Centre for Physiology and Biochemical Research (CPBR),
International Stress and Behavior Society (ISBS), The Russian Society
for BioPsychiatry (RSBP), Ukrainian Society for Biological Psychiatry (USBP),
Institute of Experimental Medicine (IEM RAMS)

Conference Proceedings

St-Petersburg, Russia
May 16-20, 2011

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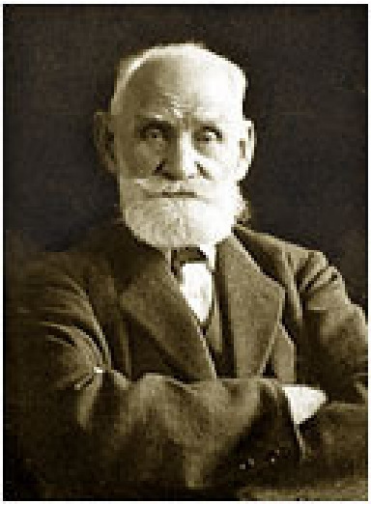
15th Multidisciplinary International Conference on Neuroscience and Biological Psychiatry

"Stress and Behavior"

Dedicated to 120th anniversary of I. Pavlov's Department of Physiology (Institute of Experimental Medicine, St Petersburg)



**St-Petersburg, Russia
May 16-20, 2011**

Day 1. May 16, 2011
Afternoon session

14.00-14.30 Opening ceremony, Welcoming addresses
AV Kalueff (Conference Chair), VM Klimenko (Program Committee Chair)

14.30-15.15 Opening Lecture:

CYTOKINES AND NEUROPLASTICITY
VM Klimenko
Institute of Experimental Medicine IEM RAMS, St. Petersburg, Russia

15.45-18.00 Special Lectures

EFFECTS OF CORTICOTROPIN-RELEASING FACTOR (CRF) ON MESOLIMBIC DOPAMINE TRANSMISSION
MJ Wanat, JC Lemos, BAS Reyes, EJ Van Bockstaele, C Chavkin and PEM Phillips
Department of Psychiatry and Behavioral Sciences,]Department of Pharmacology and Program in Neurobiology and Behavior, University of Washington, Seattle, WA; Department of Neuroscience, Farber Institute for Neurosciences, Thomas Jefferson University, Philadelphia, PA, USA

Discerning the neural pathways and cellular mechanisms underlying the effects of stress on behavior is of great importance to many psychiatric disorders. Dopamine neurons in the ventral tegmental area (VTA) and their forebrain targets, including the nucleus accumbens (NAcc), have been linked to motivational processes that are disrupted in mental illness. The stress-related peptide corticotropin-releasing factor (CRF) acts locally at forebrain structures including the VTA and NAcc. To study the interactions of CRF with mesolimbic dopamine transmission, we have used a combination of neurochemical (fast-scan cyclic voltammetry in behaving animals, anesthetized animals and brain slices), histological (immunohistochemistry and immunoelectron microscopy), pharmacological (systemic and local pharmacology in behaving animals and anesthetized animals, and bath application in brain slices), genetic (receptor knockout) and behavioral (instrumental behavior, forced swim stress and place conditioning) approaches. CRF acts in the VTA to suppress phasic dopamine transmission in a stimulus-specific manner, reducing motivation. Conversely, its action on dopamine terminals in the NAcc is to enhance neurotransmission and promote appetitive behaviors. However, this pro-motivation effect is persistently abolished following repeated stress exposure. Together, these studies identify complex and highly specific interactions between central stress and motivational systems that undergo long-term dysregulation during chronic stress. Supported by NARSAD (PEMP) and the National Institutes of Health grants F32-DA026273 (MJW), F31-MH086269 (JCL), R37-DA011672 (CC), R01-DA016782 (PEMP) and R01-MH079292 (PEMP).

GENETICS OF THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS AND ITS RELATIONSHIPS WITH BEHAVIORAL REACTIVITY

P Mormede
National Institute for Agricultural Research (INRA), Laboratory of Cellular Genetics, Toulouse, France

The hypothalamic-pituitary-adrenal (HPA) axis is central to numerous biological functions, including: metabolism, cardiovascular and immune systems, brain and behavior, and is also central to stress responses. Large individual variation has been described among individuals with profound physiopathological consequences. This presentation will focus on the molecular bases of genetic variation of HPA-axis activity and the relationships with behavioral reactivity. All levels of the HPA-axis are subject to genetic variation. For instance a quantitative trait loci study in pigs has revealed the importance of corticosteroid-binding globulin (CBG) in genetic variation in cortisol release under stress. Studies in knockout mice confirmed that CBG levels regulate the function of glucocorticoid hormones. We have studied by gene expression the sensitivity of the adrenal cortex to ACTH that is the main source of individual differences in cortisol release during stress. Another important source of genetic variation can be found at the level of corticosteroid receptors and transduction mechanisms. Less information is available about genetic variation of central (brain) regulatory mechanisms. One interesting aspect is the relationship between genetic variation in neuroendocrine and behavioral stress responses. Although divergent selection on glucocorticoid hormone release under stress has been shown to induce parallel changes in behavioral reactivity, the question is to know whether behavioral changes result from the variation in HPA-axis activity/reactivity, or whether the variation in behavioral response is an integral part of the selection trait. Recent data obtained in poultry support the latter hypothesis and suggest that the contribution of the HPA-axis to metabolism should be given more consideration, within the usual psychobiological framework of interpretation of stress mechanisms. Supported by INRA, French National Institute for Agricultural Research.

NEW ZEBRAFISH-BASED MODELS FOR BRAIN RESEARCH

AV Kalueff
Tulane University Medical School, New Orleans, LA, USA

Traditionally, zebrafish have been used in genetic testing for their ease of breeding and manipulation. In our lab, we use a zebrafish model to analyze stress, anxiety and pharmacological treatment. The novel tank exposure paradigm is an ethological model that utilizes the zebrafish's natural response to initially dive and bottom dwell in novel environments, and then gradually explore over time. The latency to explore the top half of the environment, as well as time spent in the top half, number of transitions, frequency of erratic movements, freezing, jumping, and velocity are several behavioral endpoints used to assess levels of anxiety. Other models include predator exposure, social interactions, alarm pheromone exposure and shoaling behavior assessment. We are also studying the effects of different stressors on zebrafish physiology (stress hormones, such as cortisol) and gene expression. Zebrafish are also highly sensitive to various pharmacological treatments, such as anxiolytics, anxiogenics, and antidepressants. Although zebrafish neurophenotyping is relatively simple in its design and yields robust response, the inclusion of video tracking makes this model widely reproducible, resulting in a truly high throughput model useful for pharmacological screening. The developing utility of zebrafish models to study brain disorders, including anxiety, epilepsy, drug abuse, cognitive deficits will be discussed. Supported by NARSAD YI Award, NIDA SOAR, LA Board of Regents, Newcomb College Fellows and Tulane SOM Pilot grants.

Day 2. May 17, 2011
Morning session

10.00-13.00 Special Symposium I: Novel mechanisms involved in the modulation of reward and dopamine transmission
Chair: RR Gainetdinov (Italy)

NOVEL OPPORTUNITIES FOR MODULATION OF DOPAMINE SYSTEM VIA TARGETING TRACE AMINE ASSOCIATED RECEPTOR 1 (TAAR1)
TD Sotnikova, S Espinoza, RR Gainetdinov, Italian Institute of Technology, Genova, Italy

INTRODUCTION: Endogenous trace amines of unknown biological function (beta-phenylethylamine, tyramine, octopamine and tryptamine) are structurally related to classical monoaminergic neurotransmitters and found at low concentrations in the mammalian brain. Their recently discovered group of G protein-coupled receptors, trace amine associated receptors (TAARs), may represent putative targets not only for trace amines but also for a variety of monoaminergic compounds including amphetamines and monoamine metabolites. The trace amine associated receptor 1 (TAAR1), which is in part associated with the monoaminergic neuronal circuitry controlling various functions including movement, is the best characterized of the class, though still little is known about its regulation and function.
METHODS: We performed investigation of the physiological functions mediated by TAAR1 by using knockout mice lacking this receptor. In particular, by using various experimental paradigms aimed to model Parkinson's disease in mice lacking TAAR1 we investigated the potential role of TAAR1 in movement control and regulation of dopaminergic transmission.
RESULTS: These investigations suggest that TAAR1 can exert potent modulatory influence over dopaminergic signaling and thus may represent a novel target for the pharmacology of Parkinson's disease or other disorders involving aberrant dopaminergic function. Other potential therapeutic applications of future selective TAAR1 agonists and antagonists will be also discussed.
RESEARCH SUPPORT: This work was supported in part by F. Hoffmann-La Roche Ltd. and Compania di San Paolo Fondaziona, Torino, Italy.

NEUROPLASTIC CHANGES FOLLOWING CONTINGENT OR NON-CONTINGENT COCAINE SELF-ADMINISTRATION
F Fumagalli, L Caffino, A Orrù, A Di Clemente, L Cervo, Department of Pharmacological Sciences, University of Milan; Experimental Psychopharmacology, Department of Neuroscience, Mario Negri Institute for Pharmacological Research, Milan, Italy

INTRODUCTION: Single or repeated exposure to cocaine causes long-lasting functional and structural modifications in various brain regions that participate in different aspects of cocaine abuse, including sensitization and tolerance contributing to addiction, which

can be considered a form of drug-induced neural plasticity. Recent data have implicated the neurotrophin BDNF and the immediate early gene Arc in the action of acute or long-term cocaine exposure, suggesting that they may contribute to the mechanisms which set the stage for cocaine addiction.
METHODS: To separate the direct pharmacological effects of cocaine from those associated with active drug self-administration, we employed a yoked-control operant paradigm in rats after single or repeated (14 days) intravenous cocaine self-administration sessions. After contingent or non-contingent cocaine self-administration, we examined BDNF and Arc mRNA by means of Real Time PCR, whereas BDNF and Arc proteins were measured by Western blotting.
RESULTS: Animals self-administering cocaine (S-A, 0.25 mg/0.1 mL saline/infusion, 2-h single session) did more active lever-presses than yoked-cocaine (Y-C) and yoked-vehicle (Y-V) animals. This goal-oriented behavior was accompanied by a selective increase in Arc (but not BDNF) mRNA levels in the medial prefrontal cortex (mPFC). Conversely, no effect on Arc mRNA levels was measured following repeated exposure to cocaine self-administration sessions, suggesting the desensitization of such mechanisms.

