% of ad libitum body weight were tested for six consecutive days on a FR1 schedule followed by a 42 days of rest and then another six days of daily FR2 schedule testing. Latency and response for the task completion were recorded for each rat.
Results revealed that in the FR1 schedule, treated female rats' rate of response was significantly less than female control rats, during day 3 ($\chi^2(1)=4.341,p=0.037$), 4 ($\chi^2(1)=6.874,p=0.009$), 5 ($\chi^2(1)=4.056,p=0.044$) and 6($\chi^2(1)=4.229,p=0.040$). A lower rate of response by treated females was also produced during the 6th day FR2 schedule ($\chi^2(1)=4.977,p=0.026$) when compared to control females. Control and Treated males did not show any significant difference in FR1 and FR2 schedules. Significant difference was observed in day 3 ($\chi^2(1)=2.301,p=0.050$), 4 ($\chi^2(1)=4.056,p=0.044$), 5 ($\chi^2(1)=4.341,p=0.037$) and 6($\chi^2(1)=3.598,p=0.050$) of the FR1 schedule between treated males and treated females, with evident impairment in females.
The combined treatment with cannabinoids, alcohol and nicotine in adolescence affected more adult female rats compared to males, revealing them at first glance a gender-related alteration of motivation system.

P12.10

LORCASERIN, A SEROTONIN2C/2A RECEPTOR AGONIST, PREFERENTIAL MODULATES MESOLIMBIC VS. NIGROSTRIATAL DOPAMINERGIC FUNCTION: AN *IN VIVO* ELECTROPHYSIOLOGICAL AND MICRODIALYSIS STUDY

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Serotonin-2C Receptors (5-HT_{2C}Rs) have been associated with numerous physiological responses including mood disorders, drug abuse and feeding behaviour. Very limited pharmacotherapeutic options exist to selectively target the 5-HT2CRs. Lorcaserin is a highly selective 5-HT_{2C}R agonist that has been recently approved by the FDA for the treatment of obesity disorders. The effect of lorcaserin on dopaminergic function has not yet been investigated, even though serotonin (5-HT) is known to be a major modulator of dopamine (DA) neural activity and 5-HT_{2C}Rs might be a principal mechanism by which 5-HT inhibits DA function. The aim of this study is to analyse the effect of lorcaserin on the neuronal activity of DA cells of the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc), as well as its effect on DA terminal release at the Nucleus Accumbens and Striatum.

The neuronal activity of single DA cells was recorded by standard extracellular recordings from the VTA and SNc in anaesthetised SD rats. Lorcaserin was administered in cumulative doses (5-640 μg/kg, i.v.) fashion. In the antagonism experiments, the 5-HT_{2C}R selective antagonist SB242084 (200 μg/kg, i.v.) was given 5 min before lorcaserin. The effect of lorcaserin (3-10 mg/kg) on extracellular monoamine and metabolite levels were measured using online microdialysis and the tissue levels of DA and metabolites were assessed using HPLC.
Results showed that lorcaserin (n=10) significantly reduced ($p<0.05$) the firing rate of DA neurons of the VTA when compared to controls (saline, n=10). However, lorcaserin had no significant effect on the firing rate of SNc DA neurons (n=10). Preliminary results in microdialysis experiments confirmed the lack of effect of lorcaserin on striatal dopamine release.
5-HT_{2C}Rs are involved in the 5-HT mediated inhibition of the DA function. Moreover, this data shows that the 5-HT_{2C}R-mediated inhibition is specific to the mesocortical limbic dopaminergic system rather than to the nigrostriatal system. In addition, this study suggests lorcaserin as a potential drug in the treatment of compulsive behaviours and drug abuse by preferentially inhibiting the VTA DA system.

P12.11

TEMPORAL STRUCTURE OF THE MUSCULAR DYSTROPHY X-LINKED MOUSE BEHAVIOR TESTED IN OPEN FIELD

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Duchenne muscular dystrophy (DMD) is a severe X-linked recessive disease where the cytoskeletal protein dystrophin is not expressed in muscle as well as in the nervous system. The dystrophin deficient mdx (muscular dystrophy X-linked) mouse is genetically comparable to the human form of DMD and it is the most used animal model. Despite the importance of the central deficits of the DMD (e.g. deficits in cerebellar circuitry has been observed) only little information has been obtained, until now, on the behavioral structure of this mouse strain.
To shed light on this matter, 2 different groups of mice, 5 wild type (WT) and 5 mdx were tested for 10 min in open field (OF) and their behavior recorded using a digital camera. Both quantitative and T-pattern analyses (TPA) were applied. TPA is a multivariate technique based on the assessment of critical relationships among the events in the course of time.
Quantitative analysis shows a total of 1073 events for WT mice whereas 1657 for mdx mice with an increase in walking activities and vertical explorations for the last group; in addition a reduction in static activities was observed as well. Concerning TPA, WT mice show 26 different T-patterns while mdx mice show 153 different T-patterns. As to WT mice, mean occurrences ± SE of T-patterns are 101.27 ± 16.55 with a mean length ± SE of 2.54 ± 0.13; as to mdx mice, mean occurrences are 30.33 ± 4.87 and mean length 10.42 ± 0.52.
These preliminary results suggest that the behavior of the two strain of mice tested in the OF apparatus has a complex structure characterized by close interrelationships occurring sequentially and with significant constraints on the interval lengths separating them. In comparison with WT, mdx mice show a different behavioral organization with a more articulated structure of the temporal patterns. Present study

sheds light, for the first time, on specific temporal features of behavior in an animal model of DMD.

P12.12

EPILEPSY AND AUTISM COMORBIDITY: ROLE OF *GAIN-OF-FUNCTION* DEFECTS OF Kir4.1 CHANNELS

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Dysfunctions of the astrocytic inwardly-rectifying potassium channel Kir4.1 (*KCNJ10*) result in impaired control of extracellular K+ in the brain contributing to pathogenic mechanisms underlying Autism-Epilepsy Phenotype (AEP), a condition where seizures (or EEG abnormalities) and Autism Spectrum Disorders (ASD) coexist.
To define the role of Kir4.1 variants in AEP, we sequenced *KCNJ10* in a sample of affected individuals, and performed genotype-phenotype correlations. The effects of mutations on channel activity, protein trafficking, and astrocyte function, were investigated in *Xenopus laevis* oocytes, and in human astrocytoma cell lines. An *in vivo* model of the disorder has also been explored by assessing locomotor behaviour, EEG recordings, and two-photon brain imaging of *kcnj10a* morphant zebrafish overexpressing the mutated human *KCNJ10*.
Germline heterozygous *KCNJ10* variants were found in about 5% of affected children, mainly displaying epileptic spasms and sensory processing dysregulation. All pathogenic variants revealed *gain-of-function* defects when investigated on *in vitro* cell systems. Kir4.1 mutations also recapitulated the main disease phenotype when transiently modelled *in vivo* in zebrafish embryos.
Our findings confirm that variants in *KCNJ10* deserve attention in autism-epilepsy, and provide insight into the molecular mechanisms of autism and seizures, as well as into the role of astrocyte dysfunction in abnormal synaptic transmission and electrical discharge underlying the disorder. Further work on zebrafish models is now ongoing to get larger phenotype assessments and high-throughput drug screenings, to allow focusing studies in transgenic mammalian models while seeking for new drugs for children with autism-epilepsy comorbidity.

P12.13

THE FAAH INHIBITOR NF1245 SHOWS ANTIEPILEPTIC EFFECTS IN TWO RAT MODELS OF EPILEPSY

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Temporal lobe epilepsy (TLE) is the most common form of epilepsy accounting for around 60% of all cases and although antiepileptic drugs are available they are ineffective in up to a third of patients. Thus there is a need for the development of new treatments. The endocannabinoid system has long been implicated in the generation of epilepsy due to reduced expression of CB1 receptors in several models of epilepsy, as well as a decrease in the levels of the endogenous cannabinoid anandamide (AEA) in human patients with epilepsy. Anandamide has also been associated with an on demand protective response to seizures. As a result, modulation of the endocannabinoid system has become a focus of research into epilepsy and CB1 agonists such as WIN 55,212-2 have been shown to have antiepileptic effects, although do not address the issue of detrimental effects to memory and cognition in general. A different approach to modulating the endocannabinoid system is to elevate the levels of the two endogenous cannabinoids, AEA and 2-arachadonylglycerol (2-AG) by blocking their enzymatic breakdown with selective inhibitors.
The aim of our project is to evaluate the antiepileptic effects of a newly developed fatty acid amide hydrolase (FAAH) inhibitor, NF1245 (also named ST3913), in both pilocarpine-induced status epilepticus (SE) and Maximal Dentate Activation (MDA) model of mesial TLE in Sprague-Dawley rats.
NF1245 (10 mg/kg; i.p. n = 10) administered 45 minutes prior to pilocarpine (360 mg/kg, i.p.) significantly reduced the severity of SE seizures scored on the Racine scale and also increased the time to onset of SE whilst avoiding post SE thiol oxidation damage in the hippocampus at 24 h. In the hippocampal MDA model the same dose of NF1245 10 mg/kg i.p. decreased the elongation of MDA compared to control animals (n = 6, for both groups) when administered after 1 hour of the elicitation of the MDA.
Preliminary findings show that inhibiting the FAAH enzyme may be a new therapeutic approach to treat patients with TLE.

P12.14

RECURRENT PATTERN DISCOVERY IN D1CT-7 MOUSE MODEL OF TIC-RELATED BEHAVIOR

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Transgenic D1CT-7 mice represent a pathophysiologically-grounded translational model of tic-related disorders and compulsivity, characterized by tic-like hyperkinetic vertical behaviors such as head-body twitches (HBT) and deficits in sensorimotor gating. These mice show a selective hyperactivity of cortico-striato-thalamo-cortical circuitry.
Aim of this study was to investigate the influence of such a neurobiological construct on the display of behavioral motor sequences of D1CT-7 mice tested in the open field (OF).
We tested 5 adult experimentally-naïve D1CT-7 mice and 5 wild-type controls (WT) in OF for 10 min. Video files were processed through behavioral coding. An ethogram of 13 behavioral elements, including commonly-reported mouse behaviors plus HBT, was employed. Temporal Pattern Analysis (TPA) was performed to detect behavioral sequences. TPA is a refined tool to determine whether two or more behavioral elements occur sequentially and with statistically significant time intervals.
A mean number of 830.4 elements were identified in D1CT-7 mice and 464 in WT (t-test: $t_{(8)}$=, p<0.001). This result was associated with a greater vertical activity and walking.
However, TPA did not show a consistent difference in number of behavioral patterns. We found 23 different patterns in D1CT-7 group and 26 in WT, occurring respectively 4091 and 4568 times.
From a qualitative perspective, WT showed only 5 different patterns of vertical activity recurring 440 times, whereas D1CT-7 displayed comprehensively 13 patterns of vertical activity recurring 1934 times. Among these, 1122 patterns encompassed perseverative climbing, HBT or rearing. Walking-HBT pattern occurred 348 times in D1CT-7 and was not found in WT. Besides, D1CT-7 did not display any pattern including stretched-sniffing component, a key novelty-related behavior that is, in turn, widely found in WT patterns.
D1CT-7 model summarizes some pivotal aspects of tic-related disorders. Accordingly, TPA showed a marked organization of behavioral sequences around vertical activities, suggesting perseverative features. The absence of stretched-sniffing containing patterns may be associated with impaired inhibition upon intrusive vertical activities. Further analyses are underway in our laboratories.

P12.15

IMPACT OF BINGE-LIKE ETHANOL INTOXICATION DURING ADOLESCENCE ON VULNERABILITY TO ANXIETY AND DEPRESSIVE DISORDERS AT ADULTHOOD IN WISTAR RATS

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Adolescent alcohol binge drinking constitutes a major vulnerability factor to develop psychiatrics diseases such as depression and anxiety. However, mechanisms underlying this susceptibility remain unknown. We evaluated, in adulthood, the effect of adolescent binge-like ethanol intoxication on vulnerability to anxiety-depressive behavior in Wistar rats. To model binge-like ethanol intoxication, every 2 days, rats received an ethanol injection (3.0 g/kg) for 2 consecutive days across 14 days either from postnatal day 30 (PND30) to 43 (early adolescence). In late adolescence animals (from PND45), we measured free ethanol consumption in the two-bottle choice paradigm, motivation for ethanol, both ethanol's rewarding and aversive

properties in the conditioned place preference (CPP) and taste aversion (CTA) paradigms.
In young adult animals, the intoxicated rats were exposed, for 6 consecutive weeks (from PND 46 to 88th), to an unpredictable chronic light stress (based on subjecting rats to a period of mild socio-environmental stressors) modeling depression-like behavior. From the 90th PND, the depressive rats phynoque'll be evaluate by, measurement of the activity in the familiar environment, quantification of the peeling condition, evaluation of a resignation behavior (one using the forced swim test FST and the tail suspension test TST), measuring a major criterion in the diagnosis of depression "anhedonia" bay using the sucrose preference test (SPT) or novelty suppressed feeding test (NSF). The memory and learning disorders, and the oxidative status of the brain (lipid peroxidation, catalase activity and superoxide dismutase) were also measured in adulthood.
Preliminary results of this work have shown the establishment of depressive-like affective disorders and cognitive disorders (spatial memory) in animals previously treated with ethanol. Some other results of this study, in the course of exploitation, will be communicated during symposium.

P12.16

NEUROCHEMICAL AND BEHAVIOURAL EFFECTS OF COCAINE IN HATANO HIGH AND LOW-AVOIDANCE RATS

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Hatano high- (HAA) and low-avoidance (LAA) strains were selected from Sprague–Dawley rats on the basis of their different performance in the shuttle-box task at the Hatano Research Institute (Japan) in 1985. Several studies have highlighted differences among HAA and LAA rats in the performance of other tasks (i.e. spontaneous motor activity) and in physiological parameters during and/or after stress conditions exposure. The present study was aimed to investigate among Hatano strains: 1) dopamine (DA) transmission responsiveness in the shell and core of the nucleus accumbens (NAC) induced by cocaine; 2) cocaine self-administration (SA) behavior.
To these aims, we used in both strains: 1) in vivo brain microdialysis to study the effect of cocaine (5-10 mg/kg, ip) on DA transmission in the shell and core of NAC and 2) we assessed the ability of cocaine (0.1-0.2-0.4 mg/kg/infusion) to maintain SA in fixed (FR1 and FR5) and progressive ratios (PR_{3-4}) schedules of reinforcement.
No strain or brain area-related differences in basal DA output were obtained. Acute ip cocaine administration induced a larger DA increase in the shell of LAA compared to HAA rats, whereas the opposite was observed in the core compartment. LAA but not HAA maintained cocaine SA at the dose 0.4 under FR1 schedule. Under FR5 and PR_{3-4} schedules both strains self-administered cocaine 0.4, however active nose poking, infusions and drug intake were greater in LAA than HAA. The breaking point reached by LAA strain was significantly higher compared to HAA strain. No differences were observed during extinction among strains.
Our results showed that Hatano strains differ in their neurochemical and behavioral responses to cocaine. Moreover, these data supported the hypothesis that NAC shell DA is important for the rewarding and reinforcing properties of cocaine. Further

studies in Hatano rats could clarify the role of the DA projections to NAC shell and core and genetic factors in the mechanism of drug abuse.

P12.17

PERINATAL EXPOSURE TO LEAD (PB) INDUCES ALTERATION IN GLYCOGEN METABOLISM IN DEVELOPING BRAIN OF RAT OFFSPRING

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Previous studies have provided evidence for an association between the elevated levels of lead (Pb) in the blood in children and impaired memory, concentration, learning, and lowered IQ. However, the molecular mechanism of these changes is not fully understood. Importantly, even the acceptable blood Pb concentrations in children have been shown to alter many biochemical processes in the neuronal tissue, affecting storage processes, release of neurotransmitters, signaling pathways, and energy metabolism of neurons. All these changes may result in serious neurological disorders.

Glycogen plays a key role in the brain energy metabolism; it is responsible for the correct cooperation between the neuron and astrocyte, essential for the proper brain plasticity and neurotransmission. In this study, we aimed at evaluating the effect of exposure of rats to Pb in the pre- and neonatal periods on the expression of glycogen metabolism enzymes: glycogen synthase, glycogen synthase kinase, glycogen phosphorylase, and connexin 43 – an enzyme directly responsible for the metabolic cooperation between neurons and astrocytes. The study was conducted on young rats which were given 0.1% lead acetate in utero and when fed by mother, which resulted in the whole blood Pb levels below 10 mg/dL, i.e. below the previously acceptable limits for humans. This study showed an increase in the concentration of glycogen in the prefrontal cortex, hippocampus, and cerebellum in the experimental animals compared to controls. Pb intoxication also resulted in the reduction in the expression of synthase and glycogen phosphorylase proteins in all tested brain regions. We also observed the downregulation of connexin 43 protein in all brain regions of rats exposed to Pb. There was a statistically significant increase in the expression of the phospho-GSK-3β (Tyr216) by approx. 25% in the prefrontal cortex and by approx. 30% in the cerebellum compared to controls. We observed no significant change in the expression for GSK3beta phosphorylated at Ser 9 in any of the tested brain regions.

1) Pre- and neonatal exposure to Pb, resulting in blood levels previously considered acceptable for humans, affects glycogen levels and expression of enzymes directly involved in glycogen synthesis and degradation in the developing rat brain.

2) Through the disorder of connexin protein expression Pb may impair the flow of lactate (a glycogen metabolite) between a neuron and astrocyte, thus disrupting energy metabolism of neurons.

P12.18

THE DIFFERENCE IN REACTIVENESS OF ALPHA1 ADRENERGIC RECEPTOR SUBTYPES AFTER TWENTY FOUR HOURS EXPOSURE TO ANTIDEPRESSANT DRUGS

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The adrenergic α1 receptor (α1-AR) system is involved in mechanism of antidepressant action, and its role in depressive disorders is also postulated. The α1-AR includes three subtypes, but the specific functional role of particular receptor subtype in the brain remains unclear. It was shown that imipramine exhibits a differential potency toward α1A- or α1B-AR subtypes. Furthermore studies on transgenic animals suggest different functional role of this receptor subtypes in depression. Aim of the study was to investigate if and how prolonged incubation with antidepressant drugs (citalopram (CIT), fluoxetine, reboxetine, mianserin (MIA), imipramine (IMI), desipramine (DMI)) could affect the α1A-, α1B-, α1D- AR reactiveness in vitro.

PC12 cells with stable expression of α1A- or α1B-AR and Ready-to-Assay™ α1D AR cells were seeded in 60% confluence and were incubated in standard growth medium with addition of 10μM drug concentration. After 24h cells were washed and harvested for IP1 (of α1A- or α1B-AR cells) or Ca^{2+} (α1D AR cells) measurement after noradrenaline (NOR) stimulation.

We found the subtype specific differences in response to NOR after 24h preincubation with drugs. In example DMI and IMI shifted dose response curve rightwards in case of α1A-AR (EC 50 from 15 nM to 224 and 39 nm respectively), but increased maximal stimulation of α1B- (to 230% of control level) and α1D-AR (127%). CIT increased maximal stimulation of α1A- (155%) and α1B-AR (138%) but did not show any effect in α1D-AR. In contrast to CIT, MIA augmented the maximal response to NOR (130%) and shifted dose response curve rightwards of α1D-AR (from 1.45 to 2.74 nM) with no effect in other receptor subtypes.

The differential susceptibility of α1-AR to antidepressant action is interesting in the light of reports of different role of these receptors in depressive-like behaviors in mice.

P12.19

ADOLESCENCE VERSUS ADULTHOOD: DIFFERENCES IN BASAL DOPAMINE TRANSMISSION AND RESPONSE TO DRUGS OF ABUSE

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Adolescence is a crucial period of brain development where important physiological, neurobiological, and cognitive changes take place. This stage of life is characterized by a heightened vulnerability to drug abuse, as well as being the peak time for clinical onset of most mental illnesses. Current theories posit that typical adolescent behavior is due to an imbalance between activity of cortical and sub-cortical areas. Dopamine (DA) system is particularly involved in this stage of development being a key player in reward circuitries and incentive-motivated approach behavior, as well as in decision making processes. While there is large agreement in a delayed maturation of DA mesocortical system, it is still debated if mesolimbic and mesostriatal systems of adolescents are hyper- or hypo- reactive. The aim of our study was to directly evaluate differences in mesolimbic and nigrostriatal DA

transmission between adults and adolescents rats and its responsiveness to different drugs of abuse through in vivo microdialysis.
Male Sprague-Dawley rats 5-7 or 10-12 old were implanted with dual probe, aimed at the shell and core of NAc or dorsolateral striatum (DLS) and challenged with nicotine, Δ^9-tetrahydrocannabinol (THC), cocaine, or morphine and extracellular DA levels monitored simultaneously with behavior.
Although no significant difference in basal DA levels in the NAc was observed between adolescents and adults, adolescents showed significant lower basal DA levels than adult rats in DLS. While no difference was observed in the effect of cocaine in the shell and core of NAc, a greater DA increase was observed in DLS of adolescent rats. An increased DA response was observed in the NAc shell following nicotine, THC, and morphine in adolescent as compared to adult rats. Moreover, behavioral activation differed between adolescent and adult rats.
The above differences in drugs effects might be explained by developmental changes in the endocannabinoid and opioid systems, as well as by differential expression of nicotinic receptors during brain development.
In conclusion these results while adding further insight in the development of the reward system during different stages of adolescence, provide a likely explanation for the gateway effect of nicotine and THC toward abuse of other illicit substances.