DELAYED DEVELOPMENT OF RAPID DOPAMINE SIGNALING IN THE DORSOLATERAL STRIATUM DURING COCAINE SELF-ADMINISTRATION DEPENDS ON VENTRAL STRIATAL CIRCUITRY

I Willuhn, LBurgeno, BJ Everitt and PEM Phillips, Department of Psychiatry and Behavioral Sciences and Department of Pharmacology, University of Washington, Seattle, WA, USA; Department of Experimental Psychology, University of Cambridge, Cambridge, UK

INTRODUCTION: Dopamine neurotransmission in the ventral striatum is strongly implicated in the acute reinforcing effects of drugs of abuse. After repeated drug intake, the dorsolateral striatum is thought to become increasingly involved in the control of drug taking. In a previous study, we characterized rapid dopamine release encoding drug-related cues in the ventral striatum of rats self-administering cocaine at a single time point. However, it is not known whether such dopamine signaling is expressed in other striatal regions or how it changes with drug-taking experience. Here, we measured rapid dopamine signaling simultaneously in the ventral striatum and dorsolateral striatum repeatedly over the course of 3 weeks. Furthermore, we investigated whether cue-related dopamine release in the dorsolateral striatum is dependent upon ventral striatal circuitry.
METHODS: Rats were outfitted with intravenous catheters for cocaine self-administration and given access to cocaine for one hour per day for 20 days. During a self-administration session, a nose poke elicited a cocaine infusion (fixed ratio 1 schedule, 0.5 mg/kg/infusion) that was accompanied by a 20-second presentation of an audio-visual stimulus (Pavlovian conditioned stimulus; delivery cue), during which additional nose pokes were without consequences (time out). After this time out, a separate cue signaled the availability of additional infusions (instrumental discriminative stimulus; availability cue). In one group of animals, multiple electrodes for fast-scan cyclic

voltammetry were chronically implanted in the striatum and phasic dopamine transmission was monitored during self-administration sessions. In a second group of rats, guide cannulae were bilaterally implanted in the dorsolateral striatum to permit local infusion of pharmacological agents prior to self-administration session. A final group of rats received a unilateral excitotoxic lesion of the ventral striatum (0.5-µl quinolinic acid, 0.09 M) and bilateral implantation of electrodes for fast-scan cyclic voltammetry into the dorsolateral striatum.
RESULTS: Throughout self-administration training, we observed rapid dopamine release in the ventral striatum associated with the presentation of the delivery cue, consistent with our previous studies. Dopamine release associated with the availability cue only emerged after repeated training in this brain region. In contrast to the ventral striatum, cue-related dopamine signals in the dorsolateral striatum developed a) only during later stages of training, and b) exclusively in response to presentation of the delivery cue. At the time when phasic dopamine transmission emerged in the dorsolateral striatum, there was no concomitant increase in drug consumption; however, there was a decrease in unreinforced responses (inactive nose pokes and responses during the time out period), conferring an increase in the efficiency of drug seeking. This effect was mediated by the onset of phasic dopamine transmission in the dorsolateral striatum as evidenced by bilateral injection of the dopamine receptor antagonist alpha-flupenthixol (10 µg) into the dorsolateral striatum, which decreased drug-seeking efficiency at a late (but not early) stage of training without producing a training-dependent effect on total drug consumption. Furthermore, the dependence on the ventral striatum for the development of dorsolateral dopamine signaling was demonstrated in animals that received an unilateral lesion of the ventral striatum, which blocked the development of dorsolateral signals in the ipsilateral, but not contralateral, hemisphere. Our results demonstrate that rapid dopamine signaling in the striatum in response to drug cues is dynamic and region specific, developing in the ventral then dorsolateral striatum sequentially. This progression of dopamine signaling to dorsal regions of the striatum requires intact ventral striatal circuitry. Overall, these data demonstrate recruitment of striatal circuitry for dopamine-mediated encoding of drug cues in the development of a drug-taking habit.
RESEARCH SUPPORT: Supported by Deutsche Forschungsgemeinschaft (IW) and the National Institutes of Health grant R21-DA021793 (PEMP).

MIMICKING STRESS AND DRUG REWARD RELATED DOPAMINE CHANGES IN RAT STRIATUM WITH OPTOGENETICS

EA Budygin, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA

INTRODUCTION: Optogenetics is an exciting technique based on light-sensitive ion channels called opsins. Although relatively new, optogenetics has already proven to be extremely useful, particularly since opsins can be targeted to specific neuronal subtypes, and the resultant millisecond timescale control over neuronal firing can be used to mimic natural firing patterns.
METHODS: Recently, our group has successfully employed optogenetics, combined with fast-scan cyclic voltammetry (FSCV), to manipulate dopamine (DA) release in the rat

striatum. We used a viral vector to deliver the channelrhodopsin2 (ChR2) gene to the ventral tegmental area (VTA) and substantia nigra (SN) and implanted a fiber optic (coupled to a blue laser) into these regions. The light-driven stimulation of cell body DA neurons in the VTA and SN was used to mimic real neurochemical events that take place in the terminal field.
RESULTS: In the first set of experiments, changes in the subsecond DA release in the striatum of freely moving rats were detected with FSCV during the presentation of different rewarding and stressful stimuli. As expected, drugs of abuse (nicotine and cocaine) induced marked increase in subsecond DA release in striatal subregions. The classical aversive stimuli, including a tail pinch, resulted in a unique DA signal pattern characterized by significant increase in accumbal DA release that was time locked with the painful stimulus, and which gradually declined after the stimulus was discontinued. In the second set of experiments, by combining the tight spatial and temporal resolution of both optogenetics and FSCV, we have determined the parameters of optical stimulation necessary to mimic observed DA release patterns. We were able to repeatedly evoke concentrations of DA release as small as a single DA transient (50 nM). A U-shaped frequency response curve was found with maximal stimulation inducing DA effluxes (>500 nM) that approach therapeutic levels. This unique frequency dependence is likely based on the biological properties of the ChR2 proteins. Furthermore a lack of change in extracellular pH indicated that optical stimulation did not alter blood flow. According to our results, striatal DA is very responsive to optogenetic manipulation of frequency, pulse (flash) duration, number of flashes and light pulse power. Therefore, light-driven stimulation of brain DA neurons can be used to mimic divergent patterns of striatal DA dynamics that are observed in different behavioral situations. These tools will be essential in understanding the neural microcircuitry underlying brain DA neurotransmission.
RESEARCH SUPPORT: The work was supported by NIH Grant DA021634.

ACETYLCHOLINE CONTROL HYPOTHESIS FOR PHASIC MESOLIMBIC DOPAMINE RESPONSE TO NICOTINE

M Graupner, B Gutkin, Center for Neural Science, New York University, NY USA; Group for Neural Theory Laboratoire de Neuroscience Cognitive, INSERM U960 Departement des Etudes Cognitives, ENS Paris, France

INTRODUCTION: Nicotine exerts its reinforcing action by stimulating nicotinic acetylcholine receptors (nAChRs) and boosting dopamine (DA) output from the ventral tegmental area (VTA). Recent data have led to a debate about the principle pathway of nicotine action: direct stimulation of the DAergic cells through aAChR activation or disinhibition mediated through desensitization of GABAergic interneuron nAChRs.
METHODS: We use a computational model of the VTA circuitry and nAChR function to resolve this issue. The model describes dopaminergic and GABAergic neural activity at the level of population firing rates. The model further explicitly incorporates the pharmacodynamics and the expression targets of key nAChR subtypes. Our model illustrates that the α4β2-containing nAChRs either on DA or GABA cells can mediate the acute effects of nicotine.

RESULTS: We account for in vitro as well as in vivo data, and predict the conditions necessary for either direct stimulation or disinhibition to be at the origin of DA activity increases. We show that tonic acetylcholine levels crucially determine the evoked DA response and propose key experiments to disentangle the contribution of both mechanisms. We then show how the presence of nicotine affects the impact of external stimuli on the phasic dopamine responses and how these responses depend on the cholinergic tone. Notably our model predicts that nicotine is capable of bestowing a positive motivational valence to neutral environmental stimuli and decreasing the impact of stimuli with negative valence. Together our results delineate the mechanisms by which the VTA mediates the acute rewarding properties of nicotine and suggest a new acetylcholine dependence hypothesis for nicotine reinforcement.
RESEARCH SUPPORT: This research was supported by Agence National pour la Recherche, NERF, INSERM, Ecole de Neuroscience de Paris and CNRS.

Day 2, Afternoon session

14.00-14.45 Special Presentation
INVESTIGATION OF RODENT BEHAVIOR IN THE HOME CAGE INCREASES ANIMAL WELFARE
H Russig, E Wenzler, W Foerster, TSE Systems GmbH, Bad Homburg, Germany

INTRODUCTION: Investigations of genetically modified laboratory rodents provide valuable insight into underlying mechanisms of various human diseases and can provide new tools for drug development. A major step during animal model development is the intensive in-vivo phenotyping and behavioral characterization of animals. Classical behavioral phenotyping requires large sets of animals investigated in batteries of different behavioral tests resulting in substantial experimenter-induced handling stress and data variability. In order to increase throughput and animal welfare, TSE Systems and other video-tracking companies have recently developed automated home-cage test technologies, such as the PhenoMaster or the IntelliCage. The PhenoMaster represents a modular automated test system to investigate behavioral and metabolic alterations in mice or rats 24 hours per day. Similarly, the IntelliCage is a unique solution for automated monitoring of behavior under stress-free conditions within social groups, and allows the application of a variety of freely programmable cognitive tasks, traditionally tested in classical behavioral test batteries. Behavioral domains covered by the IntelliCage range from spontaneous behavior such as exploration or anxiety to complex behavior such as discrimination learning or spatial memory. Both systems exclude animal handling induced stress, ensure increased animal welfare, and allow a reduced number of animals needed for comprehensive phenotyping. The use of automated systems increases throughput and assures high standardization of test procedures. In conclusion, automated home cage test systems open new dimensions for a variety of low-stress in-vivo research approaches in biomedical and preclinical science.

14.45-18.00 Symposium II. Translational Biological Psychiatry
Chairs: VM Klimenko (Russia), AV Kalueff (USA)

TIA-1-DEFICIENT MICE: A MODEL FOR STRESS-INDUCED ANXIETY AND DEPRESSIVE-LIKE BEHAVIOR

JB Rayman, HD Vishwasrao, ER Kandel, Howard Hughes Medical Institute; Columbia University, New York, NY, USA

INTRODUCTION: One of the most common findings in patients with major depressive disorder (MDD) is hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in persistent elevation of circulating glucocorticoids. Although a short-term increase in glucocorticoid production is vital for the adaptive stress response, continuous exposure of neurons to heightened glucocorticoid levels is detrimental to cellular function. Intriguingly, both the normal feedback mechanisms that govern the HPA-axis, as well as the cellular damage arising from excessive glucocorticoid stimulation, require a functional glucocorticoid receptor (GR). Thus, control of GR activity is both complex and dynamic. Here, we describe a novel mechanism by which TIA-1, a cellular stress response protein, contributes to post-transcriptional regulation of the synthesis of GR. To extend these findings, we have carried out studies in TIA-1 KO mice, which exhibit a variety of stress-induced behavioral phenotypes that are consistent with aberrant GR regulation in the hippocampus, one of several brain structures that modulate the HPA axis. These results provide a new level of insight into the molecular and cellular pathology of stress-induced anxiety and depressive-like behavior.
METHODS: Multiple cohorts of wild-type and TIA KO littermates were generated by repeated crosses of TIA+/- mice. Conventional behavioral paradigms (e.g., open field, elevated plus maze, contextual fear conditioning, and forced swim test) were performed. Plasma corticosterone levels were determined by ELISA. Imaging and biochemical studies of dissociated hippocampal cultures and acute hippocampal slices from TIA-1 KO mice and wild-type littermates were performed according to standard procedures. Quantitative data were subjected to statistical analysis to determine significance of effects.
RESULTS: Under basal conditions, TIA-1 KO mice are indistinguishable from wild-type control mice in a battery of conventional behavioral tests of anxiety, despair, and spatial learning and memory. However, three weeks after contextual fear conditioning, TIA-1 KO mice exhibit more anxiety and despair-like behavior than control littermates. Furthermore, these stress-induced phenotypes are associated with persistently elevated glucocorticoid levels, as well as reduction of GR protein in the hippocampus, one of several neuroanatomical structures critical for limiting HPA-axis output. Given that TIA-1 is a cellular sensor of oxidative state, and that excessive glucocorticoid secretion can induce oxidative stress in neurons, our data suggest a novel regulatory mechanism whereby TIA-1 modulates GR synthesis in response to circulating glucocorticoid levels. Post-transcriptional control of GR by TIA-1 provides an additional layer of regulation to ensure that GR protein abundance is determined in an efficient and optimal manner. Taken together, these observations support the notion that TIA-1-deficient mice

represent a model for studying gene-environment interaction in the context of stress-induced anxiety and depressive-like behavior.
RESEARCH SUPPORT: Howard Hughes Medical Institute (HHMI) and the National Institutes of Health (NIH).