P12.20

CHARACTERIZATION OF ENDOCANNABINOID SYSTEM IN AN ANIMAL MODEL OF BINGE EATING

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Stress, together with dieting and negative affects, is a common trigger of eating disorders. Binge-eating (BE) disorder is characterized by the consumption of an unusual large amount of food associated with the sense of loss of control over eating during the episode. The physiological control of BE is extremely complex, involving a balance of both central and peripheral neurotransmitters and neuropeptides that interact to stimulate or inhibit food intake. The endocannabinoid (eCB) system has long been known as a modulator of physiological functions and plays an important role in brain circuits related to feeding behaviours.
We analyzed the transcriptional regulation of eCB system genes in selected brain regions (Amygdala complex, Caudate Putamen (CP), Nucleus Accumbens, Hypothalamus (HY) and Ventral Tegmental Area) of an animal model of BE which combines cycles of food restriction/refeeding and acute stress to evoke BE for sweet high palatable food.
Analysis in the HY of stressed and exposed to restriction rats revealed a significant selective decrease of Fatty Acid Amide Hydrolase mRNA when compared to the other groups.
Moreover in the CP of stressed rats exposed or not to restriction it was observed a significant decrease of gene expression of both Cannabinoid receptor type-2 and type-3 respect to no stressed rat as well as of Vanilloid Receptor 1 in the stressed and restricted group respect to non-stressed and non-restricted rats. No changes were observed in the other brain regions analyzed.

We here provide evidence of how the exposure to stress and cycles of intermittent food restriction produced selective changes of eCB elements in the HY and in the CP. Further studies are needed to clarify the involvement of eCB system in regulation and development of BE disorder focusing on the role of environmental factors in the development of BE episodes and thus on the epigenetic mechanisms triggering the observed changes in genes expression.

P12.21

ANTIDEPRESSANT ACTION OF 2,5-DIMETHOXY-4-IODOAMPHETAMINE (DOI)

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In recent clinical studies, administration of psychedelics has been suggested to improve symptoms in patients with depression. Psychedelics, characterized by their ability to act as full or partial agonists of serotonin (5-HT) receptors, may thus play a therapeutic role in depression and other serotonin disorders.
We used rodent behavioral models, the forced swim test and the tail suspension test, to assess the antidepressant effects of 2,5-dimethoxy-4-iodoamphetamine (DOI), a selective 5-HT2 agonist with hallucinogenic properties. Rats (n=10) were injected twenty-four hours before each test. It has also been hypothesized that the antidepressant effects of psychedelics may involve interactions with other types of receptors, including glutamate receptors. We thus assessed possible interactions between DOI and metabotropic glutamate receptors (mGluR) by administering sub-effective doses of DOI with LY341495, a mGluR2/3 antagonist, twenty-four hours before each test.
DOI was shown to reduce immobility time in both the forced swim test and the tail suspension test, suggesting antidepressant action. Furthermore, the combined administration of DOI and LY341495 at sub-effective doses had no significant effect on either behavior compared to controls.
These results further confirm previous studies that hallucinogens may have therapeutic potential for depression. Additionally, our results show that the antidepressant action of DOI is independent of mGluR2/3 activation.

P12.22

THE LONG TERM BRAIN EFFECTS OF BINGING ON ALCOHOL AND MARIJUANA IN ADOLESCENT TOBACCO USERS: A BEHAVIOURAL AND NEUROCHEMICAL STUDY IN RATS: "THE PACEVILLE PROJECT I"

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Adolescence is a critical developmental period, with respect to anatomical, neurochemical and behavioural changes. Binge consumption of alcohol and marijuana, along with smoking of tobacco, is a dangerous pattern often observed in adolescents. This study focuses on the chronic effects of binge-like exposure to alcohol and marijuana in adolescent male and female Long-Evans rats that were receiving daily doses of nicotine.
Treatments began at postnatal day 30 (P30) and lasted for 28 days. Daily intraperitoneal (i.p.) injections nicotine (1 mg/kg) were given, along with administration of IP injections of WIN55,212-2 (1.2 mg/kg) and gavage feeding of ethanol (3g/kg) on two consecutive days a week, referred to as 'binging days' to 10 males and 10 females. The remaining 10 males and 10 females received vehicles with the same timing. Behavioural tests were conducted at P30, P60 and P90 and subsequent neurochemical analysis will be performed.
Changes in levels of anxiety were measured using the hole-board (HB) test and elevated plus maze (EPM). For a more detailed analysis on the long-term effects of the drug combination, temporal pattern (t-pattern) analysis will be conducted to detect hidden reoccurring patterns of behavioural elements otherwise difficult to observe. In addition, monoamine concentrations of selected brain regions typically involved in anxious states will be analysed using high-performance liquid chromatography coupled with electrochemical detection (HPLC-ED).
Results generated from HB and EPM analysis showed no significant effects of the drug combination, although differences in behavioural elements between sexes were observed. With increasing age, male rats displayed decreased mean occurrences and durations of exploratory behaviours, irrespective of treatment type.
Our findings suggest that male and female rats react differently to adolescent stress induced by the treatment procedures. Due to the critical neurodevelopmental changes that take place during adolescence, and the susceptibility to long-term damage during this period, the chronic effects of heavy drinking and drug use are important to elucidate.

P12.23

SEROTONIN-2A AND -2C RECEPTOR MODULATION OF THE LATERAL HABENULA ACTIVITY IN THE CONTEXT OF NICOTINE ADDICTION: A NEUROANATOMICAL AND ELECTROPHYSIOLOGICAL STUDY

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The aim of this study was to investigate the role of the 5-HT_{2C} receptors (5-HT_{2C}Rs) in the modulation of the lateral habenular nucleus (LHb), under normal condition, and after acute and chronic nicotine treatment in rats. Due to the high homology between 5-HT_{2C}Rs and 5-HT_{2A}Rs, we studied both 5-HT receptors subtypes.
The expression of 5-HT_{2A}Rs and 5-HT_{2C}Rs in the LHb was investigated by immunohistochemical approach using mouse anti-5-HT_{2A}R/5-HT_{2C}R monoclonal antibodies. Immunohistochemical experiments showed a diffuse 5-HT_{2A}R and 5-HT_{2C}R immunolabelling in cell bodies and neuropil of the LHb. We show for the first time that 5-HT_{2A}Rs are expressed on LHb neurons, and are present in a similar proportion to 5-HT_{2C}Rs.
Standard single cell extracellular recordings were performed *in vivo* in anaesthetized rats. The effects of intravenous (i.v.) administration of two 5-HT_2R ligands on LHb neuronal activity were investigated: RO60-0175 (preferential 5-$HT_{2B/2C}$R agonist); and TCB-2 (potent 5-HT_{2A}R agonist). RO60-01745 (5-640 µg/kg, i.v.) induced changes in 39% of the neurons treated, which responded with either an increase (9%) or a decrease (30%) in their firing rate. The change in firing activity was dose dependent, with maximum effects elicited towards the higher doses for both excitation and inhibition (+59 ± 22% and -56 ± 8%). Both effects were blocked by the administration of SB242084, a selective 5-HT_{2C}R antagonist. TCB-2 (5-640 µg/kg, i.v.) affected 79% of the neurons treated, which responded with either an increase (26%) or a decrease (53%) in their firing rate. The change in firing activity was dose dependant, with maximum effects elicited towards the higher doses (+102 ± 32% and -61 ± 12%). These effects were both reversed by the administration of MDL11,939, a selective 5-HT_{2A}R antagonist. Pre-treatment with either SB242084 or MDL11,939 significantly altered the nature of LHb neuronal response to TCB-2 (5-640 µg/kg, i.v.).
Acute nicotine treatment reduced the overall firing rate of LHb neurons and increased their irregularity in firing. Chronic nicotine treatment up-regulated 5-HT_{2C}R expression. Nicotine treatments were shown to attenuate the inhibitory response to RO60-0175 administration, and the excitation response to TCB-2 administration. Our data shows that both 5-HT_{2A}Rs and 5-HT_{2C}Rs bidirectionally modulate LHb neuronal output. These findings are important for their physiological relevance and for therapeutic intervention in the cessation of nicotine abuse and drugs of addiction in general.

P12.24

ROLE OF THE KAPPA OPIOID SYSTEM ON THE FACILITATING EFFECTS OF PRENATAL ALCOHOL EXPOSURE ON LATER ALCOHOL INTAKE

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Several experiments indicated that moderate prenatal alcohol exposure (PEE, 1-2 g/kg, gestational days 17 to 20) induces a significant, facilitatory effect on

subsequent ethanol consumption in infant or adolescent rats. This effect may be the consequence of PEE enhancing or reducing the appetitive and aversive motivational effects of ethanol, respectively. The mechanisms underlying PEE effects are, however, still elusive. The endogenous opioid system has been proposed as an important target of alcohol's actions and ethanol exposure seems to alter the developmental trajectory of opioid systems, possibly affecting the hedonic effect of ethanol. The aim of this study was to describe the effect of PEE on subsequent, voluntary alcohol consumption, and on opioid system gene expression.
Pregnant rats received daily intragastric administration of alcohol (0.0 or 2.0 g/kg). Female and male offspring were tested at infancy or adolescence. We analyzed anxiety response and ethanol-induced locomotor activity (infants and adolescents), alcohol intake (adolescents), and gene expression levels of predynorphin (PDYN) and kappa opioid receptors (KOR) in mesocorticolimbic areas of the brain (infants and adolescents).
PEE was associated with elevated anxiety response in infants and with a blunted response to the stimulant effects of ethanol during adolescence. PEE male, adolescent, rats consumed signficantly higher amounts of alcohol than control peers. Notably, several PEE-induced alterations on gene expression were observed. During infancy, PEE signficantly enhanced levels of KOR in Prefrontal Cortex and PDYN in Ventral Tegmental Area (VTA), and signficantly lowered levels of PDYN in Nucleus Accumbens. PEE adolescents exhibited higher levels of KOR in VTA, than control rats.
These results confirm that a moderate exposure to alcohol during the last days of pregnancy is a risk factor for subsequent ehancenment of alcohol intake at adolescence. The study also pinpoints alterations in behavior and gene expression that could be responsible of the facilitatory effects of PEE.

P12.25

ENDOCANNABINOID STIMULATION IN PREGNANCY: WHAT HAPPENS TO THE OFFSPRING?

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Prenatal exposure to cannabis is an underestimated matter that requires a specific focus in order to elucidate the negative consequences on the progeny.
The present study aims at assessing the alteration induced by the prenatal stimulation of the endocannabinoid system on behavioural reactivity, emotional memory and alcohol vulnerability in offspring rats. Pregnant dams received a stimulation of the endocannabinoid system from GD 5 to 20. The young offspring was tested from PND 25 onwards for behavioural reactivity in the Open Field and in the Elevated-Plus Maze test; and for fear-associated memory in the emotional-object

recognition test. The progeny was also exposed to a Binge-drinking paradigm for assessing vulnerability to alcohol drinking. Prenatal stimulation of the endocannabinoid system increased locomotor activity in the progeny, as shown by a significant increase in total distant travelled ($p<0.0020$) and in number of total entries ($p<0.0051$) in Open Field and Elevated-Plus Maze, respectively, compared to controls, although it did not modify anxiety-like behaviour. When tested for the emotional memory, the endocannabinoid-stimulated rats showed impaired declarative memory associated to aversive emotional stimuli, since they did not display avoidance of a fear-associated object and showed a significant decrease in the Emotional-Object Avoidance Index ($p=0.0255$) and in the emotional zone-related Difference Score ON-BSL ($p<0.05$), with respect to controls. In the same rats, increased vulnerability to alcohol binge drinking was recorded: the analysis of binge-drinking pattern indicated increased alcohol-intake ($p<0.001$) and preference ($p< 0.001$) when compared to controls.
In conclusion, this research highlights that prenatal exposure to cannabinoids for medical or recreational purposes, does induce complex disarrangement in the brain progeny, that arises during adolescence and involve emotionally salient memories and vulnerability to drug of abuse.

P12.26

IN VIVO ASSESSMENT OF SEROTONIN TRANSPORTER DENSITY IN THE MOUSE BRAIN: A PET/MR APPROACH

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The serotonin transporter (SERT) plays an important role in the regulation of serotonergic neurotransmission, and its aberrant expression has been linked to psychiatric conditions, including major depressive disorder (MDD). While SERT density has previously been proven to be amenable to in-vivo quantitative evaluation by positron emission tomography (PET) in humans, this approach is only beginning to be developed for rodents. Considering the important role of rodent models as experimental system for the exploration of the pathophysiology of MDD, the aim of this study was to evaluate the feasibility of using small-animal PET employing [^{11}C]DASB ([^{11}C]-3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile) as a radiotracer to measure relative SERT density in designated areas of the mouse brain.
To this end, wild-type, heterozygous and homozygous SERT knockout mice were used in a PET/MR approach. Anatomical MR images of the brain were acquired before placing the mice in a small-animal PET scanner under administration of [^{11}C]DASB for dynamic PET imaging. A simplified reference tissue model (SRTM) using the cerebellum as reference region was used to calculate the binding potential

(BP_{ND}) as a quantitative parameter of SERT density. PET data were complemented and validated by ex-vivo measurements of SERT protein expression by Western Blot and respective correlations between in-vivo and ex-vivo results were calculated.
The obtained data firstly demonstrate small-animal PET in mice as reliable and useful tool for the investigation of SERT protein density in the intact animal and suggest its application for the exploration of dynamic changes in SERT levels in animal models of MDD. The utility of this approach is currently being tested in a longitudinal study aiming to measure relative SERT density *in vivo* at baseline and in response to chronic stress exposure.

P12.27

SCHIZOPHRENIA AND CANNABINOID RECEPTOR TYPE1 GENE REGULATION: A PRECLINICAL AND CLINICAL STUDY

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Schizophrenia (SZ) is a chronic debilitating neuropsychiatric disorder, representing the eighth cause of disability in adolescents and adults. To date the causes and the molecular basis of schizophrenia are still one of the greatest challenges in psychiatry. The Endocannabinoid System (ECS) is highly represented in brain areas implicated in processing of emotionally information as well as learning and memory, such as the prefrontal cortex and several preclinical and clinical data support the hypothesis that disturbance of the ECS can have a role in the pathophysiology of schizophrenia. In this study we evaluated whether regulation of ECS genes expression might to be involved in the development and progression of SZ in a gestational rat model (prenatal administration of the mitotoxin methylazoxymethanol acetate (MAM)) as well as in human subjects.
Genomic DNA and total RNA have been isolated from rats prefrontal cortex as well as from peripheral blood mononuclear cells (PBMCs) of a cohort of human SZ and controls subjects. Quantitative Real-Time RT-PCR and Pyrosequencing have been

used, respectively, to quantitatively assess the state of ECS genes expression and DNA methylation at gene promoters.

We here report a selective increase in Cannabinoid receptor type 1 gene (CNR1) expression in the prefrontal cortex of MAM rats (2.36 ± 0.34) when compared to control rats (1.14 ± 0.26 , $p < 0.01$), as well as in the PBMCs of SZ patients ($p < 0.05$). Consistently a significant reduction in DNA methylation at gene promoter was observed in both MAM rats (MAM: 2.65% ± 0.55; Controls: 4.77% ± 0.72; $p < 0.05$) and human patients ($p < 0.01$). Overall, the present findings provide new insights into the control of pathological gene expression in SZ and suggest CNR1 gene regulation via epigenetic mechanisms as a new tool for the development of new treatment strategies in SZ.

P13.1

Magnetic Resonance Imaging Characterization of Early PD Development

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Imaging biomarkers are needed to characterize PD development as soon as possible during the long lasting asymptomatic evolution of the disease, as well as to monitor the response to therapeutic interventions.
Magnetic Resonance Imaging (MRI) plays an important role in characterizing the preclinical evolution of PD showing that different striatal areas can influence motor symptomatology. It has been recently demonstrated that MRI is able to reveal structural changes in brain grey and white matter during learning. In a previous study, we were able to reveal the presence of striatal structural changes and correlate them with task switching inabilities induced by 6-OHDA unilateral injury of the nigrostriatal pathway.
In the present study, on the basis of the behavioural effects of apomorphine treatment during the early progression of an intranigral 6-OHDA rat model, the structural properties of the Striatum were investigated by high resolution, ex vivo, MRI quantitative techniques and relaxometry (T1, T2, T2*). Neither the intact, nor the sham-lesioned whole brains showed inter-hemispheric differentiation of the main relaxometric indices. On the contrary, all lesioned brains revealed a variation in T1 and T2 values in the ipsilateral Striatum with respect to the contralateral one. The high resolution T2*-weighted images revealead a complex pattern of grey/white matter ratio, thus indicating a change in the texture of the Striatum. At present, major MRI abnormalities seen in Parkinsonism are tissue atrophy, measured in T1-weighted images, and changes of tissue signal amplitude, seen in T2-weighted images. Here we have reported a preliminary regional and temporal correlation study between behavioural and structural changes in a rat model of PD.

P13.2

DIFFERENTIAL RESPONSIVENESS OF NUCLEUS ACCUMBENS DOPAMINE TO STIMULI INSTRUMENTALLY CONDITIONED TO DRUG REINFORCERS

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Nose-poking (NP) and lever-pressing (LP) represent two different response modalities which have been utilized in the self-administration (SA) paradigm. NP is part of a rodent's natural exploratory repertoire, whereas LP requires the animal to learn the action of pressing a lever in order to obtain a reward. The objective of these experiments were to study differences in the mesolimbic dopaminergic responsiveness induced by heroin self-administration (SA) using LP and NP as operant responses.

Male Sprague-Dawley rats were trained for 10 days on an FR1 schedule to acquire heroin SA (0.05 mg/kg) using NP or LP. After acquisition of SA behaviour, microdialysis was carried during a heroin SA session on an FR1 schedule to measure dialysate dopamine(DA) in the nucleus accumbens (NAc) shell and core of animals. Next day, the animals underwent an extinction session. On the third day, a dose of 0.025 mg/kg heroin was utilised while another group underwent a passive administration of heroin.
Results show that during heroin SA, dialysate DA preferentially increased in the shell only in the NP group, while DA increased both in the shell and core in the LP group. During the extinction DA did not change from basal values in both groups. DA was observed to increase in the core of both groups during passive non-contingent presentation of heroin. When the heroin dose was halved, the NP group showed even more pronounced differences in dialysate DA released in the shell and core while the LP group showed an almost equal release of dialysate DA in both.
These results add to the growing body of evidence about the differential involvement of the NAc shell and core in different aspects of reinforcement and incentive learning. Further, they show that the specific operant response utilised for modelling SA behaviour is able to determine the pattern of activation of DA transmission in the NAc core and shell.

P13.3

CHRONIC TREATMENT WITH 1-METHYL-1,2,3,4-TETRAHYDROISOQUINOLINE PROTECTS LACTACYSTIN-INDUCED DECREASE OF DOPAMINE RELEASE

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The ubiquitin-proteasome system (UPS) is one of the important mechanisms for protein degradation. The UPS irreversible inhibitor, lactacystin induced the loss of dopaminergic neurons and increased the formation of cytoplasmatic inclusions. The UPS dysfunction plays significant role in the pathogenesis of Parkinson's disease (PD).
In our *in vivo* study we investigated the impact of acute or chronic treatment with 1-methyl-1,2,3,4-tetrahydroisoquinoline (1MeTIQ; 50mg/kg i.p.) an endogenous amine with neuroprotective and MAO-inhibiting properties on the decrease in the striatal dopamine release evoked by lactacystin (5µg/2µl) administered unilaterally to the substantia nigra. Rats received 1MeTIQ once or chronic during 7 days, and *in vivo* microdialysis study was carried out 7 days after lactacystin lesion. The dopamine and its extraneuronal metabolite, 3-MT was assayed in dialysates using HPLC with ED. Moreover, the locomotor activity of rat was measured.
The behavioral test showed that unilateral lactacystin lesion of substantia nigra did not change the rats locomotor activity however chronic treatment with 1MeTIQ combined with lesion decreased the exploratory activity. The biochemical *in vivo* study indicated that unilateral lesion with lactacystin significantly (of about 50%; $P<0.01$) reduced the dopamine release into the extracellular space. Both, acute and chronic treatment of 1MeTIQ completely antagonized lactacystin-induced impairment of dopamine system activity, and dopamine concentration was significantly elevated up to the control value. Simultaneously, the level of extraneuronal dopamine metabolite, 3-MT was strongly increased.

1MeTIQ has shown a clear neuroprotective activity in the lactacystin model of Parkinson's disease. The mechanism responsible for these effects may be connected with properties of 1MeTIQ to scavenge a free radicals production, and possible reduction of lactacystin uptake as DAT inhibitor into the dopamine neuron in the brain.
The study was financially supported through a funds of KNOW (The National Scientific Leading Center) from the Institute of Pharmacology, Polish Academy of Sciences, Krakow, Poland.

P13.4

A NOVEL THERAPEUTIC STRATEGY FOR THE PREVENTION OF THE ONSET OF DYSKINESIA IN THE THERAPY OF PARKINSON'S DISEASE

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The mixed serotonin 5-$HT_{1A/1B}$ receptor agonist eltoprazine suppressed dyskinetic-like behavior in animal models of Parkinson's disease (PD), but simultaneously reduced L-dopa-induced motility. Moreover, adenosine A_{2A} receptor antagonists, as preladenant, significantly increase L-dopa efficacy in PD without exacerbating dyskinetic-like behavior. Our previous report demonstrated that combination of eltoprazine, with preladenat produces prevention and reduction of L-dopa-induced dyskinesia, without impairing the efficacy of L-dopa in relieving motor symptoms.
On this basis, we hypothesize that the early combined administration of eltoprazine and preladenant may produce prevention of the onset of L-dopa-induced-dyskinesia in a rodent model of PD.
Unilateral 6-OHDA-lesioned L-dopa-non primed rats, were treated for two weeks with eltoprazine (0.6mg/kg) and/or preladenant (0.3mg/kg), alone or in combination with L-dopa (4mg/kg), and abnormal involuntary movements (AIMs) as index of dyskinesia, were evaluated. Four days after the last administrations all rats were treated with L-dopa. Moreover, induction of immediate-early gene *zif-268 (*an index of long-term changes correlated with dyskinesia), and microglia and astroglia markers (indexes of neuroinflammation) were evaluated.
Results show that combined administration of L-dopa plus eltoprazine plus preladenant significantly prevented and delayed the onset of dyskinetic-like behaviors induced by L-dopa.
Preliminar results showed that z*if-268* was increased in striatum of rats treated with L-dopa and L-dopa plus preladenant compared with vehicle. In contrast, rats treated with eltoprazine (with or without preladenant) had lower *zif-268* activation after treatment in L-dopa-non-primed rats.
Results suggest that combination of L-dopa with eltoprazine and preladenant may be a promising therapeutic strategy for treating motor symptoms, delaying, at the same time, the onset of dyskinesia in PD.

P13.5

THE ROLE OF METALLOPROTEINASES-2 AND -9 AND THEIR INHIBITORS IN NEUROTOXICITY OF FLUORINE

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Fluorine is a strong neurotoxin which can decrease the intelligence quotient and cause problems with learning and concentration. The Extracellular Matrix (ECM) of the central nervous system serves as the environment for neurons and glial cells, and at the same time, it plays the role of a modifier of these cells. Changes in the structure and the functioning of synapses are caused by ECM enzymes. These enzymes, especially matrix metalloproteinases (MMPs), accompany both physiological processes, such as learning or memorizing, and pathological processes. Metalloproteinases 9 and 2 (MMP-9 and MMP-2) and the inhibitors of metalloproteinases-3 and -2 (TIMP-3 and TIMP-2) seem to be particularly interesting. There is no data regarding the influence of fluorine on the expression of these enzymes and their inhibitors in the brain.
In the research, the rats were exposed to sodium fluoride (50 mg/L) already in the prenatal period until they reached the age of three months. After this time, the hippocampus, prefrontal cortex, cerebellum, and striatum were collected. In all of the aforementioned structures, the expression of proteins MMP-9, MMP-2, TIMP-3 and TIMP-2 was carried out by means of ELISA, gene expression by RT real time PCR and immunolocalization by immunohistochemistry and microscopic visualization.
On the basis of the results, it can be concluded that fluorine influences the expression of MMP-9, MMP-2, TIMP-3 and TIMP-2. In the study group, a statistically significant expression of MMP-2 was observed in the prefrontal cortex, striatum, and cerebellum, and a decrease in the expression of MMP-9 was noted in the prefrontal cortex and cerebellum in relation to the control group. We also saw the difference between TIMP-3 and TIMP-2 levels in the study group compared to control.
Our research suggests that changes in the expression of metalloproteinases and their inhibitors in the brain, caused by fluorine, could be an important factor of neurotoxicity of fluorine. The disorders of neuroplasticity processes can be considered as a biochemical basis for the decrease in the intelligence quotient caused by fluorine.

P13.6

THALIDOMIDE ATTENUATES L-DOPA-INDUCED DYSKINETIC RESPONSES AND NEUROINFLAMMATION IN THE DENERVATED STRIATUM OF EMIPARKINSONIAN RATS

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L-DOPA therapy represents the main treatment for Parkinson's Disease (PD), however long-term administration results in treatment-related motor complications named L-DOPA-induced dyskinesia (LID). Preclinical studies have suggested a role of inflammatory responses in the onset ofAbnormal Involuntary Movement (AIMs), a model of LID in the 6-OHDA rat model of PD. In this model, a L-DOPA chronic treatment eliciting AIMs is associated with astrocytosis, microgliosis and increased levels of Tumor Necrosis Factor-α (TNF-α) within OX-42-positive cells.

Thalidomide is a powerful anti-inflammatory and immunomodulatory drug through inhibition of TNF-α and suppression of Nuclear Factor kappa B. We investigated whether thalidomide may prevent the onset of AIMs and reduce L-DOPA-induced inflammatory responses in the striatum of 6-OHDA-lesioned rats.
6-OHDA-lesioned rats received ten days repeated treatment with L-DOPA+Benserazide (6 mg/Kg), Thalidomide (70 mg/Kg), or Thalidomide thirty minutes before L-DOPA+Benserazide administration. Limb, axial AIMs and contralateral turning response were evaluated daily, TNF-α immunoreactivity (IR) was quantified within OX-42-positive microglia in the denervated dorsolateral striatum one hour after the last L-DOPA administration.
Rats receiving repeated L-DOPA displayed AIMs and controlateral turning behavior, which progressively increased during treatment. Moreover, L-DOPA-treated rats displayed increased OX-42 IR and TNF-α/OX-42 colocalization in the dorsolateral striatum as compared to vehicle-treated rats. In contrast, treatment with Thalidomide + L-DOPA induced limb and axial AIMs of lower intensity than L-DOPA. In the striatum, thalidomide inhibited L-DOPA-induced increases of OX-42 and TNF-α IR.
Our results show that thalidomide reduced L-DOPA-induced dyskinetic responses as well as microgliosis and TNF-α production, suggesting that targeting the neuroinflammatory response may alleviate the development of L-DOPA-induced dyskinesia in PD.

P13.7

NEUROPROTECTION OFFERS BY AN ENDOGENOUS AMINE, 1-METHYL-1,2,3,4-TETRAHYDROISOQUINOLINE IN HEMIPARKINSONIAN RATS: THE BIOCHEMICAL AND MOLECULAR STUDY

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There is a growing body of evidence that impairment of the ubiquitin-proteasome system (UPS) in the substantia nigra (SN) plays an important role in the pathogenesis of Parkinson`s disease (PD). The loss of dopamine (DA) cells in the substantia nigra pars compacta and consequently further more in the extrapyramidal nigrostriatal DA neurons are the characteristic pathological hallmark of PD. The aim of the present study was to investigate the effect of acute and multiple (7 days) administration of 1-methyl-1,2,3,4-tetrahydroisoquinoline (1MeTIQ; 50mg/kg i.p.), an endogenous amine with neuroprotective and MAO-inhibiting properties on the biochemical and molecular markers of dopamine neurons injury evoked by UPS inhibitor, lactacystin (5μg/2μl) administered unilaterally to rat SN. The DA and its metabolites (DOPAC, 3-MT, HVA) was assayed in the ipsi- and contralateral striatum using HPLC with ED. Additionally, the level of tyrosine hydroxylase (TH) in the SN at using Western blot method and the amount of Bcl-2 protein (ELISA) in the hippocampus was also determined. The biochemical *ex vivo* study carried out 7 days after lactacystin lesion have demonstrated a significant reduction the concentration of DA (of about 65%; $P<0.01$) and its metabolites (from 35% to 50%; $P<0.05$) in the ipsilateral striatum. Similarly, the level of TH and the amount of antiapoptotic protein Bcl-2 was essentially decreased (of about 25% and 50%, $P<0.05$; respectively) in the investigated brain structures. Both, acute or multiple administration of 1MeTIQ completely antagonized the lactacystin-induced impairment of the DA system activity. The level of DA as well as the concentration of TH and Bcl-2 protein

elevated up to the control values in the joint groups. The present results add a new value to the study of 1MeTIQ-produced neuroprotection of the lactacystin-induced neurodegeneration as a valuable animal model of PD.
The study was financially supported through a funds of KNOW (The National Scientific Leading Center) from the Institute of Pharmacology, Polish Academy of Sciences, Krakow, Poland.

P13.8

INTERMITTENT HYPOXIA INCREASES TAU PHOSPHORYLATION VIA BIOLOGICAL PROCESSES COMMON TO AGING: POTENTIAL LINK BETWEEN SLEEP-DISORDERED BREATHING AND ALZHEIMER DISEASE

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The association has been suggested between sleep-disordered breathing (SDB) and Alzheimer disease (AD). Patients with SDB often have cognitive impairments, which are associated with intermittent hypoxia. Thus, intermittent hypoxia treatment (IHT) has been used as an experimental animal model for SDB. In this study, we aimed to elucidate molecular mechanisms linking SDB and AD.
Mice underwent IHT protocols, and their hippocampal samples were subjected to gene ontology (GO)-based microarray analyses and biochemical analyses. The mice were also subjected to behavioral analyses.
GO-based microarray analyses including various public data revealed that IHT and aging shared alterations in some common GO, which were also observed with kainic acid treatment, Dicer ablation, or moderate glutamate excess. Further *in silico* analyses indicated that IHT led to alterations in the imbalance of kinases and/or phosphatases and glutamatergic synapse. Thus, we performed *in vivo* analyses regarding tau, which has been focused in AD research, and glutamatergic synapse. As the results, we found that IHT significantly increased phosphorylated tau, and reduced proteins relevant to glutamatergic synapses. In addition, IHT increased phosphorylated p70 S6 kinase, indicating involvement of the mammalian target of rapamycin signaling pathway. Furthermore, IHT mice demonstrated hyperactivity in Y-maze tests, which was also observed in AD models.
These results may explain the potential link between SDB and AD. Aging is a major risk factor for AD, therefore, IHT is a novel model for investigating the pathological processes contributing to AD onset.

P13.9

SEX DIFFERENCES ON SEQUENTIAL ACTIVATION OF MICROGLIA AND ASTROCYTE FOLLOWING POSTNATAL SYSTEMIC IMMUNE CHALLENGE

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Early immune challenges induce long-lasting brain developmental and behavioral impairments and increase the risk of diseases later in adulthood. The activation of the immune system results in the release of proinflammatory cytokines, such as interleukin-1β (IL-1β), tumor necrosis factor α (TNF-α) and IL-6. High levels of these cytokines during development are associated with low resilience to diseases in

adulthood. The recent study demonstrated that the glial cells has a sequential activation, for example, the height level of cytokines production during the inflammation activate the microglia fist which leads to activate the astroglia after.
The aim of this study is: To compare the behavioral responses of the glial cells after different postnatal LPS challenge times in both of sexes. By measuring the cytokines, and oxidative stress level.

P13.10

REAL-TIME SEIZURE ONSET DETECTION USING WAVELETS AND COMMON SPATIAL PATTERN WITH EMPIRICAL MODE AND GRAPH SPECTRAL DECOMPOSITIONs.

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Epilepsy, clinically, is a medical condition associated with neurological abnormality as a result of irregular electrical discharge of a group of neurons. This aberration negatively distorts normal brain function, and the extend can vary from brief relapse in state of attention to loss of consciousness. Epilepsy is associated with recurrent, and people living with the disorder are prone to emergency room cases and social disqualification due to continuous cycle of stigmatization. One out of every three of the 50 Million patients are unresponsive to surgery and anti-convulsion treatments. Lack of effective drug therapy that can suppress seizures in epileptic patients can negatively impact on their quality of life, economic, psychological and social wellbeing.
To augment the clinical management of epilepsy, the application of signal processing and machine learning techniques have opened a new frontier in automatic seizure detection by analyzing and evaluating electrical signals captured from the brain. The fundamental problems in developing such algorithms are: How to encode knowledge domain algorithmically in the system to perform in comparison to human expert and the ability of the system to adapt to variability between different seizures and patients.
The main focus of this work is to build a robust feature extraction method and machine learning classification. A key step in the program development is decomposing EEG into main features, which involves identifying notable patterns that can distinguish between seizure and non-seizure states using mathematical and computing models. We propose the use of Wavelets and common spatial patterns (CSP) with empirical mode decomposition and graph spectral decomposition methods to describe abnormal EEG in terms of spectral, temporal and spatial information. CSP with spectral graph decomposition method is use in the preprocessing stage where the derived spatial coefficients optimally maximize variance (or band power) of seizure state class while, simultaneously, minimizing the variance of normal EEG background information. We explore graphic theoretic approach to CSP provided a link through which abnormal EEG components can be treated as a graph partitioning problem.
The features extracted are treated as binary classification problem where data are classified as either seizure, and non-seizure using machine learning approach.

P13.11

INVESTIGATING THE EFFECTS OF THE DESIGN OF TES ELECTRODES ON SKIN IMPEDANCE

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Transcranial electrical stimulation (tES) is applied in a range of biomedical applications, allowing for direct neurofeedback through the application of weak electrical current through the scalp using dedicated electrodes.
Three different categories of electrodes are mainly used in tES applications; self-adhesive, rubber carbon pads, and sponge electrodes. All three present individual benefits and can be successfully applied to tES applications. It has been widely found in literature that sponge electrodes are however best suited to current stimulation applications, primarily due to their efficiency over thick hair. This is a direct consequence of the added conductivity provided by the saline solution applied to the sponge material, which seeps through to the scalp, thereby providing direct and contiguous electrical contact.
The purpose of this study is to investigate the effect of different tES electrode designs on current stimulation. Experiments were conducted using an HD-tES device and electrodes currently being developed in-house. Electrodes and their sponge material have been designed to allow easy replacement onto a dedicated head-cap, whose design is based on the standard 10-10 EEG electrode layout, which ensures appropriate montage positioning in tES stimulation protocols.
Initial tests were conducted to determine the optimum size and amount of saline required for both square and circular sponge electrodes for the application of HD-tES, versus impedance and comfort, whilst maintaining a constant sponge thickness. Further tests were conducted to investigate the difference in impedance on the skin between square and circular electrodes in different scenarios involving the presence of hair and at different levels of skin preparedness. A control was set up using standard wet electrodes placed on the skin following preparation, and ANOVA analyses were conducted to assess the performances of the different electrode designs.

P13.12

THE ROLE OF DIFFERENT THALAMO-CORTICAL NETWORKS IN THE GENERATION OF SLEEP SPINDLES IN EPILEPTIC PATIENTS

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Sleep spindles are generated in thalamocortical networks. Thalamocortical projections include core projections to cortical layer IV and matrix projections to layer I-II. It has been proposed that sleep spindles can be generated in either of these networks.

We used physiological data from 5 human patients undergoing presurgical electrophysiological monitoring, including laminar microelectrodes with post-operative histological reconstruction of the electrode tracks, to test this hypothesis. Sleep spindles were detected automatically in electrocorticography channels and detection-triggered laminar microelectrode recordings were analyzed.
Results indicate highly heterogeneous intracortical local field potentials during sleep spindles, and maximum current source density in layer I, II and IV. Current source density in superficial layers and layer IV is moderately correlated ($r \approx 0.4$), and the ratio of the two is normally distributed with a mean of approximately 1. These results were similar for slow and fast spindles as well as localized and global spindles.
The results confirm that both core and matrix thalamocortical projections contribute to spindle generation, but most spindles appear to be generated by a combination of the two and only a small minority by only one or the other.

P13.13

NEUROBEHAVIORAL EFFECTS OF NEONATAL RETICULAR THALAMIC NUCLEUS LESION

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In all mammals, the thalamic reticular nucleus (TRN) occupies a strategic position lying within the fiber bundle that interconnects the dorsal thalamus and the telencephalon. The TRN is a structure that is solely composed of GABAergic inhibitory neurons, and as part of the thalamus, it receives input from the cortex and other thalamic nuclei and provides major inhibitory input to each thalamic nucleus, particularly the mediodorsal nucleus (MD). . As the MD is important for supporting optimal cortico–thalamo–cortical interactions from very early on during brain maturation, previous studies of our team have shown that early insult of this nucleus induced functional and structural abnormalities in the cerebral cortex; so, what about the early lesion of the NRT on the development of the MD and the cortex?. Our study assessed whether the early postnatal lesion of the RTN, reciprocally interconnected to mediodorsal thalamus, causes disruption of behavior and cognition in young adult rats.
Rat pups (postnatal day 4) were randomized in 3 groups: the first group received a bilateral electrolytic lesion of RTN, the second corresponding to RTN-sham-lesion group, and the third as a classical control group. After seven weeks, all rats were tested with the following several behavioral and cognitive paradigms, and then perfused for histological study and immunohistochemistry of glutamate.
RTN lesioned rats presented deficits in shifting capabilities and acquiring new strategies, significant hypoactivity, increasing in anxiety-like behavior and disruption of the recognition memory compared to RTN-sham-lesion and control rats. In addition, histological study showed that lesioned animals have reduced the volume of mediodorsal thalamus, and decreased number of positive glutamate cells in the PFC as well as the basolateral amygdala complex.
The different behavioral and histological alterations reported in our study suggest that early damage of the anterior part of the RTN leads to alterations may control the development of the mediodorsal thalamus-prefrontal cortex pathway.

P13.14

CYTOCHROME P450 INDUCTION IN SH-SY5Y CELLS AND ITS PROTECTIVE ROLE

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Cytochrome P450 (CYP) is one of the most important metabolic system for exogenous compounds. This isoenzyme family promote a deep systemic clearance of almost all xenobiotics, but in particular circumstances it can also lead towards cellular injury by producing toxic metabolites. In CNS it is present at different concentrations in different brain areas and can play an important role in both therapeutic effects or in toxic activation of drugs, however the effective role of CYP in the detoxification/toxic effects in brain is still under debate. In order to clarify its function, we have setup an in vitro model of CYPs modulation using human neuroblastoma SH-SY5Y cells.
Cells were treated with different well known liver-CYP inducers: beta-naphtoflavone (BNF), cyclophosphamide (CPA), and ethanol (EtOH). The expression of various CYP isoenzymes (2D, 2E1, 1A1 and 3A4) was evaluated by qRT-PCR and western blot (WB) analysis. Moreover, the CYPs cell localization was studied by confocal imaging. Finally, the toxic effect of MPP^+ was studied by Annexin V/ PI FACS analysis in control and CYP-induced SH-SY5Y cells.
The qRT-PCR and WB revealed that the treatment with BNF promoted a 1.5-fold increase of CYP2E1 and a 1.2-fold increase of CYP2D6 compared to control cells. CPA treatment increased the expression of CYP2D6 nearly 2-fold but it didn't change the expression of CYP2E1; while EtOH treatment did not increase the expression of CYP2D6, but increased about 1.5-fold the expression of CYP2E1. Confocal image analysis showed that CYP2D6 is localised in mitochondria while the other isoforms were mostly expressed in endoplasmic reticulum. Moreover, Annexin V/PI FACS analysis revealed that the treatment with BNF promoted a decrease of the toxic effect caused by MPP^+.
These data suggest that CYP can be inducible in SH-SY5Y cells and its increase can protect neurons from toxic insult promoted by MPP^+.

P13.15

CONTRIBUTION OF SPINAL 5-HT_{5A} RECEPTORS IN THE ANTINOCICEPTIVE EFFECTS OF SYSTEMICALLY ADMINISTERED CANNABINOID AGONIST WIN 55,212-2 AND MORPHINE

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The antinociceptive effects of cannabinoids and opioids have been known for centuries. Serotonin and its receptors are also known to play important roles in nociception. However, contribution of spinal 5-HT_{5A} receptors in antinociceptive effects of cannabinoids and opioids has not been studied. We conducted this study to clarify mechanisms of actions of the antinociceptive effects of cannabinoids and opioids.
Hot-plate and tail-flick tests were used to assess the antinociceptive activity in Balb/c mice.
WIN 55,212-2, a cannabinoid agonist, and morphine exerted significant antinociceptive effects at 1, 3, and 10 mg / kg doses in both hot plate and tail flick

tests. Then, we administered the selective 5-HT_{5A} receptor antagonist SB-699551 (10 nmol/mouse) intrathecally 10 minutes before the agonists. SB-699551 significantly reduced the antinociceptive effect of both WIN 55,212-2 and morphine. In the rotarod test, WIN 55,212-2 disrupted the motor coordination at the dose of 10 mg/kg, while morphine did not affect this function at any doses.
Our findings show that spinal 5-HT_{5A} receptors are involved in the antinociceptive effects of WIN 55,212-2 and morphine.
This project was supported by a grant from Trakya University Research Council (TUBAP-2106/44).

P13.16

NEUROINFLAMMATORY EFFECTS AND BEHAVIORAL CORRELATES AFTER REPEATED EXPOSURE TO THE SYNTHETIC CANNABINOID JWH-018

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The synthetic cannabinoid (SC) 1-pentyl-3-(1-naphthoyl)-indole (JWH-018) has been detected in several samples of a smokable herbal mixture termed Spice/K2 drugs, that are currently marketed as legal alternatives to *Cannabis*. Its use represents a growing public health worldwide. JWH-018 is a CB1/CB2 receptor agonist with higher affinity than Δ9-THC, the active ingredient of marijuana. JWH-018 shares with Δ9-THC CB1-dependent reinforcing and DA stimulant actions displaying a preferential effect on the NAc shell at the dose of 0.25 mg/kg ip. Despite the increasing popularity of Spice drugs, the effects of their chronic use are unknown. Recently, an *in vitro* study showed that SCs induce cytotoxicity in forebrain neuronal cultures in a concentration-dependent manner. However, modulation of the endocannabinoid system has been associated with both neurotoxic and neuroprotective effects.
In the present study, we evaluated the neuroinflammatory and neurodegenerative effects induced by a chronic treatment of JWH-018 in DAergic brain regions involved in emotional and cognitive processing.
To this end, rats were administered once a day for 14 consecutive days with JWH-018 (0.25 mg/kg i.p.) or with vehicle. Afterwards, levels of different markers (TH, DAT, GFAP, IBA-1, caspase) were evaluated in the medial pre-frontal cortex (mPFC), nucleus accumbens (NAc), caudate-putamen (CPu) and ventral tegmental area (VTA) as signs of JWH-018-induced neurodegeneration and neuroinflammation. Moreover, studies on anxiety-like (Elevated Plus Maze, EPM), and/or repetitive-like behaviors (Marble Burying, MB), and attentional processes (Prepulse Inhibition, PPI) were performed.
Results showed that JWH-018 treatment increases IBA-1 immunoreactivity in the NAc core and reactive astogliosis (GFAP) in the mPFC and in the NAc shell. Behavioral data showed that JWH-018 treatment increases anxiety-like states and repetitive-like behaviors as revealed by a decreased time spent in the open arms of the EPM and by the higher number of marbles buried in the MB test, and impairs the PPI of the acoustic startle reflex**.**
These results allow to speculate that the activation of microglia and astrocytes, that are an index of neuroinflammation, might be related to the behavioral central effects observed after the treatment with JWH-018.

P13.17

IMpact evaluation SURVEY: AFTER COMPLETION of Euro-Mediterranean Master in Neuroscience and Biotechnology ONline

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The social impact of the Euro-Mediterranean Master in Neuroscience and Biotechnology graduates' roles in their scientific environment of several Euro-Mediterranean countries remain unidentified. The Master is multidisciplinary integrating 11 partner universities located in France, Italy, Spain, Egypt, Lebanon and Morocco.

Principles of inter-professional education, such as cooperation, teamwork, flexibility, sociopolitical influence, and expertise among other actions as well as the higher parameters of learning goals for innovation and creation will compose the conceptual framework. Data collection will use Opinio, a survey online platform hosted by Ryerson. The survey has the following objectives: (a) Identify the extent of social impacts related to the use of refined professional skills towards the development of scientific expertise and practice by the Master's graduates; (b) Analyse the contribution of the Master's graduates to the professional contexts of neuroscience and biotechnology in Euro-Mediterranean countries; and (c) Enlighten Master's graduates' practice and roles by revealing their trends and knowledge gaps so as to inspire the creation of future inter-professional training programs in the fields of neuroscience and biotechnology that are able to respond to the timely scientific and societal trends in the target countries.