NITROXIDERGIC MODULATION OF THE BEHAVIOURAL AND IMMUNE RESPONCES OF STRESSFULL OPIOID DEPENDENCE AND WITHDRAWAL

M Vlaskovska, S Surcheva, I Altankova, T Marinova, L Kasakov, Department of Pharmacology, Medical Faculty, Medical University Sofia, University Hospital St. Ivan Rilski, Department of Biology, Medical Genetics and Microbiology, Medical Faculty, St. Kliment Ohridsky University, Institute of Neurobiology BAS, Sofia, Bulgaria

INTRODUCTION: Opioid dependence/withdrawal is a mono-ethiology, multi-mechanism stressful complex reaction of the organism at cellular and integrative levels. Despite recent advances in understanding the modulation of behavioral and immune responses through opioid dependence/withdrawal, the role of nitroxidergic mechanisms in this modulation is not well understood. The aim of present investigation was to study the effects of NOS inhibition in vivo on the severity and progression of withdrawal, and in vitro analysis of leukocyte proliferation, DNA fragmentation and thymocyte apoptosis in opioid-dependent state.
METHODS: Animals: Male rats (Wistar, 220-240 g, Medical University of Sofia) were used. Experiments have been approved by the Ethics Committee of the Institute of Neuroscience. Drugs: Morphine hydrochloride, Naloxone, L-NAME, Concanavaline A (CON A) were from Sigma Aldrich (St. Louis, MO). Opioid dependence/withdrawal was induced by chronic morphine administration, and scored as described previously [1]. CON A-induced lymphocyte proliferation was studied in splenic tissue by 3H-Tymidine labeling. DNA fragmentation was revealed by agarose electrophoresis and thymocyte apoptosis was studied by TUNEL reaction.
RESULTS: The effects of NOS inhibition on the progression of withdrawal syndrome is summarized as follows: Control (saline) 4.0 +/- 0.7 and 12.0 +/- 2.6, Chronic Morphine 17.5 +/- 1.1 and 42.5 +/- 6.8, Chronic Morphine + L-NAME 6.0 +/- 0.9 and 17.0 +/- 4.2, Naloxone-precipitated Morphine withdrawal 47.0 +/- 4.3 and 126.0 +/- 19.3, Chronic L-NAME prior Naloxone-precipitated Morphine withdrawal 14.5 +/- 2.4 and 39.5 +/- 7.4. Morphine suppressed and L-NAME stimulated splenocyte proliferation as follows: Control 38.75 +/- 3.77 and 23.75 +/- 1.21, Chronic Morphine 2.74 +/- 0.29 and 2.26 +/- 0.11, Chronic L-NAME 117.62 +/- 14.63 and 107.52 +/- 9.70, Cronic Morphine + L-NAME 28.84 +/- 3.58 and 19.11 +/- 2.14. L-NAME alleviated Morphine-induced thymocyte DNA fragmentation and apoptosis. In conclusion, our data suggest that deteriorating opioid behavioral and immune responses can be alleviated by nitroxidergic inhibition.
[1] Philipova, Tz., Vlaskovska, M., Kasakov, L. Effect of sex steroid estradiol on the morphine analgesia and tolerance/dependence: gender related responses. Comptes rendus de l'Academie Bulgare des Sciences, 57, 99-106, 2004.

OLFACTION, NOCICEPTION AND IMMUNITY IN MENTAL DISORDERS

T Nevidimova, V Semke, T Vetlugina, N Bokhan, G Simutkin, Mental Health Research Institute, Tomsk, Russia

INTRODUCTION: Sensory perception is an important part of mental health. Sensory and immunological abnormalities are frequently observed in patients with depression and addiction. One of example of sensory vulnerability is pica, an eating disorder related to the consumption of non-nutritive substances and subsequent changes of olfactory and taste preference. Craving for the scent of petrol or acetone is often observed in patients suffering from pica. Interestingly, pica occurs variably in patients with iron deficiency. The precise pathophysiology of the syndrome is unknown. Importantly, pica and changes of sensory perception thresholds could form a stereotype of addictive behavior. Our study aimed to determine the interactions between sensory vulnerability and immunological abnormalities in addictive and affective disorders.

METHODS: 782 patients (addictive and affective disorders) and controls were analyzed in this study. We used questionnaires, Hamilton rating scale, 40-item University of Pennsylvania Smell Identification Test (UPSIT), Alcohol Sniff Test (AST), androstenone test, taste test, pressure-pain thresholds test, and visual analog scale. Parameters of immunity and iron metabolism were also studied. Mann-Whitney, chi-square and logit-regression were used for statistical analysis.

RESULTS: Pathological gustatory and olfactory sensations were registered in childhood and adolescence in >50% cases, and signs of addiction were detected about half of the cases. Features of addiction are found often in 1.5 ($p<0,05$) times beside students having sensory disorders. Iron deficiency and eating, anxious, cognitive, depressive, and immune disorders are often found beside them. Early pica was registered in heroin addicts more frequently than in controls (43 and 22%, $p<0,05$). Sensory vulnerable persons with anamnestic pica were characterized by a maximum level of ferritin (84,63±22,6 ng/ml versus 28,66±4,2 ng/ml, $p<0,05$) and a minimum level of CD71 lymphocytes 2,31±0,6 % versus 9,56±1,8% $p<0,05$), correlating with the level of interleukin-6. Pica is a risk factor that predisposes adolescents to addiction. Other risk factors are decreased sensitivity to bitter and salty taste stimuli and the absence of aversive reactions to olfactory stimuli. The risk of formation of the primary pathological craving for psychoactive substances increase the following factors: male sex, early pica, need for sensory stimulation, immune deficiency, and anxiety. Our model can predict the risk of addiction with an accuracy of 85%. We have obtained effective sensory therapy (aromatherapy) in students, showing anxiolytic and immunoprotective effects of some fragrances (labdanum, citrus or pine). Depressed subjects had significantly decreased CD2 lymphocytes, reduced taste and olfactory sensitivity (medium anosmia) and changed pain thresholds. Pain thresholds increased from 8 to 12 units ($p<0,05$) and were related to dynamics of algy during antidepressive therapy including selective serotonin reuptake inhibitors. Sensory and immune deviations are related to development of affective and addictive disorders. Pica and olfactory craving are a behavioral pattern relieving addiction. Sensory disorders can indicate predisposition to the abuse of psychoactive substances. Perhaps physiological vulnerability may be corrected by iron therapy in some cases. Addiction-prone individuals (smokers)

responded best to aromatherapy. Parameters such as smell identification, smell and taste aversions, and pain thresholds may be used in therapy estimation in addiction and depression.

EFFECT OF MK-801 ON SUSTAINED ATTENTION IN RATS

IM Sukhanov, OA Dravolina, EE Zvartau, AY Bespalov, Institute of Pharmacology, Pavlov Medical University, St. Petersburg, Russia

INTRODUCTION: Schizophrenia encompasses cognitive impairment in areas of memory, attention and executive function. This cognitive impairment may be explained by sensory gating defects seen in studies of schizophrenic patients. Psychotic state might be characterized as a state of hyper-vigilance, in which psychotic patients appear to be flooded by stimuli whose intensity cannot be regulated through sensory gating mechanisms. The inability to filter out irrelevant information from the environment can induce information overloading of the brain. In line with this, several neuroimaging studies indicating that hippocampus, thalamus and prefrontal cortex are dysregulated and overloaded in schizophrenia patients. Overloading may induce dysfunction of these regions essential for cognition, resulting in cognitive deficits. The present study aimed to characterize the temporal dynamics of performance in operant signal detection impaired by a prototypic psychotomimetic agent, MK-801.

METHODS: Male Wistar rats were tested in the standard two-lever operant box. After initial shaping, subjects were trained to learn an operant signal detection rule. The detection task is predicated on the idea of detecting the presence or absence of a target stimulus. The animals were trained to discriminate between «signal» (the presentation of a compound target stimulus that varied in length (10, 30, or 500 ms) and consisted of a signal light illumination and 3 kHz tone (70 dB)) and «blank» trials presented in a pseudo-random order. Both signal and non-signal events were followed by 4-sec response window during which two levers were extended into the box and were remained active until a lever press occurred. Presses on the target lever were reinforced following presentation of a signal (termed as a hit), whereas presses on the other lever were reinforced following a non-signal event. Daily sessions were divided into four blocks of 25 trials. Prior to the tests, rats were pretreated with MK-801 (0, 0.03, 0.1, 0.18 and 0.3 mg/kg, i.p.).

RESULTS: Sustained attention performance was characterized by signal-length dependence of the hit rate. Rats easily discriminated between «signal» and «blank» trials when duration of stimulus was 500 ms (percent of hits reached 100%); however at 30-ms stimulus duration level, the percent of hits were reduced to 50% accuracy, and was further decreased to 30% by failure to recognize 10-ms signals. Pretreatment with MK-801 did not affect rats' performance at shorter signal durations (10 and 30 ms). In contrast, the ability of rats to detect long signals was highly sensitive to MK-801 pretreatment. MK-801 (0.18 mg/kg) produced a decline in sustained attention performance that increased over the session and reached significance only in the final stages of the test (cognitive fatigue). The results of the present study suggest that MK-801 induced time-dependent impairment of sustained attention. These results further

support the notion that sustained attention deficits induced by NMDA receptor blockade are caused by information overloading.

IMPAIRMENT OF ADULT BRAIN NEUROGENESIS ALTERS HIPPOCAMPUS-DEPENDENT BEHAVIOURAL TASKS WITHOUT REDUCING LEARNING ABILITY

P Jedynak, RK Filipkowski, L Kaczmarek, Department of Molecular and Cellular Neurobiology, Nencki Institute of Experimental Biology PAN; Department of Cognitive Psychology, University of Finance and Management, Warsaw, Poland.

INTRODUCTION: The exact function of adult hippocampal neurogenesis remains unclear, although it has been suggested to play a role in learning and memory processes.
METHODS: In our studies, we employed cyclin D2 gene knock-out (cD2 KO) mice with almost complete deficiency of newborn neurons in the adult brain (Kowalczyk et al., J. Cell Biol., 2004). These mice have also slight morphological abnormalities of the brain, including hippocampal formation.
RESULTS: Previously, we have shown for cD2 KO mice that new hippocampal neurons are not required for memory formation (Jaholkowski et al., Learn. Mem., 2009). In the present study, animals were subjected to hippocampus-dependent behavioral tests requiring (or not requiring) a learning component. cD2 KO mice showed significant impairment in such species-typical behaviors as nest construction, digging, and marble burying. They were building none or poorer nests, digging less robustly, and burying fewer marbles than WT. Moreover, in contrast to controls, cD2 KO mice showed normal sucrose preference preceded by the neophobia phase. cD2 KO mice were more active in the open field and automated motility chamber, and showed increased explorative behavior in IntelliCage. On the other hand cD2 KO mice performed normally in the cue and context fear conditioning tasks. As all those non-cognitive behaviors have previously been shown to rely on the intact hippocampus, we attribute the observed impairments either to the morphological abnormalities of the hippocampal formation, or adult brain neurogenesis impairment, or both.