They are expected to portray graduates' views of the extend of refinement of professional objectives and achievements, integration into the labor market, participation in a research community, change on ways of thinking, of understanding their practice setting and the nature of their professional service to the local and scientific communities. They will indicate which new attitudes, knowledge, awareness, skills, motivation and intentions have been influenced by the Master.

Key aspects regard to international partnerships in evaluative research within global perspectives of changes in professional practice in countries with unequal work conditions.

Participants' accounts will equally inform curriculum redevelopment as well as new areas for consolidating and expansion.

P13.18

"OXIDATIVE STRESS-INFLAMMATION-APOPTOSIS" NETWORK IN THE PATHOGENESIS OF ISCHEMIC STROKE

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Oxidative stress (OS), postischemic inflammatory response and apoptosis are the key pathogenic factors leading to uncontrolled cell damage and death, which badly influences ischemic stroke (IS) progression and outcome. The molecular

mechanisms involved in the development of these processes are not clear yet, which is limiting the identification of therapeutic targets for IS.
The aim of this study was to reveal the molecular mechanisms responsible for the development of OS, inflammatory reactions and apoptosis in human IS on the systemic level and to identify the molecular components involved in these processes.
The levels of lipid hydroperoxides, lipofuscin, 3-nitrotyrosine, 8-isoprostaglandine-F2α, matrix metalloproteinases-9, and 8-hydroxi-2'-desoxiguanosine, mannan-binding lectin (MBL), ficolins H and L as well as the activities of mannan-associated serine proteases 1 and 2 (MASP-1, MASP-2), apoptotic marker annexin-A5, the total capacity of antioxidants (TAC), ferroxidase activity of ceruloplasmin (FAC) and the activities of superoxide dismutase and catalase, as well as the possible association of IS with the *ANXA5* gene *rs11575945* (-1C/T) were assessed by using blood serum, hemolyzed erythrocytes and DNA samples of IS-affected and healthy subjects (HS).
The results obtained demonstrated an increase in the TAC and FAC, as well as in levels of lipid hydroperoxides, MBL, MASP-1, MASP-2 and annexin-A5 in response to OS at day 1 of IS-onset. In addition, it was shown that the *rs11575945* (-1C/T) polymorphism of the annexin-A5 gene is associated with IS.
Based on the data obtained, we concluded that ischemic stroke is characterized by the alterations in the "oxidative stress-inflammation-apoptosis" network, and that lipid hydroperoxides, TAC, ceruloplasmin, MBL, MASP-1, MASP-2 and annexin A5 may be considered as targets for targeted therapeutic correction of ischemia induced inflammatory reactions and destructive processes in IS.

P13.19

PHENOTYPIC OVERLAP BETWEEN DISRUPTION OF SNRNP BIOGENESIS AND SMN-GEMINS COMPLEX PERTURBATION: IMPLICATIONS FOR MOTOR NEURON DISEASE

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The neuromuscular disorder, spinal muscular atrophy (SMA), is the result of insufficient levels of the ubiquitously-expressed survival motor neuron (SMN) protein. SMN associates with Gemins 2-8 and Unrip to from the large macromolecular complex. The SMN-Gemins complex is key for chaperoning the coupling of a heptameric ring of Sm proteins with small nuclear RNAs thereby generating small nuclear ribonucleoproteins (snRNPs), the core constituents of the spliceosome. The early snRNP assembly phase involves post-translational modification and the formation of two distinct Sm protein sub-complexes each sharing pICln, which prevents premature RNA interactions. In the late snRNP assembly phase, the 7-methylguanosine cap of assembled snRNPs is hypermethylated by trimethylguanosine synthase 1 (Tgs1). The modified cap together with the Sm ring act as a nuclear-localisation signal. In view of non-canonical functions linked to the SMN-Gemins complex including a role in the axonal trafficking of mRNAs, it is still presently unclear how defects in snRNP assembly can be reconciled with the selective neuromuscular degeneration that is typical in SMA. Attempting at

addressing whether the involvement of the SMN-Gemins complex in snRNP biogenesis is imperative for a functional neuromuscular system *in vivo*, we examined phenotypes resulting from the disruption of pICln or Tgs1, two cardinal players in the snRNP biogenesis pathway, which have never been directly linked to axonal metabolism. Intriguingly, we uncover that deviations from normal protein levels in muscle tissue including overexpression of full-length pICln or enhanced Tgs1 knockdown results in adult flies with severe motor system defects, in contrast to controls but similar to flies with either muscle-restricted Gemin3 knockdown or SMN loss-of-function. We also demonstrate a genetic and physical interaction between Gemin3 and pICln or Tgs1 with such findings confirming that members of the SMN-Gemins complex work closely with snRNP assembly factors *in vivo*. Interestingly, we find that overexpression of either pICln or Tgs1 was by itself sufficient to cause motor dysfunction in *Drosophila*. Toxicity is conserved in the yeast *S. pombe* where overexpression induces a surplus of Sm proteins in the cytoplasm, indicating that a block in snRNP biogenesis is partly responsible for this phenotype. We propose that snRNP biogenesis is the pathway connecting the SMN-Gemins complex to a functional neuromuscular system, and its disturbance most likely leads to the motor dysfunction that is typical in SMA. Considering the intersection of the SMN-Gemins complex with amyotrophic lateral sclerosis (ALS) our findings have broader implications on our understanding of the mechanisms underpinning motor neuron disease.

P13.20

AMPHETAMINE AND THE 'BATH SALT' MDPV ENHANCE GENERALIZATION OF MEMORY FOR EMOTIONAL EXPERIENCES IN RATS

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The mechanisms by which drugs of abuse affect the accuracy of memory processes are not well understood. Here we tested the effects of the psychostimulants Amphetamine and the “bath salt” MDPV in an inhibitory avoidance discrimination task.

Male SD rats (350-370 g) were trained and tested in different apparatuses. During training rats were placed into the light compartment of a first inhibitory avoidance (Non-Shock box) and they were allowed to cross to the dark compartment. Then, after a 1-min delay, they were placed into the light compartment of a second, contextually distinct, inhibitory avoidance apparatus (Shock box), and they received footshock upon entering the dark compartment. Amphetamine (1-3 mg/Kg), MDPV (0.5–1 mg/Kg) or saline were administered (i.p.) immediately after training. On the 48-h retention test, rats were tested, in a randomized order, in the Shock and Non-Shock boxes as well as in a Novel box.

Controls had similar retention latencies in the Shock and Non-Shock boxes, indicating lack of discrimination. However, latencies in the Shock and Non-Shock boxes were longer than those in the Novel box, indicating that rats recognized the two training contexts. Amphetamine (3 mg/kg) increased retention latencies in the Shock box indicating an increase in memory strength. However, retention latencies in both safe environments were also increased, indicating an increased

generalization. MDPV did not enhance memory, but it (1 mg/Kg) increased retention latencies in the Novel box, inducing generalization.
Amphetamine and MDPV had differential effect on memory strength, but both drugs increased generalization of memory for emotional training. It is tentative to hypothesize that the different effects on memory strength versus generalization could be due to differences in the modulation of the monoaminergic neurotransmissions, in the recruitment of different brain areas or in the interaction with the stress response systems.

P13.21

THE EFFECT OF DISULFIRAM ON MORPHINE SELF-ADMINISTRATION AND REINSTATEMENT OF SEEKING BEHAVIOR IN RATS

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Disulfiram (DSF), the anti-alcoholism drug, is also effective in the treatment of cocaine addiction and in cocaine and alcohol co-abuse. Up to now, there are no reports indicating the effects of DSF on the behavioral actions of opioids. In our preliminary studies we have shown that DSF alleviates the symptoms of withdrawal after methadone or morphine treatment and reduces tolerance to the analgesic effects of these opioids in acute pain model.
In the present study we investigated the effect of DSF on morphine self-administration and reinstatement of seeking behavior in rats.
Male Wistar rats were trained to self-administer morphine (0.5 mg/kg/inf.) and each drug infusion was associated with contextual cue (light+tone). Another group of rats underwent morphine self-administration and extinction training. After 14 days of extinction, reinstatement of responding was induced by morphine (2.5-5 mg/kg, ip) or drug associated cue. For statistical analyses a multi-way ANOVA with repeated measures and post-hoc Newman-Keuls' test were used.
During maintenance of morphine self-administration we found that acute treatment with DSF 12.5-50 mg/kg (ip) dose-dependently attenuated behavioral responding of rats, with significant reduction in the number of active lever presses and drug infusions. Moreover, at 6.25-25 mg/kg DSF decreased morphine seeking-behavior triggered by morphine priming or cues in rats previously administered morphine. Daily pretreatment with DSF (50 mg/kg) during extinction non-significantly reduced behavioural responses at first three drug-free days. Furthermore, repeated treatment with DSF during extinction did not affect the following reinstatement of drug-seeking behavior in rats.
Our findings show that the DSF may hold promise as potential pharmacotherapies for morphine addiction as applied in the form of acute prevention for morphine relapse.
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P13.22

AGGRESSIVE BEHAVIOR AND SOMATIC PROBLEMS IN MOROCCAN STUDENTS REPORTING ABUSE AND ALCOHOLISM IN THEIR HOME

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Increased aggressive behaviour in youngsters has been coupled to the development of several negative outcomes in adulthood, such us substance use, personality disorder and criminality. Background factors explaining their deviant behaviour include both familiar and environmental factors. The aim of the present study was to compare the prevalence of atypical aggression and defined somatic problems in those children who have reported alcohol use or psychological/physical abuse at their home with these factors in.

Self-reported information from 280 (145 boys and 135 girls, ages between 15 and 18) Moroccan students were assessed during the on-going international project: "Mental and Somatic Health without borders (MeSHe)". The MeSHe survey includes, between other mental health inventories, measure of aggressive trait and gathers information about somatic health and social environmental factors.

Almost 70% of the students who reported alcohol-use problem or abuse at home also reposted headaches, and almost every fourth of them reported migraine. Of those who experienced abuse at home significantly more also indicated complains for diarrhoea or constipation, and significantly more had allergies. They had also significantly increased risk of having an atypically high level of aggression themselves (54% increase when family they had alcohol use in their family was reported and 77% increase when psychological/physical abuse accord in their family).

The presence of alcoholic parents or physical/psychological abuse in adolescence, increase the risk of atypical aggression and the risk for coexisting somatic complains.

P13.23

PLA2G4E produces a class of endocannabinoid precursors in mouse brain

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PLA2G4E is a serine hydrolase recently shown to produce N-acylphosphatidylethanolamines (NAPEs) through a calcium-dependent acyl transfer reaction when overexpressed in mammalian cells. NAPEs represent precursors of N-acyl ethanolamines (NAE), a class of bioactive lipids that includes the endocannabinoid anandamide (AEA). Though much is known about the degradation of NAEs, their biosynthesis is less well understood. In order to investigate a potential role for PLA2G4E in the biosynthesis of endocannabinoids, we generated and characterized mice with targeted disruption of the *Pla2g4e* gene.

Prior studies indicate that PLA2G4E is primarily expressed in mouse brain, heart, skeletal muscle, and testis. For our experiments, these tissues were collected from $PLA2G4E^{+/+}$ and $PLA2G4E^{-/-}$ mice and processed to obtain their membrane

proteomes. These proteomes were first studied by activity-based protein profiling (ABPP) using serine hydrolase-selective fluorophosphonate probes and were then tested for their ability to catalyze the synthesis of *N*-C16:0 NAPE in the presence and absence of $CaCl_2$ using an LC/MS assay.
The results from our SDS-PAGE and LC/MS experiments support successful knockout of PLA2G4E and confirm no other significant variations in the expression levels of serine hydrolases in these tissues. Further, we found that calcium-dependent NAPE production in PLA2G4E$^{-/-}$ brain proteomes was reduced by > 90% compared to PLA2G4E$^{+/+}$ proteomes. These data support the assignment of PLA2G4E as the primary enzyme responsible for the calcium-dependent generation of NAPEs in brain.
The endocannabinoid system is involved in many functions, including brain development and stress. Understanding the physiological role of PLA2G4E in the biosynthesis of NAEs will provide important insight into the production of endocannabinoids and potentially inform our understanding and treatment of abnormal endocannabinoid signaling in disorders like neurodegeneration and addiction.

P13.24

NANOSCALE IMAGING OF VENTRAL TEGMENTAL AREA DOPAMINE CELL INPUTS FOLLOWING PRENATAL Δ^9-TETRAHYDROCANNABINOL EXPOSURE

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Marijuana consumption during pregnancy has been associated with impairments in fetal brain, and with cognitive and behavioral disruptions long after birth. In the brain, the psychoactive compound of marijuana, Δ^9-tetrahydrocannabinol (THC), activates cannabinoid receptor 1 (CB1), which is expressed on presynaptic terminals and modulates neurotransmitter release. As a part of the endocannabinoid system, CB1 play a pivotal role in neuronal differentiation and synaptogenesis. However, preclinical studies investigating synaptic molecular changes in reward-related areas following marijuana exposure are still elusive.
In this study, rat dams were administered THC (2 mg/kg), or its vehicle, once per day from gestational day 5 to 20. Correlated confocal/STochastic Optical Reconstruction Microscopy (STORM) was performed to image with nanoscale precision synaptic changes of offspring ventral tegmental area (VTA) during peri-adolescence (PND 21-29). Particularly, immunostaining for tyrosine hydroxylase (TH) and for vesicular glutamate 1 (VGluT1) or GABA transporter (VIAAT) allowed visualization of dopamine cells and excitatory or inhibitory afferents, respectively. Concurrent immunostaining for CB1 or bassoon allowed STORM-based molecular quantification within boutons.
In the offspring of THC-exposed dams, we found a reduced number of TH positive cells and reduced bouton area in the vGluT1, but not VIAAT, afferents impinging onto these neurons. CB1 content of both vGluT1- and VIAAT-positive axon terminals was not changed. Consistently, CB1 density in vGluT1 containing boutons was higher following prenatal THC exposure. Number and clustering of bassoon STORM

localization points were the same in THC and control groups, suggesting that the active zone structure remained intact.
Our results show that exposure to marijuana during early development perturbs reward-related areas in the brain, which might result into increased vulnerability toward psychiatric disorders, later in life.

P13.25

NEUROANATOMICAL CHANGES ASSOCIATED WITH A MINDFULNESS-BASED INTERVENTION IN INDIVIDUALS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD): DESIGN AND RATIONALE FOR A CONTROLLED TRIAL

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The prevalence of the attention deficit hyperactivity disorder (ADHD) has been on the rise over the past decades. The reasons for this increase are complex and the expression of the disorder is heterogeneous, ranging from mild to severe disturbances in attention, cognition, motivation and emotion regulation. The most common treatment consists of administration of stimulants, such as methylphenidate and amphetamine. However, researchers and clinicians started exploring alternative modes of treating ADHD including mindfulness-based interventions (MBIs). Our recent meta-analysis shows that these MBIs may be moderately effective in reducing symptoms of ADHD. However, we do not know anything about the underlying neural mechanisms of this effect. Thus, the purpose of the present study is to examine neurocognitive effects of an intensive 8-week MBI on young adults with ADHD in comparison to matched healthy controls. Participants will undergo cognitive assessment, as well as magnetic resonance imaging (MRI) to evaluate structural (using diffusion tensor imaging – DTI) and functional (using resting-state fMRI) connectivity, before and after the intervention. We expect to find improvements on measures of attention, executive function and emotion regulation, in both groups, though the gains should be greater in individuals with ADHD than in controls. At the neural level, we expect to find strengthening of the central executive network (CEN) and reorganization of the default-mode network (DMN) and salience network (SN), which will be apparent especially in the ADHD group. The results should reveal the neural mechanisms underlying effectiveness of MBI for ADHD, thus reinforcing the case for using it in addition, or instead of, medication in this disorder.

P13.26

PRENATAL STIMULATION OF THE ENDOCANNABINOID SYSTEM AND THE CONSEQUENCES ON THE MOTHER-INFANT DYAD: A PRECLINICAL REMARK

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The dam-infant interaction is a fundamental relationship, functionally necessary to the infant's wellness and to the development of his own behavioural and physiological repertoire. Drugs exposure during pregnancy induces detrimental consequences, that are not limited to the direct in utero effects of the drug on fetuses, but also extend to maternal care. The present study investigates the effects induced by prenatal stimulation of endocannabinoid system on maternal behaviour along postnatal period. Female rats received a stimulation of the endocannabinoid system from gestational day 5^{th} to 20^{th}. Maternal care was assessed by recording dams' undisturbed spontaneous home-cage behaviour in the presence of their offspring. Our results show that prenatal stimulation of endocannabinoid system induced a deescalation in maternal behaviour with respect to vehicle over the postnatal period ($p<0.001$). Furthermore, the prenatally treated dams showed a significant increase in single non-maternal behavioural categories, such as self-grooming, dam self-care, rearing and general arousal when compared to controls ($p<0.01$; $p<0.001$). The outcomes of this study show that prenatal exposure to cannabinoids reduces the dams-offspring attachment and underlie the importance of modelling human drug habit and its consequences on the mother-infant dyad, in order to prevent detrimental effects on offspring development and maturation.

P14.1

AN INVESTIGATION OF THE ROLE OF CHANGES IN THE VAGUS NERVE IN OBESITY INDUCED BY A HIGH-FAT DIET: A STEREOLOGICAL AND IMMUNOHISTOCHEMICAL STUDY

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Developing technology and the increasing pace of life have reduced our need to move, while adding high-calorie foods to our diet. Deleterious changes in eating habits cause the calorie balance in the body to deteriorate. Increased calorie intake and a decrease

in calorie expenditure causes this balance to deteriorate toward excess calories and results in these being stored as fat reserves in the body. This then results in obesity. Obesity accompanying cardiovascular diseases, diabetes, psychological disorders, biliary and many other diseases prepares the ground for potentially fatal risks.

This study was intended to investigate how vagus nerve operations alter body weight, as well as the hunger and satiety centres, and to examine the relationship between the hypothalamus and the vagus nerve. Thirty-two obese *Wistar albino* rats were randomly divided into four groups - control, sham, inhibition and stimulation. No procedure was performed in the control group. In the sham group, the left vagus nerve was opened and closed with a 1-cm midline incision 2 cm below the neck region. The neck area of the subjects from the stimulation group was opened using the same surgical technique, and a special stimulator was attached to the left vagus nerve. Postoperative investigation began on the second day and lasted for 4 weeks, with vagal stimulation being applied for 5 minutes a day at a frequency of 30 Hz / 500 ms / 30 seconds. In the inhibition group, a similar incision was made, and the nerve was tightened for 30 seconds using a special clamp capable of applying 58 Newtons of pressure for damage output. After surgery, subjects were left to heal for 4 weeks. At the end of the 13th week of the experiment, all subjects were perfused, and the number of myelinated axon fibers, the average myelin thickness in vagus nerve samples, and total numbers of neuron nuclei within the hypothalamus were estimated using stereological techniques. Neurons in the hypothalamic nuclei were evaluated immunohistochemically with anti-neuropeptide Y and anti-POMC.

Arcuate, ventromedial and dorsomedial nuclei were analysed in the hypothalamic field. The mean number of neurons in the arcuate and ventromedial nucleus areas increased in the stimulation group. The mean number of neurons in the dorsomedial nucleus area decreased. The mean number of neurons decreased in all nucleus areas in the inhibition group. The number of myelinated axons increased in the inhibition group, while myelin sheath thickness and myelinated axon area decreased considerably at analyses of vagus specimens. No significant differences were observed in terms of other parameters between the other groups. Immunohistochemical analysis revealed the most active cells in the stimulation and the inhibition groups, while NPY active cells were observed in the control and sham groups. The greatest weight loss was determined in the inhibition group.

In conclusion, the neuronal increase observed in the arcuate and ventromedial nucleus areas is probably due to the secretions of these two nuclei, which regulate energy metabolism, and suggests that the stimulation mechanism in obesity occurs mainly through ventromedial nucleus secretions.

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P14.2

EFFECTS OF TOPIRAMATE ON THE VENTROMEDIAL AND DORSOMEDIAL NUCLEI AND HYPOTHALAMIC LEVELS OF OBESITY-ASSOCIATED PROTEIN IN OBESE RATS

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Obesity has become one of the most common health problems and the cause of many diseases. Investigation of the mechanisms involved in obesity has revealed that food intake and appetite are regulated by the activities of the hypothalamic nuclei, including the brain's hunger and satiety areas. This study investigated the effects of topiramate on weight loss in the hypothalamic nuclei. Fat-mass protein (FTO) levels were also investigated in these nuclei. Twenty four female *Wistar albino* rats were randomly divided into four groups of six subjects each - obese, obese-topiramate, control and control-topiramate. The obese groups received a 40% high-fat diet, while the control groups were given a standard diet throughout the study. Topiramate was administered at 0.02 mg / kg once daily for six weeks in the topiramate treatment group. At the end of six weeks, the animals were sacrificed with intracardiac perfusion, and their brain tissues were removed. The extracted brain tissues were subjected to routine histological procedures, and serial sections 20 microns in thickness were taken from the brain tissues of five animals for stereological analysis. Sections seven microns in thickness were taken from the brain tissues for immunohistochemical analysis from one rat randomly selected from each group.
Hypothalamic nuclei in the sections taken for stereological analysis were analysed using optical fraction methods. Immunohistochemical staining was performed using anti-FTO
antibody for FTO concentrations in the nuclei. The mean number of neurons in the dorsomedial nucleus was significantly lower in the obese topiramate group than in the obese control group. No significant difference was observed between the control and control topiramate groups. The mean number of neurons in the ventromedial nuclei was significantly lower in the control group than in the other groups. The mean number of neurons increased in the obese control and control topiramate groups compared to the
control group. No difference was observed between the obese control and obese topiramate groups. The largest number of FTO positive cells was observed in the obese control group and the lowest number in the topiramate control group. The results show that obesity and anti-epileptic drugs used for treatment produce different effects on the two nuclei.
We attribute this variation to the role of dorsomedial and ventromedial nuclei in the regulation of energy metabolism and body heat and the various roles played by obesity. In addition, the results are significant in terms of topiramate's weight-loss effect being based on the reduction of body heat or suppression of certain fasting proteins. FTO density study confirmed that FTO expression was increased by obesity, supporting the hypothesis that the effect of topiramate may be related to fasting proteins.

The relationship between obesity and topiramate now needs to be clarified through detailed pathway analysis of the nuclei and FTO gene expression.
This study was supported by Ondokuz Mayıs University (PYO.TIP.1904.13.024).

P14.3

ACTIVATION OF HYPOTHALAMIC 5-HT$_1$ AND 5-HT$_2$ RECEPTORS DIFFERENTLY REGULATES ENDOCRINE RESPONSES AND LIVER CYTOCHROME P450 EXPRESSION AND ACTIVITY

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Our earlier work showed that brain serotonergic system affected the expression of cytochrome P450 (CYP). Serotonergic innervation of the hypothalamic paraventricular nuclei (PVNs) had a positive effect, while that of the arcuate nuclei (ARCs) had a negative impact on growth hormone (GH) secretion and GH-dependent CYP expression. The aim of the present study was to identify 5-HT receptor types in the PVN and ARC, engaged in the regulation of liver CYP expression and activity.
The experiment was carried out on male Wistar rats. Intracerebral injections of 5-HT$_1$ receptor agonists (5-CT – 5-HT$_1$ agonist; 8-OH-DPAT – 5-HT$_{1A}$ agonist; sumatriptan – 5-HT$_{1B/D}$ agonist) or the 5-HT$_{2A/2C}$ receptor agonist DOI into the PVN or ARC were performed for five days. Liver CYP expression (mRNA, protein) and activity (testosterone hydroxylation), as well as pituitary and serum hormones were measured.
When injected into the PVN, 5-CT significantly decreased the expression and activity of the isoenzymes CYP2C11 and CYP3A, being accompanied with an increase in pituitary somatostatin and a decrease in serum GH concentration. Similar effects were observed after 8-OH-DPAT. Sumatriptan or DOI had no effect on liver CYP. In contrast, DOI, but not 5-CT, injections into the ARC caused a significant increase in the expression and activity of CYP2C11 and CYP3A.
The results indicate that – *via* stimulation of somatostatin release and a consequent decrease in GH secretion in the pituitary – 5-HT$_{1A}$ receptors of the PVN negatively regulate CYP2C11 and CYP3A. On the other hand – *via* stimulation of the secretion of GH releasing hormone and the resulting increase in GH release – 5-HT$_2$ receptors of the ARC positively regulate CYP2C11/3A (60% of total CYP).
The obtained results show involvement of the 5-HT$_{1A}$ receptors of the PVN in the negative regulation, and the role of the 5-HT$_{2A/C}$ receptors of the ARC in the positive regulation of liver cytochrome P450 expression and activity *via* neuroendocrine mechanisms.

P14.4

THE VISIBLE BURROW SYSTEM: A NEW BEHAVIOURAL PARADIGM TO ASSESS SOCIAL WITHDRAWAL IN GROUP HOUSED RODENTS

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Social withdrawal is an early symptom of a wide variety of neuropsychiatric diseases, such as schizophrenia, autism spectrum disorders, depressive disorders and

Alzheimer's disease. The paucity of objective measures to longitudinally assess social withdrawal characteristics has been an important limitation to study this behaviour, both in human and rodents. Although a small number of studies have identified ways to study social group behaviour in rodents in a longitudinal manner, it is currently unknown whether outcome measures from these paradigms will be relevant for social withdrawal behaviour observed in neuropsychiatric patients.
The aim of the present work was to study social withdrawal in rodents using a new behavioural paradigm, the Visible Burrow System (VBS). The VBS mimics a natural environment, with male and female rodents housed together in an enclosure where an open arena is connected to a continuously dark burrow system that includes 4 boxes connected by corridors. In this study, mixed-sex colonies of C57BL/6J and of BTBR mice have been investigated.
Results showed marked differences between the two strains, in terms of social interactions as well as non-social behaviours, pointing out the advantage of the use of VBS to study social group behaviour dynamics that naturally occur in a mixed-sex colony.
In conclusion, this social housing model appears to be a powerful tool to longitudinally study social withdrawal aspects that may be relevant in neuropsychiatric disorders.

P14.5

TIME DEPENDENT EFFECTS OF RESTRAINT AND CROWDING STRESS ON THE EXPRESSION OF GLUTAMATE RECEPTORS IN THE RAT PREFRONTAL CORTEX

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Stress, depending on its intensity, nature and time of exposure, can evoke maladaptive changes and lead to stress related disorders. Disturbance in glutamatergic transmission in prefrontal cortex (PFC) is considered to underlie this pathology. In presented study we measuredGluA1, GluN2B and mGluR1a/5 expression in PFC of rats that underwent different time of exposure to stress of crowding (CS) or restraint (RS). Furthermore, we assessed how sub-chronic CS affects basal synaptic transmission and induction of LTP.
Three main experimental groups of male Wistar rats were studied: control, CS and RS. Stress procedures were performed for 3, 7 or 14 days. Protein expression was assessed by Western Blot. Electrophysiological recordings of field potentials and LTP were done in layer II/III after stimulation of layer V.
Electrophysiological results revealed increased relation between stimulus intensity and field potential amplitude together with attenuated LTP in CS-3d rats. Analysis of protein expression has shown in CS-3d increased level of GluA1, GluN2B and mGlu1a/5 (respectively by 50, 112 and 56% vs. control). Similar increase (~50% vs. control) was also observed in RS-7d group. In contrast, chronic (14d) CS and RS attenuated the level of GluA1, GluN2B and mGluR1a/5 (~30% vs control).
Our data demonstrate that stress triggers dynamic and time-dependent changes in the level of glutamate receptor proteins. Because GluA1 and GluN2B are subunits that modulate membrane stability of AMPA and NMDA receptors, their augmented expression can explain increased basal activity of PFC neurons after sub-chronic stress. LTP reduction in this group suggests that observed basal over-activation is

reversely correlated with synaptic strengthening in PFC. Prolonged stress-evoked decrease of glutamate receptor proteins may contribute to PFC hypofunction observed in stress related disorders.
The study supported by statutory funds of Institute of Pharmacology PAS.

P14.6

CHRONIC STRESS EXPOSURE INDUCED THE DEVELOPMENT OF COGNITIVE DEFICITS: INVOLVEMENT OF GENOMIC VS NON-GENOMIC EFFECT MEDIATED BY GLUCOCORTICOID RECEPTORS

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Psychiatric diseases are characterized by an altered function of the HPA axis. Moreover, this system is also involved in learning and memory processes and its deregulation may lead to the development of cognitive deficits. Corticosteroids, in the brain, activate the glucocorticoid receptors (GR) and the mineralocorticoid receptors (MR) both at nuclear and membrane level.
Hence, we investigated the effect of the exposure to the chronic mild stress (CMS) on the cognitive performance and, at molecular levels, on the genomic vs non genomic activity of GR and MR in the dorsal hippocampus. Wistar rats were exposed to CMS (7 weeks), tested at weekly intervals with sucrose consumption test to assess anhedonia. At the end of the CMS, the animals were exposed to novel object recognition (NOR) test. mRNA levels analysis of GR responsive genes were carried out by Real-Time PCR, whereas Western blot was used to conduct protein assay.
Rats exposed to CMS develop an anhedonic phenotype and an impairment in the cognitive performance assessed in the NOR test. At molecular level, CMS per sè increased GR protein levels in the membrane compartment, effect paralleled by an up-regulation of SINAPSYN Ia/b phosphorylation in Ser603. Differently, NOR test exposure induced a significant increase of GR protein levels in the nucleus of no stress rats and this increase mirrors an up-regulation of the transcriptional activity of GR as demonstrated by the effect observed on Gadd45b and Sgk-1 mRNA levels.
These findings suggest that the activation of GR genomic pathway is fundamental for the correct cognitive performance, while CMS exposure induces a behavioral deficit probably interfering with this mechanism. This inactivation of GR in stressed rats might be indicative of the so-called “glucocorticoid resistant” a key feature of depressed patients. Moreover, CMS, increasing the availability of GR at membrane levels, seems to direct preferentially the action of hormones to the non-genomic pathways.

P14.7

A SPECIFIC SOCIAL INTERACTION TEST FOR THE STUDY OF A MOUSE MODEL OF SOCIAL ANXIETY DISORDER

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Social anxiety disorder (SAD) is characterized by a marked and persistent fear about social situations including social interactions, performing in front of others and participating in grouped activities. Once, largely neglected by the medical community, SAD gained more attention a decade ago but remains poorly elucidated. Therefore, animal models of SAD have been established in order to study the underlying etiology. Nevertheless, social interaction tests used to assess SAD related behavioral deficits are not specific and are far to mimic human social situations. Indeed, social behaviors in rodents are often studied in pairs under artificial and restricted conditions where no collective social activities are created. Hence, our current study aimed to establish a novel social interaction test based on the evaluation of social behavior of a mouse put in a rich environment with a group of three unfamiliar con-specifics.
To achieve this goal, we utilized a mouse model of social fear conditioning (SFC) to induce SAD and assessed, one day after, the social interaction test through the evaluation of three main parameters: i) time spent by the experimental mouse investigating arena objects when being close or away from unfamiliar con-specifics; ii) time spent exploring unfamiliar con-specifics and iii) freezing time.
Our results revealed that, one day after SFC, conditioned mice showed a significant increased individual object investigation compared with unconditioned mice which showed intensive collective object investigation. Moreover, conditioned mice showed an increased freezing time and a decreased social approach time compared with unconditioned mice.
To conclude, while most social interaction tests evaluated mainly social avoidance or social approach behaviors in the study of SAD, our test was able to provide a new experimental framework for studying social interactions in more complex situations close to those observed in humans.

P14.8

PAINT THINNER EXPOSURE ALTERS BEHAVIORS AND ADULT HIPPOCAMPAL NEUROGENESIS IN MICE

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Thinner is a highly toxic chemical solvent that has psychoactive properties when inhaled. Chronic thinner abuse causes several behavioral and functional abnormalities. However, the mechanisms involved in these effects are relatively poorly understood. Given the well-known critical role of adult hippocampal neurogenesis in learning and memory and its implication in disease conditions associated with cognitive impairment, depression, and anxiety, we investigated its possible alteration following thinner inhalation.
Tests evaluating anxiety, depression, learning and memory function were performed after acute, subchronic and chronic thinner inhalation. In addition, adult hippocampal neurogenesis was evaluated by using means immunohistochemical markers of neurogenesis.
Our results demonstrate that chronic exposure to thinner resulted in increased depression-like behaviours and an anxiolytic effect. Behavioral tests showed that while no deficits were found in acutely treated mice, significant alterations were

found in both subchronic and chronic exposed mice, indicating that long term inhalant treatment impacts also on learning and memory. In addition, long term thinner-treatment, but not acute treatment, decreased the rate of neurogenesis in hippocampal dentate gyrus as shown by reduced number of proliferating progenitors and immature neurons in this structure.
The exposure to thinner affects hippocampal neurogenesis by impairing survival of newborn cells and reducing progenitor proliferation. On the whole, these findings support a possible causal link between adult neurogenesis alteration and behavioral dysfunction associated with thinner exposure.

P14.9

DIVERSE EFFECTS OF CODEINE MICRONIJECTIONS IN SOLITARY TRACT NUCLEUS AND LATERAL TEGMENTAL FIELD ON COUGH IN CATS

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Microinjections of codeine (3.3 mM or 33 mM) in the solitary tract nucleus rostral to the obex (rNTS), caudal to the obex (cNTS) and the medullary lateral tegmental field (FTL) were performed on 27 anesthetized spontaneously breathing cats. Tracheo-bronchial cough was induced by mechanical stimulation of the trachea with a soft nylon fiber. Blood pressure, esophageal pressure (EP) and electromyograms (EMGs) of the diaphragm (DIA) and abdominal muscles (ABD) were recorded.
Microinjections of 3.3 mM codeine in the rNTS (68±4 nl for both microinjections, the total dose 0.22±0.02 nmol, 6 cats) resulted in reduced cough number, expiratory amplitudes of ABD EMG and EP and amplitudes of DIA EMG during cough. There was no significant change in the duration of cough phases in response to microinjection of codeine into the rNTS. The only altered cough related time interval was the prolongation of the period between the peak activity of DIA and ABD (from 0.24±0.01 s to 0.31±0.03 s, $P<0.05$).
Codeine microinjections into the cNTS (108±33 nl for both microinjections, total dose 1.56±0.58 nmol, 3 cats with 3.3 mM and 3 cats with 33 mM codeine) had no significant effect on tracheobronchial cough (all $P>0.1$).
Microinjections of 33 mM codeine in the FTL (66±6 nl for both microinjections, the total dose 2.18±0.19 nmol, 7 cats) reduced cough related amplitudes of DIA and ABD EMGs, inspiratory and expiratory EP amplitudes. There was no significant effect of codeine microinjections into the FTL on number of coughs and the temporal characteristics of cough.
Control microinjections of a vehicle in all selected areas had no significant effect on cough.
Our data showed that codeine has a diverse effect on cough reflex in these brainstem locations. Unlike the cNTS, the rNTS and the adjacent region of the reticular formation (rostral and dorsal FTL) contains codeine sensitive complex neuronal circuits involved in control of cough reflex in the cat.
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P14.10

REPEATED CORTICOSTERONE ADMINISTRATION ATTENUATES THE MODULATION OF GABA-ERGIC TRANSMISSION BY 5-HT$_7$ RECEPTOR IN THE RAT DORSAL RAPHE NUCLEUS

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Chronic stress and elevated level of corticosterone have been implicated in the pathology of depressive disorders. Dorsal raphe nucleus (DRN), being a major source of brain serotonin, regulates the stress response and is involved in the development of stress-related psychiatric disorders. The 5-HT_7 receptor is one of several serotonin receptor subtypes expressed in the DRN, where it modulates GABA-ergic transmissionì. The aim of this study was to determine the effects of repeated corticosterone administration on GABA-ergic inputs to serotonergic neurons of the DRN and their modulation by the 5-HT_7 receptor.
Male Wistar rats received subcutaneous injections of corticosterone (10 mg/kg, volume 1 ml/kg) or the vehicle (1% Tween 80; volume 1 ml/kg) twice daily, for 7 or 14 days. The effects of these treatments were examined 24 h after the last administration. Whole-cell recordings were carried out from putative serotonergic neurons in slices containing DRN. To assess the GABA-ergic transmission spontaneous inhibitory postsynaptic currents (sIPSCs) were recorded. In some experiments 5-CT was applied in the presence of WAY 100635 to selectively activate the 5-HT_7 receptor.
In slices originating from rats treated with corticosterone for 7 as well as 14 days, the mean frequency, but not the mean amplitude of sIPSCs, was markedly lower than that in slices originating from control animals receiving vehicle. Activation of the 5-HT_7 receptor resulted in a significant increase in the mean frequency of sIPSCs in cells originating from control animals but not in corticosterone-treated groups.
These results suggest that corticosterone treatment causes an attenuation of the GABAergic transmission and affects the function of the 5-HT_7 receptor in the rat dorsal raphe nucleus. These effects may be related to stress-induced abnormalities in the functioning of the serotonergic system.
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P14.11
GENDER DIFFERENCES IN A NEW POTENT 5HT2A AGONIST EFFECTS: NEUROCHEMICAL AND BEHAVIORAL STUDIES AFTER 25I-NBOME ADMINISTRATION

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25I-NBOMe, commonly called “N-Bomb”, is a new synthetic compound, recently abused for its psychedelic and entactogenic effects; it is available on internet as a legal alternative to LSD, and as a surrogate of methamphetamine as well. It acts as full agonist of 5-HT2A receptor with high affinity on human and rat 5-HT2A receptors (Ki= 0.044 nM and Ki= 0.087 nM, respectively). Users are often unaware of ingesting fake LSD, and several intoxication cases and some fatalities have been reported after the ingestion. Overdoses of “N-Bomb” can cause several effects such as tachycardia, hypertension, seizures, and agitation persisting for up to three days. We decided to test 25I-NBOMe in both males and females to evaluate if there were

gender differences in the pharmacological effects. In the current literature, there are no data about the abuse liability of this compound and its pharmacological effects.
By *in vivo* microdialysis studies, we evaluate the effects of 25I-NBOMe (0.3-1mg/kg/ip) on dopamine (DA) and serotonine (5-HT) transmissions, both in male and female rats, moreover, sensorimotor studies, body temperature evaluation and nociception tests, were performed in both genders.
Our results showed that the phenethylamine 25I-NBOMe is more active in females, compared to males, in increasing DA transmission in NAc shell and in the mPFC; behavioral data showed that this compound caused visual alterations in both sexes, whereas core temperature in females is heavily affected, compared to males; indeed, the highest dose tested exerts an analgesic effect prominent in male rats, compared to female rats.
Taken together these results suggest that 25I-NBOMe affects DA and 5-HT transmissions in male and females in a different way, highlighting gender differences that can influence the frequency of ingestion, as well as the psychoactive effects, and the long-term effects. Further investigations are necessary to examine in depth the reason of these gender differences.

P14.12

USE OF THE PEPTIDE CLPFFD FOR THE DESIGN OF A MAGNETIC NANOHYBRID AGAINST SENILE PLAQUES IN ALZHEIMER DISEASE

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Alzheimer's disease (AD) is an insidious condition that represents the most common cause of dementia among elderly people. The brains of Alzheimer's patients have several distinctive neuropatological features: intracelular neurofibrillary tangles, senile plaques (SP) composed mainly of extracelular beta-amyloid (βA) and neurodegeneration. Due to the importance of the SP in the initiation and progression of neurodegeneration of AD, it has become one of the principal targets in therapeutic strategies against adverse neuronal outcomes. In this sense, nanotechnology is playing a decisive role in stopping or slowing the progression of this condition.
In this work, we characterize and review the peptide Cys-Leu-Pro-Phe-Phe-Asp (CLPFFD), capable of recognize and destabilize the SP, in vitro and in vivo, once adsorbed on magnetic nanoybrid, upon electromagnetic irradiation. For this goal, Raman Spectroscopy and Atomic Force Microscopy were performed.
Our data suggest that the use of magnetic nanohybrids attached with CLPFFD could be a good strategy for dissembling cerebral SP in the AD.
Additional experiments should be done to determine the effect of this approach in the reduction of the SP load and their implications in the memory of experimental models for this disease.

P14.13

IS THE COGNITIVE CONTROL IMPAIRED IN CHILDREN WITH AN ATTENTION DEFICIT/HYPERACTIVITY DISORDER?

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The Attention deficit/hyperactivity disorder (ADHD) is one of the most common developmental disorders diagnosed in childhood and it often persists into adulthood. It corresponds to symptoms of inattention, hyperactivity and impulsivity. These symptoms lead to great difficulties in school learning, and in social and familial relationships. A deficit in cognitive control is commonly found in children with ADHD. This has mainly been interpreted as due to difficulties in inhibiting inappropriate responses. However, cognitive control involves other processes than simply the ability to inhibit. Therefore, to deeper decipher cognitive control in children with ADHD, we used sophisticated analyses of the performance instead of classical measures such as mean reaction times (RT) and error rates. These analyses allowed us to dissociate the susceptibility of subjects to trigger an automatic response from their ability to suppress it. Moreover, we investigated the effect of methylphenidate (MPH) on these processes because MPH is the most prescribed medication and it is supposed to act on dopaminergic system.
We compared interference control between 25 children with ADHD without medication, 20 children with ADHD under MPH, and 20 control children performing a conflict task (the Simon reaction time task) well known to highly involve cognitive control. This task requires to inhibit an automatic response to the benefit of the action required by the rule.
Our data have shown that: 1/ difficulties in cognitive control of ADHD children would be due to both a higher susceptibility to trigger automatic responses and an inhibition deficit, and 2/ MPH improved this control by improving the selective inhibition of the automatic response without decreasing the strength of the automatic response. This suggests that these two processes would rely on different neurotransmitter systems, and more specifically, the selective inhibition only would rely on dopaminergic system.

P14.14

EPIGENETIC REGULATION OF ADENOSINE A2A AND DOPAMINE D2 RECEPTOR GENE TRANSCRIPTION ON COMPULSIVE FOOD CONSUMPTION

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Satisfactory treatments for eating disorders, such as binge eating disorder and bulimia nervosa, are not available at present. Using a well-characterized animal model of binge eating, we investigated the epigenetic regulation of the adenosine A_{2A} receptor (A_{2A}AR) and dopamine D2 receptor (D2R) gene.
The animal model included four groups (rats fed normally, and then stressed or not, rats exposed to cycles of restriction/refeeding, and then stressed or not).
Gene expression analysis carried out on the amygdala complex of restricted and stressed rats revealed a significant increase of A_{2A}AR and D2R mRNA when

compared to non-stressed and non-restricted rats. Administration of the A_{2A}AR agonist (VT 7) induced in restricted and stressed rats a significant increase of A_{2A}AR and D2R mRNA levels when compared to vehicle group, whereas a significant decrease in rats pre-treated with the A_{2A}AR antagonist (ANR 94) was observed.
Pyrosequencing analysis revealed a significant reduction of the % of DNA methylation at A_{2A}AR promoter region in restricted and stressed rats compared to the non-stressed and non-restricted animals. We did not find any difference in D2R DNA methylation among different groups. Significant changes in the DNA methylation status of A_{2A}AR promoter were found in restricted and stressed rats after administration of VT 7 or ANR 94. We observed a decrease of DNA methylation in VT 7 treated rats and a hypermethylation in ANR 94 rats with respect to the vehicle group.
The increase in A_{2A}AR mRNA observed in restricted and stressed rats could be due to a compensatory mechanism to counteract the effect of binge eating, suggesting that the A_{2A}AR activation, inducing receptor gene up-regulation, could be relevant to reduce food consumption. We here demonstrated for the first time the epigenetic regulation of A_{2A}AR in an animal model of binge eating.