ALTERED DAT FUNCTION IN A MOUSE MODEL OF PARKINSON DISEASE

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INTRODUCTION: Since the identification of a number of Parkinson's disease (PD) genes in humans, much effort has been spent at developing models of the disease in the mouse. Disappointingly, mice bearing targeted deletion of critical genes such as Parkin, Pink1 or DJ-1 do not show any significant loss of dopamine (DA) neurons or any major motor disturbances. Although the reason for this is unclear, the absence of DA neurons loss could actually be an advantage for PD research since these mice may allow us to identify perturbations of the central or peripheral nervous system that are early markers of the disease, prior to DA neuron cell death

METHODS: We have recently been using fast scan cyclic voltammetry (FSCV) to study the kinetics of DA release in Parkin knockout (KO) mice.
RESEARCH SUPPORT: This work was supported by the Neuroscience Canada Brain Repair Program. Damiana Leo was supported by a postdoctoral fellowship (PDRF) from the Department of Foreign Affairs and International Trade of Canada and by a postdoctoral fellowship from the Fonds de la Recherche en Santé du Québec (FRSQ).
RESULTS: We found that while DA release evoked by single stimuli is normal, there is a marked deficiency in extracellular DA accumulation in response to repetitive activation of DA axons. Our data show that this deficiency is entirely due to increased DA reuptake through the membrane DA transporter (DAT), because no difference between the genotypes persists in the presence of a DAT antagonist. Moreover, we also identified a marked increase in DAT protein levels in Parkin striatum (STR), mostly present at the cell surface. Identification of such early markers may eventually lead to early diagnosis, which would represent an exceptional advance because it would make it possible to attempt to prevent the death of DA neurons through the use of neuroprotective strategies.

PARTICIPATION OF GLYCOPROTEIN 130 IN THE MECHANISM OF HEREDITARY CATALEPSY IN MICE

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INTRODUCTION: Catalepsy (animal hypnosis, or tonic immobility) is a state of prolonged motor inhibition and represents a type of passive defensive behavior. Its exaggerated form is a syndrome of psychopathological disorders, such as schizophrenia and affective disorders. Using quantitative trait loci (QTL) analysis, selective breeding and genetic recombination, the linkage between the Il6st gene encoding the glycoprotein 130 (gp130) and the hereditary catalepsy was shown. Glycoprotein 130 is involved in the signal transduction pathways from interleukin-6 (IL-6) and related cytokines that participate in the regulation of immunity, neurogenesis, inflammation and behavior.
METHODS: The main aim of the study was to compare the Il6st gene expression and the gp130 sensitivity to bacterial lipopolysaccharide (LPS) in male mice of catalepsy-resistant AKR strain and catalepsy-prone congenic AKR.CBA-D13Mit76 strain created by transferring the gp130 gene allele from catalepsy-prone CBA/Lac to the genome of AKR/J strain. In this study, we analyzed the effects of LPS on catalepsy, behavior in the open field and social investigation tests, and expression of gp130-regulated glial fibrillary acidic protein (GFAP) coding gene in AKR and AKR.CBA-D13Mit76 mice.
RESULTS: No difference in the gp130 expression in the frontal cortex, hippocampus and midbrain between AKR and AKR.CBA-D13Mit76 mice was found. However, AKR.CBA-D13Mit76 mice were more sensitive to LPS. Low dose of toxin (50 μg/kg, i.p.) significantly increased mRNA level of the gene encoding gp130-regulated glial fibrillary acidic protein (GFAP) in midbrain ($p<0.01$ vs saline), decreased locomotor activity in the open field ($p<0.05$) and reduced duration of social behavior ($p<0.001$ vs saline) and level of aggression ($p<0.05$) in the social investigation test in AKR.CBA-D13Mit76 (but not in AKR) mice. Moreover, only high dose of the toxin (200 μg/kg, ip) induced catalepsy in

60% of AKR animals, while both doses of LPS (50 and 200 μg/kg, ip) significantly increased duration of cataleptic immobility in AKR.CBA-D13Mit76 mice ($p<0.001$ vs saline). Our results confirm the association between gp130 and hereditary catalepsy in mice. The CBA allele of Il6st gene determines the alteration of gp130 functional activity that leads to increased sensitivity to LPS and ensures high predisposition to catalepsy in AKR.CBA-D13Mit76 mice. The AKR.CBA-D13Mit76 congenic strain provides a new experimental tool to study the role of gp130-related cytokines in the regulation of normal and pathological behavior.
RESEARCH SUPPORT: Program 'Molecular and Cellular Biology' of the Presidium of Russian Academy of Sciences (grant 22.9); Russian Foundation for Basic Research, Contract grant 11-04-00266-a

GENE POLYMORPHISMS ASSOCIATED WITH AGGRESSION IN PIGS

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INTRODUCTION: Aggression between pigs occurs when unfamiliar pigs are mixed (on farms, on trucks transporting animals to the slaughterhouse, and during lairage). Aggression affects pig welfare (e.g., elevated social stress, biting resulting in skin lesions), production efficiency, and product quality (carcass yield because of skin lesions, meat quality). A genetic component to individual aggressiveness has been described in pigs, mice and other species. It is therefore possible to consider genetic selection against excessive aggressive tendencies; however, direct phenotypic selection is difficult in the context of commercial facilities. An alternative strategy is to search for molecular genetic polymorphisms associated with aggressive tendencies and use these for marker-assisted selection. We sought polymorphisms in genes known from the literature to be associated with aggressive behavior. Our primary interest is the components of the brain serotonergic system that has been identified as a primary neurochemical system involved in the regulation of aggressive behavior in pigs.
METHODS: Individual aggressive tendencies (aggressiveness) were measured after weaning at five weeks of age following a standardized mix. Phenotypic information, DNA and pedigree are available for 523 animals. Candidate genes, selected from the literature, are involved in the regulation of the serotonergic system, the dopaminergic system and vasopressin. The sequences of candidate genes were obtained from the most recent databases (http://www.ensembl.org/Sus_scrofa/Info/Index). The software packages CodonCode Aligner and BioEdit were used for sequence assembly and polymorphism detection. All animals were genotyped for the selected SNPs using the Sequenom® mass spectrometry-based genotyping assay technology (Germany, Hamburg). Association studies were performed using the R statistical software system.
RESULTS: In the present study, 120 new SNPs were detected in the promoter and coding regions of the selected genes. We discovered 9 SNPs in four specific genes (SLC6A4, HTR2C, DRD2, AVPR1A) significantly associated with aggressive tendencies.

Our study contributes to a better understanding of the genetic architecture of aggressiveness in pigs. These results can be used in marker-assisted selection to reduce livestock aggression.
RESEARCH SUPPORT: INRA-RFBR grant 09-04-92858

MODULATION IN ANTIPSYCHOTIC EFFECT OF ZIPRASIDONE WITH NIMODIPINE
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INTRODUCTION: Voltage-gated calcium channels have a key role in controlling secretion of neurotransmitters such as dopamine. Drugs affecting neurotransmission within the mesocorticolimbic dopaminergic system may be effective in treating schizophrenia. Interestingly, it antipsychotics may have calcium channel blocking activity, and similarly that calcium channel inhibitors have potential antipsychotic effects. We aimed to examine the role of nimodipine, a dihydropyridine calcium channel blocker, on the effects of ziprasidone, an atypical antipsychotic drug, on experimental psychosis models.
METHODS: Amphetamine-induced hyperlocomotion, haloperidol-induced catalepsy, apomorphine-induced climbing were used for models of experimental psyhosis. 1 and 10 mg/kg doses of ziprasidone were given to mice i.p. for 10 days. Nimodipine was used i.p. as single injection at a dose of 0.5mg/kg. Nimodipine was also combined with 10mg/kg dose of ziprasidone. Mice in control groups were given saline i.p. for 10 days.
RESULTS: 10mg/kg but not 1mg/kg ziprasidone significantly decreased amphetamine-induced hyperlocomotion compared to amphetamine group. 1mg/kg but not 10mg/kg ziprasidone significantly alleviated catalepsy time compared to haloperidol group. Both doses of ziprasidone significantly reduced climbing time compared to all other groups. Nimodipine had no significant effect on amphetamine-induced hyperlocomotion, climbing and catalepsy time compared to control however, when combined with ziprasidone, a significant increase in locomotor activity, and in climbing time but no significant difference in catalepsy time compared to 10mg/kg ziprasidone were observed. Conclusion: Nimodipine, when combined with ziprasidone, inverted the reducing effect of ziprasidone on locomotor activity and climbing time, but did not change its effect on catalepsy time. Our data suggest that calcium channels may mediate antidopaminergic, thereby antipsychotic effect of ziprasidone, but no involvement of calcium-dependent mechanisms in the cataleptogenic effect of ziprasidone, are suggested.

CRANIAL ELECTROTHERAPY STIMULATION FOR TREATING STRESS-RELATED DISORDERS IN HORSES
K Nagy, R Kovács, Á Povázsai, R Fischer, M Garamvölgyi, C Aurich, S Ottó, G Bárdos, SzIU, Faculty of Veterinary Medicine, Budapest, Hungary; Graf Lehndorff Institute for Equine Science, University of Veterinary Science, Vienna, Austria; Hungarian National Police Force; ELTE, Department of Physiology and Neurobiology, Budapest, Hungary

INTRODUCTION: Recent studies describe an effective and drug-free alternative in the treatment of human depression, anxiety and sleeping disorders by using a cranial

electrostimulator which utilizes small pulses of electric current (1-2 mA) across a patient's head. Such cranial stimulator exists also for horses (Happy Halter, Fisher Wallace Laboratories). To test objectively the calming effect of the Happy Halter, police horses were used in collaboration with the Hungarian National Police Force. These horses are frequently exposed to severe conditions (e.g. football matches), and a huge proportion of them have been reported to cope less successful in their stressful environment.
METHODS: Police horses (n=18) were allocated into 3 groups (control, treated and placebo). All three groups contained 3 horses showing more and 3 showing less anxiety than the average (anxiety level was calculated by using a previously validated personality questionnaire). Horses in the treated group received a 30-day treatment with the Happy Halter (20 min/day, level 1 intensity as recommended for human patients). The Happy Halter device was placed on the head of the placebo horses the same way as on the treated horses, but no stimulation was given. No manipulation occurred in control horses. Before and after the 30-day treatment, baseline values of heart rate, heart rate variability (HRV) and salivary cortisol concentrations were measured. The physiological reaction to the first and the last Happy Halter treatment was measured, as well as the stress coping ability of horses before and after the 30 day long treatment.
RESULTS: Groups did not differ in baseline cortisol or HRV values before treatment. Heart rate in control horses tended to be slightly lower compared to the treated group ($p=0.083$) and was significantly lower than in the placebo group ($p=0.006$). Happy Halter and placebo-treated horses did not differ significantly. Horses showing more anxiety had significantly lower vagal tone (high frequency HRV component (HF): 39.1±14.0, mean +/- SD) compared to horses showing less anxiety (46.0±14.0, $p=0.015$). During the first treatment, an increase in parasympathetic tone (HF) could be observed in the treatment group ($p<0.001$), but not in the placebo group. There were no differences in cortisol concentration and heart rate. During the last Happy Halter treatment, changes in HF in the treated group became less evident ($p=0.077$), and the overall cortisol level tended to be higher in the treated group compared to the placebo group ($p=0.067$). There was no difference in heart rate. During the stress-test conducted at the end of the 30-day treatment, treated horses started with higher vagal tone to the other two groups, and showed a greater flexibility when facing the stressor. One week after the last treatment, there were no more differences in HF or cortisol amongst groups. Behavioral changes during the test period were only evident in one of the 18 examined horses. This horse belonged to the treated group, had shown high anxiety, and became much calmer following the 30 day period, perhaps due to the Happy Halter treatment. Our preliminary results suggest that Cranial Electrotherapy Stimulation for treating stress-related disorders in horses may be promising. However, further studies involving more horses with markedly high anxiety levels, and perhaps treatment with greater intension and for longer period, may be needed to support or reject the effectiveness of Happy Halter treatment in horses.
RESEARCH SUPPORT: Supported by the Hungarian International Relations Committee (NKB) grant 2010/15935.

CHRONIC PAIN STRESS ASSOCIATED WITH AUTONOMIC DISFUNCTION: ROLE OF HYPERVENTILATION AND INTEROCEPTION

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INTRODUCTION: It is known that chronic pain represents a stress condition. Some publications postulate the causal links between interoception and emotion experience (S.Wiens, 2005, M.P.Paulus, M.B.Paulus, 2010, and others). Recently, new concepts were developed regarding pain as a homeostatic emotion (Craig A.D., 2003) and autonomic interoceptive afferent pathways (Janig W., 2009). The aim of this study was to analyse the autonomic interoceptive sensations in patients with chronic migraine (CM).
METHODS: Three groups of female patients were studied: 1st group - patients with CM, (N=38, average age 37.3 years); 2nd group – patients with generalized anxiety disorders (GAD) without migraine (N=28, average age 35.2 years); 3rd group - healthy control subjects (N=27, average age 38.1 years). An original questionnaire (Moldovanu I., Vovc V., 2010) to determine the profile of autonomic interoceptive disorders (PAID) was used. PAID includes 8 scales with 102 items related to autonomic interoceptive disorders.
RESULTS: Most of PAID scales results were significantly different in patients with CM and GAD than in control subjects. PAID parameters had higher values in CM than in GAD patients, but significant differences were found only at breathlessness (14.5±0,5 vs. 10.5±0.4; $p<0.05$), cardiovascular dysfunction (29.1±0.3 vs. 23.3±1.9; $p<0.05$) and musculoskeletal pain (10.2±0.1 vs. 7.3±0.4; $p<0.05$) scales Overall, patients with CM have markedly increased breathlessness, cardiovascular dysfunction and musculoskeletal pain scales compared with patients with GAD, representing an interesting unexpected feature of interoceptive changes specific for CM. Additionally, PAID seems to be a sensitive tool for clinical study of interoceptive disorders in patients with CM.
RESEARCH SUPPORT: Academy of Sciences of the Republic of Moldova research grant.

THE EVOLUTIONARY PECULIARITIES OF THE NEUROPEPTIDES ANTISTRESS AND CEREBROPROTECTIVE EFFECTS

TN Sollertinskaja, MV Shorokhov, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, St. Petersburg, Russia

INTRODUCTION: The correction of disturbed brain functions, especially of cognitive disorders, influence an organism's perception of and interaction with stressor stimuli, representing one of the most critical problems of modern medicine. Currently, the ability to treat brain disturbances is largely affected by active peptides, such as Semax (Sem) and Selank (Sel). The experimental data on the Sem and Sel compensatory influence on the Higher Nervous Function disturbances in lower mammals are numerous; however, they are absent in primates. Furthermore, the antistressor influence of these peptides has not yet been studied, and the role of Sem and Sel in the hemispheric motor asymmetry has not been investigated. It is known that the morphology of limbic structures such as Hippocamus (Hipp) and Amygdala (AM) contain many different neuropeptides; however, the role of such structures in mediation of Sem and Sel

influence on neocortex has not been analyzed in detail. The present work is devoted to the study of Sem and Sel cerebroprotective and antistress influence on altered brain functions, functional asymmetry and Hipp and AM role in their possible neurochemical mechanism for the ascending row of the mammals.
RESULTS: The experiments were carried out under the conditions of free behavior and primatological chair (monkeys), using multiparametric computer registration and analysis of EEG, vegetative and motor indices of Higher Nervous Activity. Sem and Sel drugs were operated intranasally or intramusculary (0.5-5 mkg/kg and 30-100 mkg/kg, respectively). It has been found that the compensatory role of Sem and Sel in hedgehogs with neurosis is wholly uniform and more expressed at the inherent forms of behavior and vegetative background. It has also been shown in hedgehogs that Sem and Sel cause motor functional asymmetry within 5 days after their administration. The effects on the Sel background are more significant. Additionally, cerebroprotective effects of Sem and Sel on the disturbed brain functions after Hipp (field CA1) destruction has been established. In rodents, contrary to insectivores, there is a distinct tendency of differentiation of Sem and Sel compensatory effects on the brain function disturbances. Furthermore, it has also been shown that, in rats, Sem and Sel differentially affect motor functional asymmetry regulation. Interestingly, CA1 Hipp and AM destruction cause Sel to exert the compensatory effects on the abnormal brain functions, and following Hipp destruction, cerebroprotective effects of Sel on the functional motor asymmetry is more significant. In neurotic non-human primates, it has also been shown that the anti-amnestic and cerebroprotective effects of Sem and Sel are different and manifest differently across various types of neurosis. Importantly, Sel compensatory effects are especially significant and prolonged. In the present study, we have shown that the preliminary intranasal administration of Sel (30 mg/kg) doses led to increases in organism stability in response to highly stressful stimuli across the selected parameters of Higher Nervous Activity. We also investigated the antiepileptic Sel activity in neurotized monkeys, and demonstrate that its low doses led to ablation of pathological forms of the focus activity (the peak-waves complex) in the frontal cortex and the normalization of the frequency-amplitude spectrum of EEG. Our data provide a neurophysiological underpinning for the differential application of Sem and Sel in psychiatric treatment of neuroses.

Day 3. May 18, 2011
Morning session

9.15-10.45 Special Presentations

METRIS BV, NETHERLANDS: HIGH-QUALITY SIMULTANEOUS MEASUREMENTS OF RODENT BEHAVIOR & PHYSIOLOGY PARAMETERS

R Bulthuis, L Bachdasarian, E Molewijk, M Boscaro, E Rieux, Metris B.V., Hoofddorp, Netherlands; Data Sciences Internationa, Minneapolis, MN, USA

Metris B.V. offers and supports highly advanced non-invasive laboratory equipment for *in vivo* research with freely moving rodents. The systems are highly modular, complementary and ready to be coupled to other systems. A recent development is the integration of LABORAS with the Data Sciences (DSI) Telemetry system which measures wirelessly a number of physiological parameters. Validation of the integrated solutions shows an improvement of the quality of research while decreasing time, money and number of experiments and animals.
LABORAS: *Automated Behavioral Scoring and Tracking.* LABORAS is an efficient and validated noninvasive technology, based on force measurement and pattern recognition techniques. The triangular shaped sensor platform records all movements evoked by the animal. Each behavior has its own unique signature of vibration/force characteristics, which can be detected by the LABORAS software to identify a behavior. The system is currently the only validated equipment on the market that is able to determine a large number of different behaviors without a human observer. LABORAS can detect a wide range of different behaviors such as climbing, drinking, eating, grooming, immobility, locomotion and rearing. In addition it provides tracking parameters – position, speed, maximum speed, average speed, travelled distance and position distribution. Metris continuously offers new validated behavior detection software to detect both normal and drug induced behaviors such as hind-limb licking detection, scratching behavior and circling behavior. The unique functionality enables the researcher to perform behavioral research faster, more consistently and more efficiently than possible with human observation or other technologies.

LABORAS Advantages

For Management	*For Researchers*
• Increases efficiency of research. • 'One stop shop' for rodent tracking and automated behavior identification. • Reduces experimental lead time, animals and costs. • GLP-compliance (21CFR/Part 11). • Speeds up experimental throughput. • Combines quality and efficiency. • Efficient use of equipment. • Replaces several dedicated systems. • Flexible update and extension options.	• Objectivity and standardization of data collection. • Reduces inter- and intra-observer bias. • Easy to use and matches specific research needs (as it was designed for and with the help of researchers). • Measurement in total darkness possible (no video cameras or light required). • Limited amount of data (raw data can be kept, no large video data files). • Home cage type environment. • Standard data output (time-tagged files).

- Exportable Result summaries

LABORAS data is reliable and free of inter- and intra-observer bias or anticipated scoring, thereby providing a standard behavioral measurement worldwide. LABORAS enables the researcher to carry out more behavioral experiments in a shorter time with fewer animals and less equipment, while obtaining higher quality data. The LABORAS system can be a valuable tool to standardize behavioral measurements, particularly for disciplines falling under good laboratory practice (GLP) regulations.

DATA SCIENCES TELEMETRY: wireless measurement of physiological parameters in animals. Data Sciences International (DSI) provides complete systems for monitoring and collecting data from conscious, freely moving laboratory animals. No wires or tethers are needed, resulting in higher quality research data. The DSI telemetry system facilitates the monitoring of animals while they move freely within their cages. A miniature transmitter implanted in each animal measures one or more parameters (e.g. blood pressure, temperature heart rate, ECG, EEG, etc.) and transmits the data via radio frequency signals to a nearby receiver. Animals are implanted with a transmitter (shipped sterile and ready for implantation) that sends data to the acquisition system. DSI transmitters and receivers are available in a variety of models, allowing optimal performance for various animal models (from mice to large animals as dogs and primates) and cage types. DSI also provides external telemetry, for the monitoring of ECG, Temperature, Respiration, Blood Pressure and Activity in large animals in group-housing conditions.

DSI Telemetry Advantages

For Management	***For Researchers***
• Increases efficiency of research. • Telemetry is among the most humane means of monitoring animals. • Speeds up experimental throughput. • Combines quality and efficiency. • Reduces experimental lead time, animals and costs. • GLP-compliance (21CFR/Part 11).	• Animal Handling is minimized • Stress-induced artifact is significantly reduced • Measurements are free from the effects of anesthesia • Allows animals to be chronically instrumented and used sequentially as their own control or in several studies. • Exit site infections are eliminated • Data obtained by telemetry contain no cables or commutator artifact such as in thether systems • Monitor blood pressure, ECG, EEG, temperature and more

INTEGRATION OF LABORAS AND DSI TELEMETRY (BEHAVIOR AND PHYSIOLOGY). Metris co-operates with several alliance partners to work towards a ‘total solution’ in automated behavior analysis, which will help to gain most out of a single experiment. Therefore high priority is given to development of integrated methods. The integration of LABORAS and the DSI Telemetry system enables the researcher to obtain the accurate behavior analysis provided by LABORAS in combination with precise ECG, EEG, EMG, temperature and blood pressure data of the Data Sciences telemetry implants, all in one experiment. The parallel data acquisition greatly enhances the efficiency and quality of animal experiments. It also reduces the number of experiments and it saves animals, time and money and makes efficient use of equipment

compared with serial testing. It eliminates external variation and thereby enhances the power of experiments. It helps to establish causal relationships in datasets by direct time-matched coupling of several parameters – from different biological systems– in one single animal. This leads to a better interpretation of biological processes than using separate data.