P14.15

DETERMINATION OF GLUCOCORTICOIDS ACTION IN AN ANIMAL MODEL OF COEXISTENCE OF DEPRESSION AND OBESITY

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Epidemiological studies have indicated a frequent coexistence of depression and diabetes and similar changes in the structure and function of the central nervous system's cells are observed in animal models of both of these disorders. Chronic stress, especially acting during prenatal period, is considered as a factor involved in pathogenesis of depression and diabetes and responsible for metabolic and morphologic changes occurring in these disorders. The aim of this study was to identify the markers which determine the potency of glucocorticoid action in the brain.
The study was conducted in adult male Sprague Dawley rats derived from mothers which were subjected to immobilization stress in the last week of pregnancy.
Animals, which underwent prenatal stress were divided, based on the results of the forced swimming test, into two groups: responsive and nonresponsive to stress. Half of the animals in control and stress groups received standard diet and the other high-fat diet. The concentration of corticosterone, glucocorticoid receptors (GR) and factors which regulate GR function - immunophilin FKBP-51and four translational Bag-1 isoforms were determined in the hippocampus and frontal cortex by ELISA and Western blot methods.
It has been found that none of the factors (prenatal stress, high-fat diet) affect the level of the GR in the hippocampus, while prenatal stress decreases the expression of the GR in the frontal cortex. There were no significant differences in the immunophilins FKBP-51concentrations in any of the examined brain structures. Among the studied Bag-1 isoforms, prenatal stress decreased level of Bag-1M, but not Bag-1L and Bag-1S, in the prefrontal cortex, whereas in the hippocampus prenatal stress and high-fat diet did not affect Bag-1 isoforms.

The obtained results indicate that reduction of Bag-1M concentration, a protein that inhibits the GR function and attenuates process of apoptosis, may increase glucocorticoids action and lead to cells damage in frontal cortex in prenatally stressed rats. Reduced level of GR in this structure can on the one hand, attenuate inhibitory mechanism of HPA axis regulation, but on the other hand may reduce direct, adverse effects of glucocorticoid.
This research was supported the grant nr 2014/13/B/NZ7/02278 financed by National Science Center, Poland.

P14.16

APAMIN-SENSITIVE SK CHANNELS MODULATE TONIC AND PHASIC DOPAMINE RELEASE IN THE NUCLEUS ACCUMBENS SHELL: A MICRODIALYSIS STUDY

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Midbrain dopaminergic neurons have two different firing patterns: single spike firing, associated with tonic dopamine (DA) release and burst firing, associated with phasic DA release. Burst firing in DA neurons is controlled by apamin-sensitive Ca++-activated K+(SK) channels. Electrophysiological studies showed that the blockade of SK channels by apamin increases DA burst firing while activation reduces it. In order to demonstrate that microdialysis technique is able to detect phasic dopamine release, we evaluated the effect of intra-ventral tegmental area (VTA) and intra-substantia nigra (SN) administration of apamin on dialysate DA in the striatum.
By in vivo microdialysis studies, we locally injected apamin (1.7 pmol/1 µl; 3.3 pmol/1 µl) or vehicle into the VTA and the SN, and we measured extracellular DA levels in the ventral striatum (nucleus accumbens, shell and core) and in dorsal striatum (dorsomedial and dorsolateral CPu). Intra-VTA apamin, at doses of 1.7 and 3.3 pmol, dose-dependently increased dialysate DA in the NAc shell but not in the NAc core. Doses of 3.3 pmol apamin increased NAc shell dialysate DA by 75% over basal after 40 min, reaching a plateau of 100-125% over basal at 80 minutes post-drug. The infusion of the dose of 1.65 pmol did not affect the dopamine transmission on dorsal CPu. Intra-SN apamin at the highest dose (3.3pmol) increased extracellular DA levels in dorsomedial CPu but not in the dorsolateral CPu, nor in the ventral striatum.
Collectively these observations are consistent with the idea that NAc shell dialysate DA can provide a correlate of phasic stimulation of in vivo DA transmission as a result of activation of DA neuron burst firing. Our observations contradict the common belief that brain microdialysis only reflects the tonic modality of DA transmission in vivo.

P14.17

CHARACTERIZATION OF SF-11, A SELECTIVE BRAIN PENETRANT ANTAGONIST OF THE NEUROPEPTIDE Y Y2 RECEPTOR: RAMAN SPECTROSCOPY AND BEHAVIORAL STUDIES

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Recent studies have shown that Y2R antagonists, such as BIIE0246 and JNJ-31020028 produced antidepressant-like effects in a rat model of depression. The complex structure and high molecular weight of BIIE0246 limit its usefulness as an in vivo pharmacological tool.
In this report, we described Raman (RS) and surface-enhanced Raman spectroscopy (SERS) studies of the structure of SF-11 [N-(4-ethoxyphenyl)-4-(hydroxydiphenylmethyl)-1-piperidinecarbothioamide], which is a novel, brain penetrant and low molecular weight Y2R antagonist. The knowledge of the molecular structure of SF-11 and its behavior at the solid/liquid interface is important for biomedical and biochemical research. The SERS spectra of SF-11 were recorded after its immobilization onto colloidal silver and gold nanoparticles. Moreover, the possible antidepressant-like activity of SF-11 was investigated. The drug was injected intraperitoneally into rats in a dose of 3 or 10 mg/kg and forced swim test (FST) was performed 1 h later.
The present SERS analysis was based on the observed changes in the position, enhancement, and broadening of the corresponding RS and SERS. For the colloidal silver SERS-active nanoparticles the significantly enhanced bands due to the *para*-substituted benzene ring and amine group vibrations, occurred. On the other hand, for the colloidal gold nanoparticles, the strong intensity bands related to the aromatic ring vibrations, were noticed. Our behavioral findings showed that SF-11 at a dose of 10 mg/kg, but not at a dose 3 mg/kg, produced a significant decrease in the immobility time in the FST in rats.
The obtained data indicate the SF-11 is adsorbed onto both SERS-active nanoparticles mainly through the benzylamine moiety. Moreover, the amine group strongly participates in the molecule/silver nanoparticles interaction. Our results also indicate that SF-11 exerts an antidepressant-like effect in rats and can be a useful tool for studying the role of Y2R in mood disorders.

P14.18
INSULİN-LİKE GROWTH FACTOR-1 EXPRESSİON İN CEREBELLUM OF DOGS İNFECTED WİTH CANİNE DİSTEMPER VİRUS

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Insulin-like growth factor-1 (IGF-1) is a neurotrophic factor that inhibits demyelination by protecting oligodendrocytes from damage and inhibiting their apoptosis. This study aims to investigate expression of IGF-1 in white matter of dogs cerebellum which has infected by canine distemper virus (CDV) and showing signs of demyelination.
Paraffin blocks of 20 cerebellum naturally infected with CDV and 10 cerebellum of healthy dog were used in the study. CDV and IGF-1 expression levels were immunohistochemically determined in dog cerebellum sections.
IGF-1 expression was present in both control and CDV infected cerebellums but in CDV group, expression of IGF-1 was significantly higher in immunoreactive astrocytes. IGF-1 expression was not seen in the center of demiyelination areas

while its expression was increased surrounding demiyelination areas. Our findings shows no correlation between IGF-1 expression and demyelination severity and CDV intensity.
As a result, it was considered that IGF-1 expression was increased around the sites of demyelination in CDV infection, which could be interpreted as an effort to prevent demyelination by reducing oligodendrocyte damage. From present findings it may considered that IGF-1 supplements may alleviate demyelinating diseases at the early stage by reducing oligodendrocyte damage and demyelination. This research was supported by Ondokuz Mayis University Research Fund (PYO.VET.1901.16.009).

P14.19

CEREBROSPINAL FLUID AND GENETIC BIOMARKERS IN EARLY DETECTION OF ALZHEIMER'S DISEASE

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Early diagnosis of Alzheimer's disease (AD) in asymptomatic individuals is crucial because potential therapeutics should be administrated as early as possible, when neurodegeneration is not yet advanced. In this study we assessed whether the diagnostic potential of cerebrospinal fluid (CSF) biomarkers amyloid β_{1-42} ($A\beta_{1-42}$), total tau (t-tau), tau phosphorylated at epitope 181 (p-tau_{181}), epitope 199 (p-tau_{199}), epitope 231 (p-tau_{231}) and visinin-like protein 1 (VILIP-1) could be improved by genetic biomarkers related to serotonin metabolism (*5-HT2A*, *5-HT1B*, *5-HT2C*, and *MAOB*), inflammatory pathways (*IL1α*, IL1β, *IL10*, *IL6*, and *TNFα*), catecholamine metabolism (*COMT*, *DBH*), and survival of neurons (*BDNF*). We compared levels of $A\beta_{1-42}$, t-tau, p-tau_{181}, p-tau_{199}, p-tau_{231}, and VILIP-1 between patients with different *DBH* (rs1611115), *IL1α* (rs1800587), *IL1β* (rs1143623), *IL6* (rs1800795), *IL10* (rs1800896), *TNFα* (rs1800629), *5-HT2A* (rs6313), *5-HT1B* (re13212041), *5-HT2C* (rs3813929), *COMT* (rs4680), *BDNF* (rs6265), and *MAOB* (rs1799836) genotypes. The study was conducted on 115 AD and 53 mild cognitive impairment (MCI) patients, 10 healthy controls and 56 patients with other causes of dementia (14 with vascular dementia [VaD], 23 with frontotemporal dementia, 7 with dementia with Lewy bodies, 3 with AD + VaD, 1 with corticobasal degeneration, 1 with hydrocephalus, 2 with Parkinson's disease, 1 with epilepsy, and 4 with unspecified dementia). Levels of t-tau, p-tau_{181}, p-tau_{199}, p-tau_{231} and VILIP-1 were significantly higher in subjects with AA compared to GG and AG *TNFα* genotype (in patients with other dementias and in AD patients). Levels of p-tau_{199} and p-tau_{231} were significantly higher in patients with other dementias with CG compared to CC *IL1β* genotype. Levels of t-tau, p-tau_{181} and p-tau_{231} were significantly higher in patients with other dementias with AA compared to AG *COMT* genotype, while levels of $A\beta_{1-42}$ were significantly lower in AD patients with GG compared to AG *COMT* genotype. Levels of p-tau_{181} were significantly higher in patients with other dementias with TT

compared to CC and TC *IL10* genotype, while levels of p-tau$_{199}$ and p-tau$_{231}$ were significantly higher in AD patients with CC compared to TC *IL10* genotype. Levels of VILIP-1 were significantly higher in MCI patients with GC compared to GG *IL6* genotype, while levels of p-tau$_{199}$ were significantly higher in MCI patients and levels of t-tau were significantly higher in patients with other dementias with GC compared to CC *IL6* genotype. Levels of p-tau$_{181}$ were significantly higher in AD patients with GA compared to AA and GG *BDNF* genotype and in MCI patients with CT compared to CC *DBH* genotype. Levels of Aβ_{1-42} were significantly lower in MCI patients with AA compared to GG *MAOB* genotype. The potential of *TNFα* (rs1800629), *IL1β* (rs1143623), *COMT* (rs4680), *IL10* (rs1800896), *IL6* (rs1800795), *BDNF* (rs6265), *DBH* (rs1611115) and *MAOB* (rs1799836) polymorphisms in early diagnosis of AD should be tested further and validated on larger cohorts of patients. *This work was supported by Croatian Science Foundation grant IP-2014-09-9730*.

P14.20

INHIBITION OF GLYCOGEN SYNTHASE KINASE-3 AS A PROTECTIVE STRATEGY AGAINST MUTANT HUNTINGTIN'S-INDUCED TOXICITY

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Glycogen synthase kinase-3 (hereafter GSK-3), a serine-threonine protein kinase with essential roles in diverse biological processes, has been identified as a therapeutic target for diverse neurodegenerative diseases. These diseases share common pathological characteristic of accumulation of aggregated neurotoxic proteins. This is often coupled with impaired autophagy and lysosome activity. We hypothesized that inhibition of GSK-3 may alleviate these toxic effects by balancing cellular clearance activity.
Our laboratory develops substrate competitive GSK-3 inhibitors. L807mts is a highly selective and potent GSK-3 inhibitor that functions as substrate-converting into an inhibitor.
In these studies we investigated if GSK-3 inhibition protects cells from mutant huntingtin-induced toxicity (mHtt), and whether mechanistic target of rapamycin complex-1 (mTORC1) and autophagic pathways are involved. We used SH-SY5Y cells that were transiently transfected with GFP-mHTTQ74 plasmid and express ploy-glutamine mHtt. GFP-mHtt aggregates were formed 48 hours post transfection, and treatment with Torin1 or L807mts reduced the content of these aggregates. Furthermore, Like Torin1, L807mts supported cell viability of cells expressing mHtt. Moreover, L807mts increased mTORC1 activity and levels of autophagy markers such as LC3-II, p62/SQSTM1 and beclin-1. We suggests that GSK-3 inhibition increases autophagic activity, that in turn, alleviates cellular stress induced by mHtt, activates mTORC1, and protects cells from mHtt toxicity and cell death.

P14.21

FITOHORMONE ABSCISIC ACID TREATMENT AMELIORATES NEUROINFLAMMATION AND COGNITIVE IMPAIRMENT INDUCED BY HIGH FAT DIET

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Many neurological diseases have an inflammatory etiology and insulin resistance is a key factor in Alzheimer disease. Molecules inhibiting neuroinflammation might also be efficacious in the prevention and/or treatment of neurological disorders of inflammatory etiology. The abscisic acid (ABA) is the main phytohormone involved in abiotic stress responses. However, this compound is not only found in plants but also in other organisms, including bacteria, fungi and animals. Interestingly, it can be synthesized and secreted by a variety of human cells. Recent studies suggest a role of ABA regulating immune response and insulin action. Taking these data together we decided to ascertain if ABA has a protective effect in neuroinflammation, and brain insulin metabolism.
We chose a model of neuroinflammation that involved feeding the animals with a High Fat Diet (HFD), this model induces glucose resistance and an increase of proinflammatory markers in peripheral tissues. Experimental groups included, HDF alone; HFD with ABA; and control diet with and without ABA.
We confirmed that, in our model, ABA restores glucose tolerance in HFD rats, to levels of control diets rats' levels. Behavior paradigms show that HFD impairs lightly but significantly animal memory in T-maze but not in novel object recognition. Interestingly, ABA restores the cognitive performance of HFD fed animals to control levels. In hypothalamus and septum, ABA can restrain microglia increase induced by high fat diet. Moreover, ABA can curtail the number of cytokine and other insulin resistance and inflammatory markers in hypothalamus. The mRNA levels of IRS1 and IRS2 are reduced by HFD and ABA reverse lightly but not significantly this effect in hippocampus.
These results suggest that ABA might become a new therapeutic molecule improving cognitive and metabolic processes associated to neuroinflammatory conditions and insulin resistance.
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P14.22

CLUSTER ANALYSIS OF BRAINSTEM NEURONAL DISCHARGE PATTERNS SUGGESTS THE EXISTENCE OF DISTINCT CLASSES OF BREATHING MODULATED FIRING RATES

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There has been no generally accepted quantitative description of the respiratory modulation of brainstem neuron firing rates. More significantly, the question remains whether there exist distinct classes of respiratory modulated neurons or rather they constitute a continuum. Building on previous work, we have developed a quantitative, reproducible clustering classification protocol to address these issues.
We surveyed historical recordings of extracellular potentials of spike trains in respiratory related brainstem regions, i.e. lateral respiratory column (ventral respiratory group, pre-Bötzinger, Bötzinger), pons, raphé, and dorsal lateral medulla

including the dorsal respiratory group. We calculated 100-bin normalized cycle triggered histograms (CTH) of 1,373 spike trains. Ward clustering with Cartesian distance in 100-space (the normalized CTH bins) first differentiated the spike trains with significant respiratory modulation (n=573) into three groups: predominantly inspiratory, predominantly expiratory and low respiratory modulation.
Application of the same clustering paradigm to each of these 3 groups yielded a set of 24 respiratory archetypes consisting of averaged histograms of the elements of each cluster. We used those archetypes as clustering centroids on naïve recordings of 229 spike trains; all were matched, i.e clustered, with 20 of the archetypes.
Preliminary analysis suggests the existence in brainstem neurons of distinct classes of respiratory modulation. Support: OT2OD023854-01, HL109025.

P14.23

THE CROSS TALK BETWEEN PREFRONTAL CORTEX AND PRIMARY VISUAL CORTEX THROUGH THE BALANCE ACT BETWEEN EXCITATION/ INHIBITION

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Could the balance act between excitation/ inhibition (E/I) within and across different cortical areas shape the cortical neuronal activity in normal and pathological conditions? Accumulated evidences showed the critical impact of balance act within the cortical areas in optimizing the cortical plasticity and functional connectivity. Subsequently, number of studies reported about the imbalance between excitation inhibition in certain neurological and psychiatric disorders such as autism spectrum disorders (ASDs) and schizophrenia. Now, the question is how this balance act could shape the neuronal activity across different cortical regions (i.e., the primary visual cortex (V1) and the prefrontal cortex (PFC)), and what goes wrong in case of pathological condition. Based on the current literatures, there are several evidences showing the critical impact of the balance act in V1 and PFC. However, implications of the balance act (E/I) between these two regions at the neuro-circuit level remain elusive. Therefore, we aim at highlighting this issue in normal and pathological condition focusing on the functional projection from V1 to PFC and vice versa in rodents.
We propose using integrated approach combining optogenetic, in vivo recording and behavioral tasks. The aim is to study the changes in excitation/inhibition balance locally (within V1 and PFC) and globally (across V1 and PFC) at the microcircuit level.
According to the previous findings, Parvalbumin (PV) neurons of the rodents but not somatostatin (SST) neurons are essential for establishing E/I balance. As for PV neurons, they exist in both V1 and PFC, and develop earlier in V1 in comparison to PFC during cortical development. Additionally, PV protein has higher expression in V1 in comparison to PFC in adolescence rodents. In terms of the distribution of PV neurons across layers in V1 and PFC, PV neurons reside layer II-VI of both areas though layer II/III of PFC, which has less PV neurons. In V1, PV neurons play a critical role in equalizing E/I balance by offset the excitatory neurons of layer IV. Nevertheless, this phenomenon has not been demonstrated in PFC. Interestingly, direct projections between V1 and PFC have been found recently. As for visual deprivation, it was suggested to rapidly reduce the number of PV interneurons, and

thus disinhibit the pyramidal neurons of layer II/III (of V1). Furthermore, PV reduction in V1 induces a significant increase in the number of PV neurons in layer II/III, and layer V/VI of PFC.
Rodent's studies show that PV interneurons in V1 and PFC play a vital role in E/I balance. However, the interaction between these two areas is not investigated enough despite its critical neurological impact in health and disease.
In conclusion, we aim at shedding the lights on the ultimate need of establishing more research in this area (balance act between E/I between V1 and PFC) so that we can understand the diseased model better.

P14.24

PRESYNAPTIC *N*-METHYL-D-ASPARTATE RECEPTOR INHIBITS CA^{2+} CURRENTS AT A RAT CENTRAL GLUTAMATERGIC SYNAPSE

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N-methyl-D-aspartate receptors (NMDARs) play diverse roles in synaptic transmission, synaptic plasticity, neuronal development, and neurological diseases. In addition to their postsynaptic expression, NMDARs are also expressed in presynaptic terminals at some central synapses, and their activation modulates transmitter release. However, the regulatory mechanisms of NMDAR-dependent synaptic transmission remain largely unknown.
In this study we performed whole-cell voltage-clamp recordings from giant presynaptic nerve terminals called the calyx of Held as well as postsynaptic medial nucleus of trapezoid body (MNTB) neurons in the rat auditory brainstem, and pharmacologically examined the property and mechanism of presynaptic NMDAR-dependent synaptic modulation.
Activation of NMDARs in nerve terminals at the calyx of Held synapse inhibits presynaptic Ca^{2+} currents (I_{Ca}) by means of GluN2C/2D subunit-dependent manner, thereby suppressing nerve-evoked glutamate release. Neither presynaptically-loaded fast Ca^{2+} chelator BAPTA nor non-hydrolyzable GTP analogue GTPγS affected the NMDAR-mediated I_{Ca} inhibition. Repetitive activation of I_{Ca} in the presence of a glutamate uptake blocker attenuated the decline of I_{Ca} amplitude, suggesting that endogenous glutamate has a potential to activate presynaptic NMDARs.
We conclude that presynaptic NMDARs can attenuate glutamate release by inhibiting voltage-gated Ca^{2+} channels at a central glutamatergic synapse in the rat brainstem.

P14.25

INHIBITORY EFFECT OF RXFP3 ACTIVATION ON MAGNOCELLULAR PVN NEURONS *IN VITRO* - A POTENTIAL NEURONAL MECHANISM OF OREXIGENIC RELAXIN-3 ACTION IN MALE AND FEMALE RATS

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Relaxin-3 is a stress-responsive, orexigenic peptide present in nucleus incertus neurons and their projections throughout the rat forebrain, including the hypothalamus. The hypothalamic paraventricular nucleus (PVN) is an established site for the induction of feeding following central relaxin-3 administration. Notably, relaxin-3 produces stronger orexigenic effects in female than male rats, but the neural mechanisms underlying this difference are unknown. Our *in vitro* studies in male rats revealed that relaxin-3 receptor (RXFP3) activation inhibits PVN magnocellular neuron activity. The aim of the current study was to investigate possible differences in the effects of, or sensitivity to, RXFP3 activation in PVN neurons from male and female rats.
Whole-cell, patch clamp recordings in current- and voltage-clamp mode were performed on hypothalamic slices from male and female Sprague-Dawley rats (6-8-week old) to assess possible changes in membrane potential, whole cell current and synaptic transmission elicited by RXFP3 activation. All drugs were applied via bath perfusion.
In current-clamp experiments, the RXFP3-selective agonist RXFP3-A2 (600 nM) decreased the spontaneous firing frequency of the majority of PVN neurons recorded in both sexes (by 2.2 ± 2.4 Hz, $p<0.05$, n=11, in males; and by 2.0 ± 1.7 Hz, $p<001$, n=12, in females; with no significant difference in response between sexes, p=0.78). The effect persisted in the presence of TTX and glutamate and GABA receptor antagonists, leading to membrane hyperpolarisation of 2.6 ± 1.5 mV, $p<0.01$, in males; and 2.7 ± 1.5 mV, $p<0.001$, in females; with no significant difference in response between sexes, p=0.88). In voltage-clamp experiments RXFP3-A2 (600 nM) application increased outward whole cell current by 30.3 ± 14.3 pA, $p<0.0001$, n=11, in males; and by 28.5 ± 16.1 pA, $p<0.0001$, n=12, in females; with no difference in response amplitude between sexes, p=0.78). No significant differences were observed in the baseline spontaneous firing frequency or whole cell current in the male and female magnocellular PVN neurons recorded.
Our data indicate that an inhibitory influence of relaxin-3/RXFP3 signalling on magnocellular PVN neurons is associated with feeding control in both sexes. Current studies are aimed at investigating potential sex differences in electrophysiological properties of magnocellular PVN neurons as well as in signalling pathways and ionic mechanism activated by RXFP3 in male and female rats.