Integrated LABORAS + DSI Telemetry Advantages

For Management	***For Researchers***
• Increases efficiency of research; – increases the information from a single animal; – reduces the number of separate or serial experiments; – increases overall research capacity (throughput); – Saves animals, time and money. • Efficient use of equipment; – replaces several dedicated systems; – flexible extension options; – software of both systems runs on one PC at the same time; and – no hardware changes to existing systems. • Next step towards integration with more systems.	• Better understanding of biological processes; – establishing causal relationships (between behavior and physiology). • New insights in area of phenotyping transgenic animals; – measures more independent parameters; – measures various biological systems simultaneously such as Cardiovascular (CV) and Central Nervous System (CNS) • Increased quality of data by simultaneous testing; – parameters like activity (DSI) and locomotion (LABORAS) can be used to check data quality by cross checking the data of both systems.

FUTURE OF IN-VIVO RESEARCH. Ultimately in-vivo research will move to simultaneous multi-modal measurements enabling high throughput screens for animal behavior, position tracking, physiology, sleep stages and vocalizations in a single experiment. For literature references, please refer to: www.metris.nl/en/products/laboras/laboras_publications ■

STRESS HORMONES IN THE POSTMORTEM BRAIN OF TEENAGE SUICIDE VICTIMS

GN Pandey, X Ren, HS Rizavi, Y Dwivedi, Department of Psychiatry, University of Illinois at Chicago, Chicago, IL, USA

INTRODUCTION: Suicide is a major public health concern, as there are more than 30,000 annual suicides in the United States alone. In teenagers, it is the second most leading cause of death. Stress and depression are the major risk factors for suicide, and there is as strong association between the hypothalamus-pituitary adrenal (HPA) axis dysfunction and suicide. The levels of corticotropin releasing factor (CRF), a stress hormone involved in the HPA-axis, is regulated by the levels of glucocorticoid receptors as well as its binding to a protein known as CRF binding protein (CRF-BP). Therefore, we have examined the role of CRF in teenage suicide.

METHODS: We determined the protein and mRNA expression of CRF, CRF-BP and the CRF receptor (CRF-R1) in the prefrontal cortex (Brodmann area 9), the hippocampus and the amygdala obtained from 18 suicide victims and 18 control subjects (13-19 years of age). The postmortem brain samples were obtained from the Maryland Psychiatric Research Center (Baltimore, MD). Subjects were diagnosed using DSM-IV criteria by interviewing the family members or friends. Protein expression was determined using Western blot, and gene expression (mRNA) was determined using quantitative RT-PCR (qPCR).

RESULTS: Protein expression of CRF was significantly higher in the prefrontal cortex and amygdala of teenage suicide victims, while CRF-BP and CRF-R1 expression was significantly lower in the prefrontal cortex and amygdala compared with age-matched control subjects. The mRNA expression of CRF was markedly increased, and the mRNA of CRF-BP and CRF-R1 was significantly decreased, in the prefrontal cortex and the amygdala (but not hippocampus) of suicide victims compared with normal control subjects. These results suggest that teenage suicide may be related to increased protein and gene expression of CRF and decreased levels of CRF-BP and CRF-R1, and further that CRF dysregulation may be related to suicidal behavior of teenagers.

RESEARCH SUPPORT: Supported by NIMH grant RO1 MH048153.

10.45-13.00 Symposium III: Cognitive Mechanisms
Chairs: YuF Pastuhov, IV Ekimova (Russia)

CELLULAR PRION PROTEIN PLAYS A ROLE IN PAIN AND DEPRESSION THROUGH A NMDA RECEPTOR-DEPENDENT MECHANISM

VM Gadotti, GW Zamponi, Department of Physiology and Pharmacology, Hotchkiss Brain Institute, University of Calgary, Calgary, Canada

INTRODUCTION: Glutamate is the excitatory neurotransmitter controlling synaptic excitability and plasticity in most brain circuits and in the spinal cord, including areas involved in depression and pain transmission. Our laboratory recently showed that cellular prion protein (PrPc) mediates neuroprotection in the hippocampus through inhibition of NR2D subunits of the NMDA subtype of glutamate receptors. The NMDA receptor plays an important role in pain transmission and its increased activity in the hippocampus is associated with depression. Thus, we investigated the possible role of PrPc in two models of predictive depression [the forced swimming test (FST) and tail suspension test (TST)] and in two models of acute nociception (formalin test and NMDA test).
METHODS: Ten week old male C57/BL6 PrP-/- and PrP+/+ mice were used (30-35 g). In the FST, mice were individually forced to swim in an open cylindrical container filled with water at 23-25°C, and duration of immobility was scored over 6 minutes. The TST was carried out with mice that were acoustically and visually isolated, suspended 50 cm above the floor, and immobility onset and duration were recorded for 6 min. For the formalin test, animals received 20 µl of formalin solution (0.7 or 1.25%, prepared in PBS) injected intraplantarly in the ventral surface of the right hindpaw. Animals were individually observed from 0-5 min (neurogenic phase) and 15-30 min (inflammatory phase), and time spent licking or biting the injected paw was recorded with a chronometer and considered indicative of nociception. In the NMDA test a volume of 5 µl of NMDA (30 or 300 pmol/site, prepared in PBS) was injected intrathecally (i.t.) in the subarachnoid space between L5-L6 vertebras. Animals were observed individually for 5 min following NMDA injection. The amount of time spent licking or biting the tail, hindpaws and abdomen was recorded with a chronometer and considered indicative of nociception.
RESULTS: We observed that PrPC null mice exhibited a decreased nociceptive threshold when compared to the wild type mice in the formalin and NMDA tests. The decreased nociceptive threshold observed for PrPC null mice in the formalin test was blocked by the NMDA receptor antagonist MK-801 (3 nmol i.t.). In addition, PrPC null mice showed a depressant-like behaviour when compared to the wild type mice in both models of predictive depression used (e.g., FST, TST). This depressive-like effect observed for PrPC null mice was reversed in the TST by the treatment of mice with the tricyclic antidepressant imipramine (10 mg/kg i.p.) or the NMDA receptor antagonist MK-801 (0.01 mg/kg i.p.). Our finding is the first to demonstrate a role of PrPc in depression and nociceptive transmission.

RESEARCH SUPPORT: Alberta Heritage Foundation for Medical Research – AHFMR, Hotchkiss Brain Institute – HBI, Prionet Canada, Alberta Prion Research Institute – APRI, Canadian Institute of Health Research – CIHR.

INVESTIGATION OF NEUROPROTECTIVE RESERVES OF HSP70 IN THE SUBSTANTIA NIGRA IN THE MODEL OF A PRECLINICAL STAGE OF PARKINSON'S DISEASE

IV Ekimova, IV Guzhova, IV Romanova, YuF Pastukhov, Sechenov Institute of Evolutionary Physiology and Biochemistry, Institute of Cytology, St. Petersburg, Russia

INTRODUCTION: Parkinson's disease (*PD*) is a progressive neurodegenerative disorder which most commonly manifests between the fifth and seventh decade with bradykinesia, tremor and postural rigidity. At disease onset, a large proportion of dopaminergic (*DA*) neurons in the substantia nigra pars compacta (*SNpc*) have degenerated, resulting in a depletion of dopamine in the striatum. Increasing evidence indicates that deficits in mitochondrial function, oxidative stress, the accumulation of aberrant or misfolded proteins, and ubiquitin-proteasome system (*UPS*) dysfunction may represent the principal molecular pathways or events that commonly underlie the pathogenesis of *PD* [Moore et al., 2005]. It is important to note that proteasome dysfunction has been linked to early-onset *PD*. Heat Shock Proteins 70 kDa (*Hsp70*) provide a line of defense against misfolded or aggregated proteins, and are among the most potent suppressors of neurodegeneration in animal models. Progress in *PD* treatment is associated with elaboration of preclinical stage models of *PD* and determination of early non-motor symptoms and neuroprotective compensatory reserves of nigrostriatal system [Ugrumov, 2008 – 2010; Pastukhov et al., 2009, 2010].

RESULTS: Recently, on the basis of suppression of *UPS* by lactacystin (*LC*), a model of the preclinical stage of *PD* was developed in rats [Pastukhov et al., 2009, 2010]. It was shown that in response to the degeneration of less than 60% of neurons in the *SNpc*, an increase in the level of tyrosine hydroxylase and total time of rapid sleep occurs despite the absence of changes in motor behavior. The determination of neuroprotective reserves of chaperone Hsp70 in DA-ergic neurons of SNpc in the model of preclinical stage of PD was not conducted. Immunohistochemistry assays and confocal microscopy elicited that 77% *DA*-ergic neurons contain *Hsp70* in control rats. In addition, a small number of non-*DA*-ergic neurons containing *Hsp70* occurs in the optic slice of the SN. 14 days after a two-fold injection of *LC* into the *SNpc*, a number of *DA*-ergic neurons containing *Hsp70* decreased at the average of 15%; however, the level of immunoreactivity of *Hsp70* in survived neurons increases. Our data suggest that *Hsp70* may involve in the mechanism of protection of *DA*-ergic neurons in response to attenuation of *UPS* activity. There is good reason to think about the search for new drugs (e.g., chaperone inductors) increasing a content of *Hsp70* in the brain at the preclinical stage of *PD.*

RESEARCH SUPPORT: This study was supported by the RAS program "Fundamental sciences for medicine".

INFLUENCE OF NEONATAL TREATMENT WITH INTERLEUKINE-1B ON REACTIVITY OF THE DOPHAMINERGIC SYSTEMS OF BRAIN OF ADULT RATS AT LEARNING IN STRESS

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INTRODUCTION: One of the currently popular theories of pathogenesis of cognitive disorders (in particular, schizophrenia) is the so-called "Two-hit" hypothesis (Bayer et al., 1999). It is assumed that the first challenge is different types of perinatal pathology: infectious diseases and physiological trauma (i.e., the states, attended with the high production of pro-inflammatory cytokines, in particular, Interleukin-1β). By the second challenge, there are stressors experienced in pubertal or adult age. Early studies have shown that an increase of IL-1β levels in early postnatal ontogenesis results in delayed deficits in cognitive functions, showing up at learning of adults of animals in stressful terms (at conditioning with the use of negative reinforcement). The present research aimed to examine probable involvement of the dopaminergic systems of brain in the mechanisms of IL-1β-induced cognitive deficits. Introduction of IL-1β carried out during the first 3 wk of postnatal life (age-related analogue of ending of prenatal period for a man). For cognitive loading, we used conditioning of active avoidance: a conditional stimulus light was illuminated, and an unconditional reinforcement (electro-skin pain irritation) was performed in conjunction. Level of biogenic amines and their metabolites were estimated in tissues of striatum and frontal cortex by the method of high-efficiency liquid chromatography.
RESULTS: It has been shown that distinctions between experienced and control rats in maintenance of dopamine and its metabolites in frontal cortex, but not in striatum. Different learning mechanisms vary in their influence on metabolism of dopamine for the experienced and control rats: activity increases in control rats, whereas dopamine metabolism decreases in experienced rats. There were also no dysregulatiuons in the serotonergic and noradrenergic systems of frontal cortex and striatum. Our study confirms possible connection of increase in IL-1β levels in a perinatal period with the subsequent cognitive dysfunctions of learning with the use of negative reinforcement.
RESEARCH SUPPORT: Supported by RFBR Grant 08-04-01335.

THE ROLE OF OXIDATIVE STRESS IN PATHOGENESIS OF POSTTRAUMATIC STRESS DISORDER IN A CONTINGENT OF INTERNATIONAL OPERATIONS

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INTRODUCTION: The Contingent of the International Operations (CIO) – a subject of various extreme factors action, which can cause Posttraumatic Stress Disorder (PTSD). At the same time marked decrease in Antioxidant enzymes (AOE) can lead to uncompensated Oxidative stress (OS) because of the accumulation of the excess of the

reactive oxygen species. Neuronal membrane phospholipids are especially vulnerable to damage, and injury leads to receptor-mediated signal transduction and, furthermore, information processing disorders. Indeed, there are difficulties in rating and interpreting data, due to inhomogeneous factors, including gender, race, age, nutritional, deployment factor (e.g., reservists or regular personnel), and different stressful military experiences in various Peace Support Missions (PSM). Our research aim was to assess PTSD and OS levels, and analyze their correlation in CIO.
METHODS: A total of 143 participants were assessed in this study: Latvian CIO, regular personnel, male Europeans, average age of 27.4, before and after the same PSM in Afghanistan were examined. The Latvian language “military” version of the PCL-M questionnaires were used for PTSD evaluation. Activity of AOE – Glutathione peroxidase (GPx) and intensity of lipid peroxidation – Malondialdehyde (MDA) as OS indicators in blood were determined. Data were processed using SPSS 15.0.
RESULTS: Before PSM, response rate (RR) 97.9% of study participants corresponded to PTSD diagnosis necessary criterions, with constituent 1.4%, GPx level decreased in 33.0%, and MDA level increased in 75.5% of samples. After PSM: RR 93.8%, PTSD 6.7%, GPx level decreased in 51.7%, MDA level increased in 80.0%. There was correlation between increase of OS and PTSD levels in CIO, further study required.
RESEARCH SUPPORT: Supported by the European Social Foundation co-financing: Project for Doctorants support in Riga Stradins Univercity. The views expressed in this abstract do not reflect the official policy or position of the Latvian National Armed Forces, the Latvian government, or any of the institutions with which the authors are affiliated.

EXAMINATION OF THE TOXIC RAT MODELS OF PARKINSON'S DISEASE
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INTRODUCTION: Parkinson's disease (PD) is a chronic pathology characterized by degeneration of dopaminergic neurons of the nigrostriatal system. Absence of valid animal models causes complication of diagnostic and treatment of this disease. Nowadays, there are two types of experimental animal models of Parkinson's disease: genetic and toxic. There are two variants of toxic models. One of them is inducible by injection of a toxin into the substantia nigra or nigrostriatal pathway of rat’s brain and the other one is based on i.p. treatment with a toxin. Mostly, Parkinson's disease is caused by toxins. Therefore, toxic models of this disease are preferable. Two toxic impacts in rats cause symptoms of Parkinson's disease: single injection of 6-OHDA and protracted administration of rotenone. Unlike 6-OHDA effect of rotenone on dopaminergic neurons accompanied by intracellular accumulation of protein, that is immunoreactive for ubiquitin and alpha-synuclein. Valid model is considered to demonstrate basic symptoms of Parkinson's disease; which are hypokinesia, tremor, and postural disorders.This study was aimed to a comparative evaluation of effectiveness of modeling of the basic symptoms of Parkinson's disease in 6-OHDA and rotenone models at different stages after injection of neurotoxins.
METHODS**:** The study was carried out in male Wistar rats. 5 µl of 6-OHDA hydrobromide (Tocris Bioscience, UK) was injected into nigrostriatal pathway in accordance to the

stereotaxic coordinates: AP – 5,5 mm posterior to bregma, L – 2,0 mm lateral to the midline, V – 8,0 mm below the surface. Before this, 120 rats (270-290 g) were treated with 15 mg/kg Anafranil for nerve ending protection. 20 rats of the control group were injected with physiological saline solution. The rotenone model was replicated in rats weighing 300-490 grams. They were daily administrated intraperitonial with rotenone for 35 days (2.75 mg/kg). Rotenone was dissolved in the mixture of DMSO:5mygliol (2:98). The control group of 10 rats was administrated with saline solution or vehicle. Neurological impairment and weight were assessed daily observing muscle tone, posture, motor activity, postural stability, salivation, width of palpebral fissures, and tremor. At 0, 7, 14, 21, 28, 35 days after neurotoxin administration behavior of rats was assessed with set of tests such as open field test, adjusting steps test, foot print test, beam-walking test, and rail-walking test. After behavioral tests morphological study was carried out. Selective detection of substantia nigra neurons was performed using monoclonal antibodies to tyrosine hydroxylase at the serial brain sections.
RESULTS: The basic symptoms of parkinsonism such as muscle rigidity, hypokinesia and postural disorders were observed 72 h after 6-OHDA administration and gradually became marked 7 days after rotenone administration. Most marked symptoms were observed 2 hours after a neurotoxin injection. Both models showed marked postural impairment, instability of posture, and muscle rigidity. But hypokinesia was more marked (sometimes even catalepsy by Morpurgo) in the rotenone model. One of the behavioral manifestations of one-side impairment of the nigrostriatal pathways with 6-OHDA was rotation (frequently spontaneous). Some rats had tremor in 6-OHDA model but not in the rotenone one. Salivation was a typical symptom of the rotenone model but not the 6-OHDA one. Both neurotoxins caused decrease of horizontal and vertical activity in the open field test. In the rail-walking test 6-OHDA administration caused more marked impairment than rotenone one. Most of rats were not be able to move on rails, and number of downfalls increased. In addition to that in rotenone model was also postural impairment, speed of rail walking decrease, but amount of downfalls and episodes of freezing was less than in the case of 6-OHDA administration. In the beam walking test was reduction of distance that rat was able to overcome without any mistakes. And this reduction associated with intensity of locomotor dysfunctions. 6-OHDA injection into substantia nigra caused ipsilateral neuron death in the same region of the brain. Immunohistochemical staining of tyrosine hydroxylase was not overt at the ipsilateral side unlike the contralateral one. The rotenone treatment also caused decrease in the number of neurons, and some animals had more loss of DA-neurons at the right side. Thus, 6-OHDA model of PD is effective in symptoms modeling of hypokinesia, postural disorders and postural instability. But this is a model of hemiparkinsonism and as such, is not entirely valid because Parkinson's disease is characterized by bilateral though asymmetrical symptoms. The advantage of the rotenone model is a gradual progression of symptoms of Parkinson's disease, which makes it possible to investigate the mechanisms of neurodegeneration DA-neurons in order to find early markers of neuropathological process and identify effective neuroprotectors.
RESEARCH SUPPORT: Supported by pharmaceutical company “Vertex Ltd”.

ENZYMES METABOLISING AMYLOID-BETA PEPTIDE AFFECT COGNITIVE FUNCTIONS IN RAT AFTER PRENATAL STRESS

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INTRODUCTION: In adult males Wistar rats (3-4 months) subjected to prenatal hypoxia (7% O2, 3 h, E14), a disruption of memory was observed. Prenatal hypoxia also led to a decrease in the brain cortex of the levels of expression and activity of metallopeptidases neprilysin (NEP) and endothelin-converting enzyme (ECE-1), which metabolize some neuropeptides and are the primary beta–amyloid degrading enzymes. To find a link between the impairment in rat behavior and changes in the activity of investigated metallopeptidases, we analyzed the effects of injections of the compounds capable of changing NEP and ECE-1 expression and activity on memory in rats.
METHODS: In rats, we tested working memory in a two-level radial maze, and short-term and long-term memory in an “Object recognition” test after i.c. infusion of NEP and ECE-1 inhibitor phosphoramidon (2x10-3 M, by means osmotic minipumps 0.25 ul per hour during 28 days) or after i.p. (200 mg/kg, during 24 days, daily) injections of sodium valproate, which increases NEP expression in neuronal cell culture models.
RESULTS: We observed disruption of various kinds of memory after decreasing NEP activity in rat cortex. In contrast, increasing NEP activity led to an improvement of learning and memory in the radial maze and “Object recognition” test in rats subjected to prenatal hypoxia. Additionally, there was correlation between NEP activity and neuronal plasticity (number of labile spines) in rat cerebral cortex and hippocampus. Our data suggests that a decrease in the level of expression and activity of beta–amyloid-degrading metallopeptidases might be one of the reasons of cognitive dysfunction after prenatal hypoxia.
RESEARCH SUPPORT: Supported by RAS “Fundamental Sciences to Medicine”, RFBR N 10-04-01156.

SOCIAL STRESS IN ZEBRAFISH: THE ROLE OF COGNITIVE APPRAISAL ON SOCIALLY DRIVEN CHANGES IN BRAIN TRANSCRIPTOME

RF Oliveira, JM Simões, AC Oliveira, ISPA-IU, Lisboa, Portugal

INTRODUCTION: Unlike physical stressors that can be conveyed directly by sensory experiences, social stressors do not represent physical features of the world and therefore need to be evaluated through an appraisal mechanism. Thus, the response to a social stressor is expected to involve a cognitive evaluation of the stimuli that assesses its valence and salience to that organism at that moment in time. In this study we investigated the role of cognitive appraisal on the activation of a genomic response to a social stressor (staged agonistic interaction) in zebrafish.
METHODS: After a period of social isolation, male zebrafish were subjected to one of three treatments for 30 min: (a) fight with an opponent; (b) fight with its mirror image; (c) remain in social isolation (control group). In the opponent fight condition, winner and loser subjects were established by behavioral analysis. It is expected that if no cognitive

appraisal is involved in the activation of a brain response to social stress, both opponent and mirror fighters that engage in aggressive behavior should express similar genomic responses. In contrast, if appraisal of the outcome of the conflict is performed, then a response is only expected in opponent fighters, as mirror fighters do not experience winning or losing despite expressing aggressive behavior. The neurogenomic response was measured for whole-brain samples using a commercially available (Affymetrix) zebrafish genome microarray.
RESULTS: Cluster analysis of changes in gene expression at the transcriptome level correctly grouped all individuals according to social experience (i.e. opponent winners or losers, mirror fighters and controls). An analysis of differentially expressed genes using the control group as reference (with a FDR of 10%) identified a set of genes altered in males fighting an opponent (23 in winners, 133 in losers, 64 of which were shared by both cohorts), but no effect was detected in mirror fighters. Microarray analysis confirmed a sub-set of differentially expressed genes using qRT-PCR. These results suggest that it is not the objective structure of the event that triggers a genomic response to a social stressor, but rather that the appraisal of the putative stressor evokes the physiological response. For males fighting an opponent, losing had a higher impact on gene expression than winning, suggesting that it has a higher salience to the subject, and a stronger impact in biological processes.
RESEARCH SUPPORT: Funded by Fundação para a Ciência e a Tecnologia (FCT, Portugal) research grant PTDC/PSI/71811/06.