Thursday, 15th June 2017

P15.1

EFFECT OF CERVICAL HEMISECTION ON SWALLOW AND AIRWAY PROTECTION

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The effects of cervical hemisection on swallow have not been determined. We hypothesized that cervical hemisection would increase swallow excitability and shift the pattern of swallow breathing coordination to maintain pharyngeal clearance. Electromyograms of the mylohyoid, geniohyoid, thyrohyoid, thyroarytenoid, thyropharyngeus, cricopharyngeus and diaphragm (costal and crural) muscles were recorded in anesthetized, spontaneously breathing anesthetized cats prior to and

after a C2 hemisection. Swallow was elicited by infusion of 3ccs of water into the oropharynx. Acute C2 cervical hemisection significantly increased EMG amplitudes across all upper airway muscles during swallow, and swallow frequency increased from 3.3 ±1.2 to 8 ±1.4 per infusion. Significant changes in swallow-breathing coordination were noted with all swallows occurring in E1 (as opposed to late E2), significantly increasing the risk for potential aspiration. These results support a theory of spinal cord inhibition/modulation of the swallow pattern generator and upper airway muscle excitability, as well as the importance of its role in swallow/breathing integration. Supported by R00- HL 111215, The Kentucky Spinal Cord and Head injury Trust, The Commonwealth of Kentucky Challenge for Excellence, the Rebecca F Hammond Trust and RCS-VA RR&D B9249S. The contents of this abstract do not represent the views of the DVA or US government.

15.2

MAPPING CFOS EXPRESSION AFTER CEREBELLAR AND MEDIAL PREFRONTAL DEACTIVATIONS IN RATS TRAINED TO ACQUIRE COCAINE-INDUCED PREFERENCE CONDITIONING

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Pavlovian memories of preference for drug-related stimuli are crucial components to drive motivational trigger of drug seeking and drug taking behaviours. Despite growing data in the last years, the cerebellum has remained excluded from the circuitry sustaining these behaviours. However, the cerebellum presents close anatomical and functional connectivity in several key regions in the striatum-cortico-limbic circuitry. Recently, we have found two cerebellar hallmark signatures of conditioned preference for cocaine: an increase in cFos expression in cells at the apex of the granule cell layer and a strong expression of the perineuronal nets in the same region of the cerebellar vermis. In the present investigation, we evaluated the effects of different medial prefrontal cortex (mPFC) and cerebellar deactivations in rats before starting with the conditioning training to acquire preference for an olfactory stimulus paired with cocaine. Two groups of rats were subjected before training to a temporary prelimbic or infralimbic inactivation by lidocaine. Another two groups were treated with quinolinic acid for a permanent lesion in the dorsal or ventral area of lobule VIII in the cerebellar vermis. Sham control rats received vehicle in the same regions. cFos expression was evaluated in different areas of the striatum-cortico-limbic circuitry to analyse changes in activity patterns after these brain interventions. The inactivation of infralimbic cortex or the lesion of the dorsal cerebellar vermis promoted the acquisition of cocaine-induced preference conditioning. Interestingly, the combined lesions of both areas regions prevented the facilitation of this conditioned response. Opposite results were found after either prelimbic deactivation or ventral cerebellar lesion. The change in cFos expression patterns was restricted to specific regions of amygdala and thalamic complex after dorsal cerebellar lesion. In this case, cFos expression increased significantly. Also, neural activity in either infralimbic cortex or cerebellum was enhanced after deactivations of each of these distal sides. The results suggest that the infralimbic cortex and dorsal posterior cerebellum work together and take part in the circuit that allow the inhibitory control of drug-related emotional memories.

P15.3

SERUM AND PLASMA LEVELS OF MATURE AND PRO-BDNF IN HEALTHY, AND EARLY MCI AND AD SUBJECTS OF VARIOUS AGES. PRELIMINARY CLINICAL SCREENING DATA

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The primary objective of this study was to investigate and potentially establish typical or average range levels of mature circulating BDNF in serum and plasma collected from: a) healthy subjects with age ranges from 25-35, 45-55 and 55-65; and, b) in people experiencing early symptoms of mild cognitive impairment (MCI) or Alzheimer's disease (AD) within age range of 55-65. Our secondary objective was to measure amounts of BDNF detected in circulating exosomes isolated from serum.
Serum and plasma samples were collected from 50 subjects within each age group and condition, for a total of 250 people. Serum collection and exosomes isolation were regularly performed in the morning after subjects had fasted at least 10 hours.
Collected data on serum and exosomal BDNF was correlated with age and health conditions in order to establish possible "healthy" BDNF ranges in young subjects, as well as potentially providing comparison criteria between healthy and unhealthy subjects. Analysis of exosomal BDNF levels supplied additional information related to the ratio between free circulating BDNF and exosomal BDNF that may pass BBB.
Preliminary analysis showed that levels of circulating BDNF (free and exosomal) are seem to be related to age and conditions. Analysis of serum-collected exosomes may provide more specific information about blood cells and their role in the release of exosomal BDNF. Preliminary results of these analyses are herein presented.

P15.4

A CRITICAL ROLE OF CA1 ACTIVITY FOR TEMPORAL BINDING

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Cognitive aging involves the prominent deterioration of declarative memory. Development of therapeutic approaches to cognitive aging may improve identifying processing mechanisms underlying this memory and their neurobiological bases. Previous work identified temporal binding, the capability to associate temporally distant stimuli, as a critical process for remembering complex associations among events, i.e. declarative memory. The CA1 subfield of the hippocampus is involved in memory of temporal associations, but its function remains to be specified. Based on the discovery of time cells, which fire at successive moments in temporally structured experiences, an hypothesis was recently proposed: activity of CA1 cells would bridge the gap in memory for discontiguous events.
To test this hypothesis, first, we confirmed that CA1 activity is related to successful temporal binding in memory by combining trace fear conditioning procedure at different levels of temporal binding demand (tone-shock interval length) to Fos

neuroimaging. We found that successful tone-shock binding in memory only occurs for a tone-shock interval of 20 seconds and that CA1 is the sole area in which activity is increased by successful temporal binding compared to the other learning conditions under which no temporal binding occurs. Then we demonstrated that CA1 activity is necessary during temporal gaps between the (to be-associated) stimuli for successful temporal binding by combining trace fear conditioning to an optogenetic approach. We inhibited CA1 activity specifically in or out of the trace interval during acquisition of 20 seconds trace conditioning. We found that successful tone-shock binding in memory requires CA1 activity during temporal gap between the tone and the shock. In conclusion, our findings validate the “time cells” hypothesis that CA1 activity is critically needed during learning to bridge temporal gaps between discontiguous events in memory.

P15.5

BOOSTING PERCEPTUAL LEARNING WITH TRANSCRANIAL RANDOM NOISE STIMULATION RESULTS IN MORE EFFECTIVE VISUAL FUNCTION IMPROVEMENTS IN ADULTS WITH AMBLYOPIA

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Amblyopia is a neuro-developmental disorder characterized by several functional impairments in spatial vision (even with the best optical correction) in absence of any organic defects of the eye. Several studies have shown that extensive visual perceptual training can improve visual acuity (VA) and the contrast sensitivity function (CSF) in people with amblyopia, even in adulthood. With the present study we assess if the application of a high-frequency transcranial random noise stimulation (hf-tRNS) concurrently with a short perceptual training on adults with anisometric amblyopia is more efficacious in improving visual functions than the same perceptual training with Sham stimulation. Twenty participants were recruited and divided into two different groups: the experimental group underwent a short (8 sessions) contrast-detection monocular training with concurrent hf-tRNS while the control group underwent the same training with Sham stimulation. Results showed that, while a significant and clinically relevant improvement in VA and CSF occurred in the experimental group (mean VA improvement in the amblyopic eye was 0.18 LogMAR), no significant improvement in VA was seen for the control group.
Thus, in comparison with previous studies where a large number of sessions with a similar training regime was used, here an improvement of CSF has been found in both groups in just eight sessions of training, furthermore by adding hf-tRNS we have been able to transfer the enhancement to VA, a fuction not trained.
Our results support the idea that, by boosting the rate of perceptual learning via the modulation of neuronal plasticity, hf-tRNS can be successfully used to reduce the duration of perceptual trainings and, at the same time, to increase generalization of perceptual learning to other nonpracticed visual function such as VA in patients with amblyopia.

P15.6

APPARENT EMOTIONAL EXPRESSION PREDICTS PERCEIVED TRUSTWORTHINESS WITH CHANGES OF HEAD POSTURE

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People make trustworthiness judgments on the basis of facial cues rapidly and with high consensus. Emotional expressivity, as trait cues that humans use, plays an important role in detecting trustworthiness. Neuroimaging studies have provided evidence that trustworthiness judgements are linked to emotional expressions and that trustworthiness decisions are associated with activation of brain areas, such as the amygdala, that generally process emotional information. Changes in emotional expressions are likely to affect perceived trustworthiness but the effects of variation in head posture on apparent trustworthiness are not known.
Our studies therefore examined how head posture (level, up, or down) affects perceptions of trustworthiness. In Study 1, participants rated faces in three postures for apparent trustworthiness on seven-point Likert scales. In Study 2, participants scrolled through face images and manually manipulated vertical head angle to maximise perceived trustworthiness.
Results of ratings reveal that the head down posture decreased perceived trustworthiness compared to the level and raised head; the head up posture was perceived as less trustworthiness compared to the neutral posture. The optimal head angle to make the facial images most trustworthy was found to be slightly lowered with respect to the level posture. This posture made the facial expression appear more positive.
Our results suggest a profound effect of posture on apparent trustworthiness with a change in head posture. Our analysis reveals that apparent emotional expression provides an explanation of perceived trustworthiness. Together with recent neuroimaging evidence of brain localization of non-verbal cues processing, these findings highlight the functioning of head postures as social signal in social interaction.

P15.7
POTENT INHIBITION OF HUMAN CYP3A4 BY THE NOVEL ATYPICAL ANTIPSYCHOTIC DRUG ILOPERIDONE
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Inhibition of cytochrome P450 (CYP) isoenzymes in the liver and brain is the most common cause of harmful drug-drug interactions. Iloperidone is a novel atypical antipsychotic drug approved for the acute treatment of schizophrenia in adults. The aim of the present study was to evaluate the inhibitory effect of iloperidone on the main human CYP isoenzymes involved in the metabolism of psychotropic drugs.
Experiments were performed *in vitro* using pooled human liver microsomes. CYP isoform activities were determined using the following CYP-specific reactions: caffeine 3-N-demethylation (CYP1A2), diclofenac 4'-hydroxylation (CYP2C9), perazine N-demethylation (CYP2C19), bufuralol 4'-hydroxylation (CYP2D6) and testosterone 6β-hydroxylation (CYP3A4). The rates of CYP-specific reactions were measured by HPLC in the absence and presence of iloperidone (0.01-50 μM). Inhibition constants (K_i) for the inhibition of CYP-specific reactions by iloperidone were obtained using a non-linear regression analysis (Program Sigma Plot 8.0; Enzyme Kinetics). The obtained results showed that iloperidone potently inhibited CYP3A4 (K_i = 2 μM) and weakly diminished the activities of CYP1A2 and CYP2D6 (K_i = 64 and 98 μM, respectively). On the other hand, iloperidone did not affect the

activities of CYP2C9 and CYP2C19.The presented findings may have significant implications for the prediction of potential interactions involving iloperidone and CYP3A4 substrates (e.g. antidepressants, benzodiazepines, calcium channel antagonists). Since the metabolic interactions found in the liver may also occur in the brain, the influence of iloperidone on brain CYP3A4 activity may be important for the metabolism of endogenous neuroactive substrates (e.g. neurosteroids), and for the local biotransformation of psychotropics: such interactions may modify their pharmacological action.
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P15.8
HDAC5 IMPAIRMENT IN FEAR MEMORY DEFICITS IN A NEURODEVELOPMENTAL MODEL OF SCHIZOPHRENIA
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Several findings indicate that deficits in emotional memory, i.e. fear memory might be related to impairment in epigenetic mechanism, i.e. histone H3 acetylation. Our previous study demonstrated fear memory deficits in trace fear conditioning (TFC) task induced by postnatal administration of CGP37849, a competitive antagonist of NMDA receptors. In the present study, we investigated whether the fear memory deficit in CGP-treated rats might be related to impairment in the regulation of histone H3 acetylation in the adult mPFC. To accomplish this task, we determined the level of histone deacetylase 5 (HDAC5) and its phosphorylated form pHDAC5 as well histone H3 acetylation at lysine 9 (H3K9ac) during memory retrieval in TFC. Immunoreactivity of HDAC5, pHDAC5 and H3K9ac were analyzed by western blot in nuclear and cytosolic fractions of the mPFC. We also examined the impact of the non-selective histone deacetylase inhibitor, sodium butyrate (SB) on memory retrieval and the level of epigenetic markers in TFC task. Postnatal blockade of NMDA receptor induced the increase in HDAC5 in nuclear fraction and the decrease in pHDAC5 in cytosolic fraction of the adult mPFC during memory retrieval. At the same time the decrease in H3K9ac was observed in nuclear fraction of the mPFC. In addition, SB administered 2 h after memory acquisition prevented the deficit in fear memory induced by postnatal CGP administration. Furthermore, SB also inhibited alterations in the level of HDAC5, pHDAC5 and H3K9ac in CGP treated animals.The obtain results indicate that postnatal blockade of NMDA receptor altered HDAC5 regulation by impairing phosphorylation-dependent nuclear export of HDAC5 and also affected histone H3 acetylation in the mPFC. The above impairment in epigenetic regulation might suppress expression of genes involved in memory formation and evoke fear memory deficits.

P15.9
IDENTIFYING THE INTERACTION BETWEEN CHROMOGRANIN A / PHOSPHATIDIC ACID AT THE LEVEL OF TGN MEMBRANE TO ELUCIDATE ITS ROLE IN THE BIOGENESIS OF SECRETORY GRANULES IN NEUROENDOCRINE CELLS
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Neuroendocrine cells are specialized in the secretion of neurohormones through the biogenesis of dense core-secretory granules (DCSG). These organelles bud from the TGN membrane after the interaction of neurohormone aggregates induced by soluble glycoproteins called chromogranins. Since the main member of this family, chromogranin A (CgA), acts as an on/off switch regulating the formation of DCSG, we decided to study the interaction between CgA and membrane lipids to highlight the molecular mechanisms mediating this process. Using lipid-protein overlay assays, we observed that recombinant CgA specifically binds to phosphatidic acid (PA). Phosphatidic acid being known as a crucial actor in the formation of secretory granules and in the process of membrane curvature, we are currently studying the interaction between CgA and phosphatidic acid in neuroendocrine cells and its role in the regulation of hormone secretion. The quantitative and comparative analysis by LC-MS/MS of the membrane lipidome of purified CgA granules and Golgi apparatus revealed an enrichment of PA in the granule membrane, and the predominance of PA36:1, PA38:2 and PA40:6 species. Moreover, using a pull-down assay with liposomes enriched with various phospholipids including phosphatidylserine, phosphatidylcholine or distinct PA species, we showed that CgA from cell lysate specifically interacts with the predominant PA species identified by the lipidome study. We postulate that CgA interaction with PA at the level of the TGN membrane is at the origin of microdomain formation that could govern the TGN membrane curvature and/or the recruitment of cytosolic proteins involved in the DCSG trafficking crucial to neurohormone secretion. To study these phenomena in living cells, we are currently working with organic chemists on the synthesis of biocompatible and photoactivatable PA analogues, and with biophysicians on the analysis of CgA/PA interaction-induced microdomains using of Fluorescence Correlative Spectroscopy.

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P15.10

INTERACTION OF GLUTAMATERGIC AND CHOLINERGIC TRANSMISSION IN ANIMAL MODELS OF SCHIZOPHRENIA

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Schizophrenia is a severe mental disorder that is characterized by the prevalence of positive (hallucinations, delusions), negative (flattened affect) and cognitive (memory and attention deficits) symptoms. Unfortunately, currently available drugs induce many adverse effects and poorly affect negative and cognitive symptoms. Recent data suggests that disruption in dopaminergic, glutamatergic, but also cholinergic transmission may underlie the pathology of schizophrenia. Our previous experiments show that positive allosteric modulation of muscarinic M_4 receptors has clear antipsychotic effect in animal models of schizophrenia. Thus, the aim of this study

was to evaluate whether mGlu4 receptors are involved in antipsychotic activity of VU152100.
Male Albino Swiss mice were used in all behavioral tests. MK-801-induced hyperactivity, DOI-induced head twitches, modified forced swim test, social interaction test and novel object recognition test were used to assess the potential interaction between $mGlu_4$ and M_4 receptors in the context of antipsychotic activity.
Simultaneous administration of sub-effective doses of LSP4-2022 (selective $mGluR_4$ agonist) and VU152100 (positive allosteric modulator of M_4 muscarinic receptors) reduced the MK-801-induced hyperactivity, however it had no effect on the number of head twitches. Co-administration of both substances increased the time and the number of social episodes in social interaction test and reduced the immobility time in modified forced swim test. Moreover, it reversed the MK-801-induced deficits in novel object recognition test.
Our results indicate that $mGlu_4$-M_4 interaction can be beneficial in animal models of positive, negative and cognitive symptoms of schizophrenia. This suggests that concomitant administration of ineffective doses of substances acting on aforementioned receptors could provide an efficacious and safe alternative in treatment of schizophrenic patients as it could potentially minimalize adverse effects.

P15.11
THE PUTATIVE ANTIPSYCHOTIC-LIKE EFFECTS OF MGLUR7 RECEPTOR LIGANDS
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Variety of the previous research showed that the role of glutamatergic system in the pathology of schizophrenia plays very important role. As the data concerning the role of the IIIrd group of metabotropic glutamate receptors (mGluR) is rather scarce and considers mainly mGlu4 receptors ligands. The main interest of the present study was to investigate the role of mGluR7 receptor in animal models in schizophrenia.
In our research, we examined the effects of two mGluR7 ligands: selective, allosteric antagonist - MMPIP and negative allosteric modulator – ADX-71743. We conducted behavioral tests commonly used in antipsychotic drug discovery, such as MK-801-induced hyperactivity, DOI-induced head twitches, modified forced swim test, social interaction test and novel object recognition test.
Both tested compounds dose-dependently inhibited MK-801-induced hyperactivity and DOI-induced head twitches. Moreover, the same effects we noticed in novel object recognition test, where MMPIP and ADX-71743 reversed MK-801-induced disturbances. However, the efficacy of drugs in the social interaction test was observed only for positive allosteric modulator of mGlu7 receptor, ADX-71743.
The present studies showed that mGlu7 receptor ligands may be considered as a target for antipsychotic drug discovery. However, due to limited number of available ligands more studies are needed.

P15.12
EXTINCTION FAILURE IN VULNERABLE TRAUMATIZED MICE
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Post traumatic stress disorder (PTSD) is a debilitating disease triggered by the exposure to one or many traumatic events. Epidemiological studies indicate that PTSD prevalence can reach 23% to35% in highly traumatized populations. Besides, clinical studies report that patients with PTSD have difficulties in fear extinction acquisition. Even though the traumatic event has the same intensity, the probability of developing PTSD following a similar level of exposure varies across individuals. Many animal models havebeen designed to study PTSD, but in most of them, the data collection and analysis are generally expressed as a function of exposed vs non-exposed populations, regardless of individual variation in response.
Using an animal model of PTSD previously developed by our team, we individually examined the performance of animals in three behavioral tests (avoidance, fear sensitization and the elevated plus maze tests). An animal is labeled as “susceptible” to develop PTSD-like symptoms if its performance is more than one standard deviation from the mean of the control group in at least 2 tests. Concerning fear extinction, we re-exposed each animal to the trauma-associated context during 5 sessions. An animal is considered having difficulties in extinction learning if its performance is more than one standard deviation from the mean of the control group in at least 3 extinction sessions.
In this context, our data revealed two subgroups of animals: PTSD-like susceptible subgroup with 34.6% of mice, and PTSD-like resilient subgroup with 65.4% of mice. Some of the mice in the PTSD-like susceptible subgroup were also characterized by poor extinction (higher scores during the first two extinction sessions).
These results indicate that vulnerable traumatized mice in our study expressed the most common features of PTSD. Our model seems therefore more relevant for animal PTSD studies.

P15.13

A ZONE OF CONNECTIVE SIMILARITY CONVERGENCE WITHIN THE TEMPORAL LOBE

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The temporal lobe underpins functions such as audition, olfaction and vision, to higher level functions such as speech perception culminating with the high level integrative function of semantics. A fundamental assumption of brain function is that it is dependent on the underlying structure of the brain and its connections. This project aims to identify, using diffusion magnetic resonance tractography, the area that demonstrates greatest connective similarity to all other areas and hence in an optimal location to perform integrative functions such as semantics. 24 healthy, right handed participants (11 F) were recruited. Diffusion weighted MRI images were acquired in 61 no-collinear directions. A T1 weighted image was acquired for visualisation purposes. Tractography was carried out using the probability index of connectivity tool. Unconstrained tracking was performed from every voxel in the temporal lobe giving each voxel a connectivity profile that can be represented as an ordered vector of connectivity values. The matrix of pairwise connective similarity between voxels was then computed as the cosine of the angle between the profile

vectors of every pair of voxels. A spectral embedding algorithm was used to warp voxels into a connectivity space. Each voxel was given an RGB colour value that denoted their location in the connectivity space. The centre of mass of the cloud of voxel positions in the connectivity space was computed to identify the voxels that had connectivity profiles that were most similar to all other voxel profiles. Sharp connectivity boundaries were found between the medial temporal lobe and the lateral temporal lobe. Graded transitions were found within the lateral temporal lobe. The area which demonstrated connectivity profiles that were maximally similar to all other regions was on the anterior end of the ventral temporal lobe. The location of the convergence of connective similarity corresponds to regions known to be involved in semantic cognition. This lends support to the hypothesis that areas of the brain that have connectivity profiles that are maximally close to all other areas in a region may perform integrative functions such as semantics.
This work supports the idea that the anterior temporal lobe is an integrative hub.

P15.14
EFFECT OF PHOSPHODIESTRASE 10A INHIBITOR, MP-10 COMPOUND IN THE RAT IOWA GAMBLING TASK
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Pathological gambling (PG) is a form of behavioural addiction. Both substance and behavioural addictions are characterized by the impairment in decision-making processes and impulsive responding. These components of PG can be investigated in a rat Iowa Gambling Task (rIGT). MP-10 is an inhibitor of phosphodiestrase 10A (PDE10A). These novel principles increase the level of cAMP and cGMP in the medium spiny neurons of the striatum and resemble the neurochemical consequences of dopamine D2 receptor inhibition and dopamine D1 receptor stimulation. Because it is postulated that dopaminergic systems are implicated in decision-making processes, including risky/safe choices, we investigated whether MP-10 could affect gambling behaviour in rats. We employed a novel model of PG in rodents, called the rat Iowa Gambling Task. In this task, the rats are trained in the Skinner boxes. The animals choose among four nose-poke holes, which differed in the amount of reward they provide, and in the probability and duration of punishing time-out periods, during which the reward cannot be earned. Subjects were trained to earn as many sugar pellets as possible within 30 min. After reaching a stable baseline, the test was performed. MP-10 was administered at doses 0.03, 0.1 and 0.3 mg/kg, P.O., 120 minutes before the test.
We report that MP-10 did not influence gambling behaviour at any dose. Examinated compound did not change the patter of choices in Iowa gambling task. Risky/safe choices in this paradigm is complex behaviour and more studies are needed to explore this aspects of decision-making processes.

P15.15
RELAXIN-3 AGONIST ALTERS SOCIAL CO-SPECIFIC SOCIAL MEMORY AND INCREASES ERK ACTIVATION IN THE AMYGDALA SPECIFIC NUCLEI
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In mammals, the amygdala is the central core for processing of social and emotional information. Amygdala function is involved in valence processing (positive and negative affective), reward, decision-making and recognition of emotional facial expressions in humans. The ability to identify and recall familiar conspecifics is crucial for a correct social interaction and its absence leads to impaired social abilities. Social memory formation and recall depends on circuits involving amygdala, septum and hippocampus. The nucleus incertus of the pontine tegmentum projects to both amygdala and hippocampus. Neurons of the nucleus incertus produce the neuropeptide relaxin-3, which is co-released with GABA. Thus, relaxin-3 could be one of the modulators of social processing or memory formation. To assess whether the relaxin-3/Relaxin family peptide 3 receptor (RXFP3) system may be affecting social interaction and/or memory we have intracerebroventricularly (icv) infused a RXFP3 agonist and quantified Erk phosphorylation (pErk) by immunoblot and immunohistochemistry in the amygdala. Then, we studied the pErk pattern distribution in the amygdala related to the receptor distribution-density. Finally, we have studied if icv agonist infusion interferes with discrimination between a conspecific subject and an inanimate object or the formation of social memories in a 3-rooms maze paradigm. The results show an increase in Erk activation in amygdala in immunoblot assays 20 minutes after the infusions of agonist when compared to vehicle. Furthermore, the medioventral part of the stria terminalis, the oval nucleus of the stria terminalis, the central amygdala and the posteroventral part of the medial amygdala showed a significant increase or Erk activation. This increase is consistent with the behavioral 3-rooms maze paradigm results where agonist subjects interact more with conspecifics than with inanimate objects but have a clear impairment of social memory. This effect is specific on the social recognition as in the first encounter, in which the animals are challenged to discriminate between subject and object, both vehicle and agonist infused animals showed the same tendency to explore more the co-specific than the inanimated object. These results stand for a first time a role of the NI/RLN3/RXFP3 system in modulating social behavior through specific neuronal types in specific nuclei of the amygdala. As a whole, the system may act as a potential centre of social memory modulator in relation with anxiety and/or stress.

P15.16

AMPLIFICATION OF MGLU5-ENDOCANNABINOID SIGNALING RESCUES BEHAVIORAL AND SYNAPTIC DEFICITS INDUCED BY A DIETARY POLYUNSATURATED FATTY ACIDS IMBALANCE

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In the last century, the rapid expansion of Western Countries has been associated with drastic changes in the diet reflected by low levels of essential omega-3 polyunsaturated fatty acids (n-3 PUFAs). Our previous studies demonstrated that lifelong n-3 PUFAs dietary deficiency ablates endocannabinoid synaptic plasticity in the medial prefrontal cortex (mPFC) and nucleus accumbens (NAc). These synaptic

alterations were correlated with impairments in emotional-related behaviors. However, the onset of these deficits has never been studied.
To address this issue, C57BL6/J mice were fed with an n-3 deficient diet (rich in linolenic acid, LA, 18: 2n-6) starting at postnatal day (PND) 28 until adulthood (PND 90) when they were tested for synaptic plasticity and emotional and cognitive outcomes. Our results showed that starting nutritional deficits in dietary n-3 PUFAs during adolescence decreased n-3 PUFAs levels in both mPFC and NAc, increased anxiety-like behavior and decreased cognitive function in adulthood. Importantly, we discovered that endocannabinoid/mGlu5-mediated long-term depression in the mPFC and NAc was abolished in adult n-3-deficient mice. Additionally, mPFC NMDAR-dependent long-term potentiation was also lacking in the n-3-deficient group. Pharmacological enhancement of the mGlu5/eCB signaling complex, by positive allosteric modulation of mGlu5 or inhibition of endocannabinoid 2-arachidonylglycerol (2-AG) degradation, fully restored synaptic plasticity and normalized emotional and cognitive behaviors in malnourished adult mice.
Our data support a model where nutrition is a key environmental factor influencing the working synaptic range into adulthood, long after the end of the perinatal period. These findings have important implications for the identification of nutritional risk factors for disease and design of new treatments for the behavioral deficits associated with nutritional n-3 PUFAs' deficiency.

P15.17

WHY DO ONLY SOME ARM RECOVER AFTER STROKE? OF MIRROR NEURONS IN BA44

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Cortex and cortical function can be regarded as modular, with separate areas involved in processing sensory information and the initiation of motor movement. The blood supply supporting cortex is, like the brain itself, modular. Disruption in blood flow leads to a multiplicity of dysfunctions like the frequent co-occurrence of aphasia and right upper limb hemiparesis.
A review of the stroke literature reveals a correlation between Broca's aphasia and upper limb motor recovery. The precise reason for the correlation is not known but this paper proposes one. Our argument is that speech impairment is indicative of damage to Brodmann area BA45 but that the motor deficits are due to damage to the proximal, but functionally discrete area BA44. BA44 is a multisensory area. But experiments on tone-deaf or stutters, radiological tools like fMRI and DWI, studies of the neuro-ontogeny and development in babies, findings of genetic, epigenetic and embryology, all point to BA44 playing a central role in visuo-motor integration.
We have analysed data from 3780 stroke patients. Two groups were compared: patients with aphasia and right upper limb motor deficit and patients with just motor deficit without aphasia. Patients with Broca's aphasia show slower and poorer motor recovery of right arm compared to non-aphasic ones. Intact BA44 offers a source of unimpaired input to a damaged motor system from primary visual pathways and the cortico basal-ganglia thalamic loop. However, when damaged, the motor system is starved of one important source of signal for effective retraining and recovery.

P15.18

MALTESE STUDY OF INTRACRANIAL VASCULAR MALFORMATIONS

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Intracranial vascular malformations (IVMs) are responsible for over a third of spontaneous intraparenchymal brain haemorrhage in the young population. These may cause recurrent intracranial bleeds, focal neurological deficits, seizures and chronic disability. The aim was to study the incidence of arterio-venous malformations (AVMs) and cerebral cavernous malformations (CCMs) in the Maltese population, assess mode of presentation, patterns of interventions, outcomes and follow-up of the lesions. A word search through the radiology information system was carried out, identifying cases of IVMs between January 2008 and October 2016, which presented at Mater Dei Hospital. Brain or dural AVM, carotid-cavernous fistulae and CCM were included in the study. A participant was identified as the 'incident' case at the time of first diagnostic image, be it computed tomography, magnetic resonance (MR) or catheter angiogram. Interventions, follow-ups and complications were noted. Of the 82 participants, 47 had AVMs and 35 had CCMs. The majority of patients with AVM presented with headaches. MRI was the prevalent imaging modality used at the time of diagnosis followed by angiography which was performed in 51% of patients. 61.7% had follow-up imaging within a year since diagnosis. AVM size was documented in 46.8% of cases. 42.6% of patients received radiosurgery with the commonest modality used being gamma knife. The most common complication was haemorrhage. Out of the 35 individuals with a CCM, seizures and focal signs were common presenting symptoms. In 80% of cases, dimensions of the CCM were reported and up to 65.7% of patients were followed-up with further imaging modalities within one year of diagnosis. The majority of patients were followed-up and not offered any interventions.
IVMs may cause significant morbidity in patients and timely recognition is essential. The risk of haemorrhage in patients with AVMs is 2-4% per annum and it is this risk that directs management. Cerebral angiography provides further information to help assess the risk of bleeding. Presently, decisions regarding CCMs are made on a case-by-case basis. There is need for guidelines, which would help direct clinicians on the evidence-based management of AVMs and provide further information on when repeat imaging should be undertaken.

P15.19

MYCOPLASMA PNEUMONIA ASSOCIATED ENCEPHALOPATHY: A CASE REPORT

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Mycoplasma Pneumonia is a common respiratory pathogen causing community-acquired pneumonia. The commonest neurological manifestations of this infection include encephalitis, myelitis and aseptic meningitis. Encephalopathy is a recognised complication in the paediatric age group. We describe a case of generalised encephalopathy in an adult. 68 years old previously healthy woman presented to accident and emergency after being found unresponsive. She had travelled to Malaysia 4 weeks prior to admission and had a one week history of flu-like symptoms. Clinical examination revealed no localizing signs. She was apyrexial with

no neck stiffness, reactive miotic pupils and she withdrew to pain. Intubation and ventilation were required on admission to intensive care where she developed a fever. CT Brain showed evidence of chronic sinusitis but was otherwise normal as was magnetic resonance imaging. She was started on Ceftriazone and Aciclovir empirically. Full toxicology screen, initial inflammatory markers, cerebrospinal fluid and autoimmune screen were negative. CT thorax demonstrated left sided consolidation with positive *M. pneumonia* IgM. Electroencephalogram showed diffuse slowing with sharp triphasic waves in keeping with encephalopathy. She was given sodium valproate empirically. Ceftriazone was changed to Tazobactam and she improved drastically. She became responsive and within one week had no residual neurological deficit.
M. pneumonia was undetected in the CSF, pointing against direct invasion of the CNS. Immune mediated processes occurring after infection could be a likely explanation although the patient improved without the use of steroids. Further research is required in determining whether encephalopathy in such rare presentations is secondary to an immune-mediated process.

P15.20
BRAIN TISSUE LEVEL OF NERVE GROWTH FACTOR IN A MOUSE MODEL OF CUPRIZONE-INDUCED DEMYELINATION
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Demyelination refers to the destruction of myelin sheath and is caused by inflammatory events, infectious and autoimmune diseases and toxic agents that damage the myelin sheath. Nerve growth factor (NGF) is a neurotrophic factor that is important for the development, maintenance and survival of the neurons. The aim of this study was to determine the brain level of NGF in a mouse model of cuprizone-induced demyelination. Twenty male C57BL6 mice, 6-8 weeks old were used in this study. To induce demyelination, 10 mice were fed chow containing 0.3 % cuprizone and control group were fed standard chow during 5 weeks. Mice were sacrificed under xylazine and ketamine anaesthesia and brain tissue removed at necropsy. Brain tissues were used for histopathological examinations and NGF analyses. For determination of demyelination, corpus callosum sections stained with Luxol fast blue. Protein extraction was performed from brain tissues for NGF analysis. In brain tissue extracts, NGF concentrations were measured by enzyme-linked immunosorbent assay. Brain tissue NGF concentrations in demyelinated group and control group were 0.81±0.13 ng/g brain tissue and 2.23±0.45 ng/g brain tissue, respectively ($p<0.05$). In conclusion, findings from the present study suggest that demyelination is associated with decreased NGF level in brain tissue. This research was supported by Ondokuz Mayis University Research Fund (PYO.VET.1904.09.001).

P15.21
NEUROPROTECTİVE EFFECTS OF EPİDERMAL GROWTH FACTOR
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Epidermal growth factor (EGF) is a growth factor in protein structure that stimulating division, differentiation, survival, proliferation, growth and migration of the cells which is involved in many physiological and pathological processes of the organism. EGF exerts its biological effects through EGF receptor (EGFR) which a transmembrane protein. Epidermal growth factor receptors are located on the cell surface of many tissues that include lung, stomach, duodenum, pancreas, kidney, pituitary gland, thyroid gland, mammary gland, ovary, uterus, placenta, cornea and glia. EGF activates the mitogen-activated protein kinase, extracellular signal-regulated kinase 1/2 and phosphatidylinositol 3 kinase (PI3K)/Akt signaling pathways stimulating cell proliferation and survival through binding to EGFR. EGFR plays a role in proliferation and differentiation of astrocytes and survival of postmitotic neurons. EGFR is also known to have an important role in oligodendrocyte development. In acute spinal cord injury, EGF treatment alleviates the deterioration in the blood-spinal cord barrier permeability via PI3K/Akt/Rac1 pathway and increases locomotor activity. Intranasal heparin-bound EGF treatment increases the formation of new oligodendrocytes from progenitor cells and induces functional recovery in newborn brain injury model. Plasma EGF levels is suggested that a biological marker of cognitive decline in patients with Parkinson disease and Alzheimer disease. EGF is evaluated as a key molecule for remyelination in patient with multiple sclerosis. EGF treatment is seen as a novel approach to the treatment of nervous system diseases.

P15.22

INVESTIGATION OF BRAIN-DERIVED NEUROTROPHIC FACTOR CONCENTRATION OF BRAIN TISSUE IN NEUROINFLAMMATION MODEL

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Neuroinflammation is the inflammation of nervous tissue that can leads to neurodegeneration. Brain-derived neurotrophic factor (BDNF) is a neurotrophin which affectes growth, function and survival of neurons in peripheral and central nervous system, enhances the stabilization of synapses, regulates synaptic function and branching of dendrites and axons. BDNF is believed to be involved in the pathophysiology of central nervous system diseases associated with neuroinflamation. Possible changes in decline of BDNF in brain tissue with neuroinflammation has not been reported before. The aim of the present study was to determine the concentration of BDNF in brain tissue of mice with neuroinflammation.

A total of 20, 8–10 weeks-old, male Swiss albino mice were used in this study. Twenty mice were randomly divided into two groups which received either intraperitoneal injection single dose of 0.9 % NaCl solution (control group) or 5 mg/kg lipopolysaccharide (neuroinflammation group). Mice were sacrificed by ketamine and xylazine anesthesia after 48 hours. Lesions that related with neuroinflammation in the brain tissue were determined with histopathological examination. The brain

tissue BDNF concentrations were determined using mouse specific enzyme-linked immunosorbent assay kit following the procedure as described by the manufacturer. The brain tissue concentrations were determined to be 0.33±0.08 ng/mg protein and 0.65±0.08 ng/mg protein in the neuroinflammation group and control group, respectively ($p<0.05$). These findings suggest that BDNF concentration may be used as a marker of disease characterized by neuroinflammation in the central nervous system. This research was supported by Ondokuz Mayis University Research Fund (PYO.VET.1904.15.012).

P15.23

ACTIVATION OF IMMEDIATE EARLY GENES IN THE TELENCEPHALON OF RATS FOLLOWING LESIONS OF THE NUCLEUS INCERTUS AFTER SOCIAL RECOGNITION TEST

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The specific NI projections to the amygdala may indicate a putative role of this tegmental nucleus in social behaviour. To study a specific participation of this system in modulating social recognition, the patterns of c-fos activation were measured in different telencephalic areas following NI lesions after a 3-rooms maze. Lesions were performed in 300-350 gr male wistar rats by stereotaxic injection of quinolenic acid in the NI. Sham animals received the same injection in the cerebellum. Animals were allowed to recover for 7 days. The 3-rooms maze consisted in two trials. In a first trial, the subject had free access to two rooms in one room, there was a co-specific and in the other room an object. In the second trial, the object was substituted by a novel conspecific. Sham cases tended to visit more the novel subject than the familiar one, but lesioned animals did not differentiate between the familiar and the novel. animals were anesthetized intracardially perfused with saline and fixative 1 h after the end of the behavioural paradigm. Then, ICC for c-fos was performed in 40um sections. Images were taken at 20x magnification for selected areas of the hippocampus, amygdala and septum and quantified by using ImageJ software.
When applied the t-test, significative differences were observed in the horizontal limb of the diagonal band and in the nucleus triangularis septalis. There were a significant difference between sham and lesion group on piriform cortex and in the central nucleus of the amygdala. The rest of amygdala nuclei did not show significant differences. We also observed significant differences between both lesioned and sham groups in CA1, CA2, and CA3 of hippocampus. However, the granule layer of the dentate gyrus did not displayed significant differences. These results point at this structures as targets modulated by the NI during performance of social recognition test.

P15.24

WIN55,212-2 ACUTE ADMINISTRATION INDUCES BEHAVIORAL AND SYNAPTIC CHANGES IN A SEX- AND AGE-DEPENDENT MANNER

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Marijuana use in adolescents has been associated with impairments in cognition related with several domains influenced by the prefrontal cortex (PFC) such as social behavior, an important form of social interaction in mammals. Previous work has suggested that the endocannabinoid system is involved in its modulation and that it seems to be sex-dependent. We combined electrophysiological and behavioral approaches to determine the effect of the synthetic cannabimimetic WIN55,212-2 on PFC synaptic plasticity and social interaction. Male and female rats at different ages received a single injection of WIN55,212-2 (s.c. 2 mg/kg) 24 h before behavioral evaluation and slice electrophysiology.
The results show that WIN55,212-2 administration altered N-methyl-D-aspartate receptor NMDA receptor (NMDAR)-dependent long-term potentiation (LTP) and social interaction. Both LTP magnitude and social behavior in male were affected while female juvenile rats were resistant to the cannabis-like compound. In marked contrast pubescent rats of both sex were not affected. Finally, adult rats also presented sex-dependent alterations in LTP.
These results suggest that the impairment of PFC plasticity induced by a single exposure to a cannabimimetic co-variates with social behavior changes. These alterations differentially affected male and females rats, indicating a sex-dependent modulation of PFC plasticity and social behavior by cannabis.

P15.25

ROLE OF THE NUCLEUS INCERTUS IN THE MODULATION OF THE SOCIAL RECOGNITION IN ADULT MALE RATS

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Modulation of hippocampal and amygdala function depends on ascending subcortical projections. We have focused our research on the nucleus incertus (NI), a tegmental centre involved in telencephalic modulation. NI displays projections to the hippocampus, amygdala, prefrontal cortex and medial septum. NI uses GABA as neurotransmitter that colocalizes with the neuropeptide relaxin-3 (RLN3). RLN3 belongs to the superfamily of relaxin and insulin peptides. Most neurons expressing RLN3 in the brain are concentrated in the NI. Tracing studies suggest that NI pathways may play a relevant role in the integration of information related to memory and attention. In addition, the occurrence of RLN3 fibers in the medial amygdala may indicate a relevant role of this system in modulating social behaviour. Thus, the aim of this work is to study the putative effect of NI inactivation on social recognition by using the 3 rooms maze. In this study, adult male wistar rats were NI lesioned by stereotaxic infusion of quinolenic acid. After 1 week of recovery from surgery. the social recognition of three chambers was done. The paradigm was developed in two trials. On the first trial, the problem subject was allowed to explore between two chambers, in one chamber, there was an inanimated object and in the other one

another subject. On the second trial, the object was substituted by a new subject so that the problem subject was allowed to explore the familiar and the novel subjects.
Both, lesioned and sham animals were able to readily differentiate between the subject and the object on the first trial. However, sham animals spent significantly more time exploring the novel subject compared to the familiar one during the second trial. In contrast, the lesioned animals were unable to differentiate between familiar and novel subjects and explore equal time both subjects in the second trial. These results clearly demonstrate a role of the nucleus incertus in social recognition in rats.

P15.26
IS BIOLOGICAL MOTION VIEWPOINT DEPENDENT?
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There has been much debate as to whether and how objects can be recognized across viewpoint changes. Here we ask whether viewpoint changes affect performance when participants make judgements about human actions depicted as point-light stimuli. Previous research has suggested that bodies may be “special” objects and may thus be immune to such viewpoint costs.
We used a concurrent matching task in which 3 dynamic point-light figures performed familiar actions taken from a standard biological motion database. On each trial the action performed by the central “target” figure was also performed by one of the two flanking figures. The participants task was to make a speeded left/right response to indicate which flanker was copying the target. The depth orientation of the target figure was randomly assigned and the matching flanker could either have the same orientation or appear with an offset of 45° or 90° relative to the target. The orientation of the non-matching flanker was random as were the step cycles of all three figures.
We found viewpoint changes affected both speed and accuracy. Repeated measures ANOVAs indicated significant main effects of viewpoint for both dependent measures. Post-hoc analysis showed that participants were faster and made fewer errors when the target and matching flanker had the same depth orientation compared to either viewpoint change condition. There were clear trends for better performance in the 45° compared 90° conditions, although these did not reach significance.
In the current experiment we have shown clear costs in recognizing the same action across viewpoint changes. This indicates that the recognition of human bodies depicted as biological motion stimuli is viewpoint-dependent, as with many other types of object. We also suggest that concurrent matching is a flexible tool for exploring biological motion as decisions can be made on a variety of actions without the need for explicit action-naming or training.