FEATURES OF PERCEPTION AND INFORMATION PROCESSING IN ANXIETY DISORDERS

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INTRODUCTION: The state of excessive anxiety is accompanied by a change in perception and information processing. High anxiety contributes to disruption of attention and memory. Clinically, disruptions of attention manifest themselves in disturbance of concentration, attention stability, rapid exhaustion, and deficits in switching attention. The aim of the study was to explore the features of perception and information processing in anxiety disorders.
METHODS: The study included 101 subjects with anxiety disorders (panic disorder (PD) – N=63; phobic disorder (PhD) – N=22; obsessive-compulsive disorder (OCD) – N=14). The experimental-psychological computer technique for determining the perceptual and information processing (modification of Korostelev) is based on subjects reading flashing words off the computer screen. The exposure time of the first word lasted 30 ms, the exposure time of further words increased by 3 ms. All words were divided into three groups: "behavior", "emotional", and "cognitive" dictionaries. We recorded the time threshold of awareness, the total number of recognition errors, the number of unrecognized and incorrectly recognized words for each dictionary.
RESULTS: In the general anxiety disorders group, we observed an increase in word recognition time and the number of unrecognized words, as well as a decrease in incorrectly recognized words. Likewise, the subjects with PD presented errors in

emotional and behavioral dictionaries, subjects with PhD exhibited errors in the emotional dictionary, and subjects with OCD performed poorly in behavioral and cognitive dictionaries. The increase in word recognition time occurs due to an “affective load” of right brain. The lack of a right-brain perception is formed, which provides the integral recognition of words, and the left brain compensates by providing the letter by letter recognition of words. This explains the recognition errors in general. In addition, recognition errors of words from the defined dictionaries correlate with deficits of the relevant semantic field: for patients with PD – in emotional and behavioral, for patients with PhD – in the emotional, for patients with OCD – in behavioral and cognitive semantic fields.

Day 3, Afternoon session

14.00-14.45 Presentation: NEW APPROACHES TO BEHAVIORAL ANALYSES
Y Liang, CleverSys, Inc., Reston, VA, USA

15.00-17.00 Workshop: DYNAMICAL SYSTEMS THERAPY: CAN WORDS CHANGE BRAINS?
Y Shapiro, University of Alberta, Edmonton, Alberta, Canada

INTRODUCTION: A dynamical systems approach to neural network functioning offers the most comprehensive foundation for psychotherapy currently available. Recurrent patterns of thinking, feeling, and relating can be analyzed by modeling cortical and sub-cortical network processes. Our current understanding of neural network dynamics also provides empirical constraints in validating various psychotherapeutic perspectives and their integration with biological intervention. We are finally in the position to resolve such age-old questions as the nature-nurture debate, the primacy of affect vs. cognition, and the role of implicit vs. explicit processes in self-awareness and action planning.
METHODS: The concepts of dynamical systems theory, such as E-landscape, attractor states, and bifurcations will be reviewed and related to normal psychological functioning, individual development, and psychopathology. Selected neuroimaging studies will be reviewed. The postulates of the DST framework will be used as a bridge to unify relational psychodynamic and psychobiological perspectives.
RESULTS: Dynamical Systems Therapy (DST) stands as a trans-theoretical model with the explanatory power to integrate systems of synaptic networks with systems of meaning. It strongly argues for shifting the emphasis from maladaptive patterns as the problem to be fixed – to seeing these patterns as the patient's imperfect solutions to their inner and relational conflicts. We begin to see patients as active agents that create their own subjective meaning and interpersonal reality based on their specific developmental templates. The targeted therapeutic relationship defined as the intersection of two complex dynamical systems becomes our tool in reshaping the topology of the patient's neural network landscape and reestablishing self-organizing process.
RESEARCH SUPPORT: University of Alberta, Edmonton, Alberta, Canada. Original version was presented as a course at the LIX Annual Canadian Psychiatric Association Meeting, St. John's, NF, 2009.

17.00-18.30 POSTER SESSION

STRESS, FEAR, ANXIETY, DEPRESSION: USE OF NICOTINE AS AUGMENTATION AGENT IN DEPRESSION AND ANXIETY

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INTRODUCTION**:** Growing evidence support the notion that nicotine, besides the negative connotation of the last decade, has been used for many centuries for its therapeutic qualities by many nations and cultures worldwide. Acetylcholine nicotinic systems and serotonergic systems are known to interact. In this review we are trying to explore the possibilities of nicotine use as a therapeutic agent in depression and anxiety.
METHODS: Thorough research was performed using main literature databases, and web search engines such as Goggle, for relevant studies, by using appropriate keywords. We scrutinize them independently, before reaching consensus about their appropriateness.
RESULTS: In non-smokers, drug naïve patients diadermal administration of 17.5 mg nicotine for 4 days reduced depressive symptoms; 3.5 mg nicotine TTS for 8 days reduced depressive symptoms in another study. However, other studies reported the reversal of these positive results after cessation of nicotine. Chronic nicotine or cigarette use results in decreased monoamine oxidase A and B activity and a substantial reduction in alpha -sub-4beta -sub-2 nicotinic acetylcholine receptor (nAChR) availability in thalamus and putamen. The desensitization of DRN 5-HT neurons after chronic single daily injections of 1 mg/kg of nicotine suggests an antidepressant-like effect of chronic nicotine. Nicotine has complex interactions with other neurotransmitters in the brain. Investigations into the neurobiology, and biophysical and pharmacological properties of nicotinic acetylcholine receptors (nAChRs), have led to an improved understanding of their role in a variety of neuropsychiatric disorders for the treatment of depressive and anxiety symptoms not only to smokers after abstinence, but also to non-smokers.

THE TRANSGENERATIONAL AND DEVELOPMENT STRESS EFFECTS ON THE FAMILY AND THE ADOLESCENT

MS Trandafir, University of Medicine "Carol Davila", Bucharest, Romania

INTRODUCTION: No life-cycle stage reflects the chaos in ourselves, family, society and culture better than adolescence. Life events in this developmental period act like stress factors that generate anxiety and depression, as well as changes in family functionality and in adolescent behavior.
Study case: Ana, 17 years old, elicits strange aberrant behavior: is sad, does not sleep, dreams that she will die in December, and sees blood coming from her cut veins. Her foster family that has raised her since the age of 10 offered her affection, decent life conditions, and the possibility to study. She learns well, is obedient and exhibits model behavior. At the age of 17, she started to have crises of lost of conscience, diagnosed by

the pediatric psychiatrist as conversive disturbance. At the horizontal stress factors from the biological family (Carter 1978) – the death of her mother, her alcoholic father, the uncertain situation of her sisters and their handicap, the existential difficulties of her older brothers, and stress factors from her foster family are added – the family will receive a new member. Over these stress factors comes the general fear generated by the stress of living in a certain time and place – orphanages can only sustain adolescents until they are 17. The goodbye letter her parents found is generated by the intensity of the horizontal stress which acts upon Ana and her foster family, and by the intersection with vertical stress (the separation from her biological family and the violence present in her youth) transmitted by emotional triangles (Bowen 1978).
METHODS: Family psychotherapy-strategic techniques (rehabilitation of the hierarchy, the direct and paradoxical intervention), activating the adolescent reference systems and eclectic techniques (systemic and narrative).
RESULTS: The problems of adolescents are complex and related to the characteristics of this life period (winning independence, the involvement in systems: the family, the adults' system, and the system of peers). The horizontal stress that appears in the family system during transitional periods of the life cycle creates interruptions by symptomatology and dysfunctionality. Additionally, the vertical current of the stress which acts upon the family is generated by the relationship patterns which are transmitted by the emotional triangles during the family generations. Finally, a multidisciplinary approach is imposed, involving a psychiatrist, a psychotherapist, a social worker, a school psychologist, teachers, colleagues and religious authorities.

IMMUNOHISTOCHEMICAL INVESTIGATION OF CART-PEPTIDE IN STRIATO-NIGRAL PROJECTIONS AT DOPAMINE LOSS

IV Romanova, AY Chesnokova, AL Mikhrina, Russia

INTRODUCTION: Recently it has been shown that CART (cocaine-amphetamine regulated transcript) peptide is involved in different dopamine (DA) areas of the brain. From the CARTergic nucleus accumbens (nAcc) neurons, the primary innervation project to substantia nigra compacta (SNc) DA neurons. In earlier studies, immunochistochemically activating the effect of CART-peptide on DA neurons in SNc has been shown in vitro (100 nM). The positive correlation of CART and tyrosine hydroxylase (TH) immunoreactivity (an enzyme of DA synthesis) in SNc was also shown. The available data support the notion that the physiological role of CART is as a modulator of functional activity of DAergic brain neurons (Romanova, 2007, 2009). Recently, an experimental model of Parkinson's Disease has been developed in Wistar rats via lactacystin (LC) injections in SNc (Pastukhov et al., 2010). Thus, the reduction of 30-35% of TH-immunopositive neurons in SNc was shown through immunohistochemistry, but did not reveal a reduction of optical density in TH in the SNc, and in their processes in the dorsal striatum. The purpose of the present research was to examine the influence of DA reduction on CART-system in nAcc and SNc.
METHODS: The experiments were carried out on male Wistar rats. 0,4 µg LC, or a phosphate buffer, were injected two times at a one week interval, using a conducting cannulae bilaterally inserted into the SNpc (AP= -5 mm, L=2.0 mm, V=8,5 mm).

Following the second injection, rats have been subjected to transcardial perfusion by 4 % paraformaldehyde on 0,1 M phosphatic buffer. After cryoprotection in 30 % sucrose, brains were frozen at -42℃ and stored at -80℃. Free-floating coronal brain sections (20 µm) from nAc and SNc areas were analyzed through polyclonal rabbit anti-CART-55-102 antibodies (Phoenix Pharm. Icorp., CA, USA), diluted 1: 5000, goat anti-rabbit biotinilated secondary antibodies (Vector Lab, CA, USA), diluted 1:200 and streptovidin-peroxidase method. Computer imaging analysis was performed, and optical density CART-immunoreactivity in nAcc neurons and processes is SNc was measured.
RESULTS: Our data indicate a substantial increase of CART optical density in neurons of nAcc (68 %, $p < 0,05$), and their processes in SNc (60 %, $p < 0,05$). Furthermore, our data show that the activating influence of a CART-peptide on functional activity of the remained 65-70% DA brain neurons and participation of CART in compensatory mechanisms of brain at DA deficiency.

SENSORIMOTOR INTEGRATION AT FEMALES WITH DIFFERENT JUVENILE DEGREE

KI Pavlov, VG Kamenskaya, Herzen State Pedagogical University, St. Petersburg, Russia.

INTRODUCTION: Juvenility is a main characteristic of constitution, with the tendency of evolutionary development. Juvenile development is expressed in increases of cerebral cranium while subsequent decreases of visceral cranium occur. It is known, that high-juvenile individuals have a low level of aggression, authoritativeness, seldom are leaders in groups, and their nonverbal intelligence and creativity is higher, compared to that of their peers. The aim of our research is to study the psychophysiological characteristics of sensorimotor integration of female students (18-23 years old) with different juvenile degrees.
METHODS: The experimental group consisted of 37 students (females) of faculty of psychology and were divided into 2 groups (gr): low-juveniles students and high-juveniles students. The juvenile degree was measured on sagittal circles of a head. The features of sensor-motor integration were studied using computer RT-method- «The research of physiological characteristics of reactions of the being tested on streams of stimulus of the controllable order of time» by Kamenskaya and Uritski. Visual (circles of red, green and dark blue colors) and acoustic (beeps) stimuli were organized in series with fractal interstimulus order, which were shown on the screen of PC monitor. Females being tested should press the button after each signal, except for circles of red color.
RESULTS: The reaction time for acoustic stimulus is more significant in II gr., than in I gr. ($P < 0,01$), probably because high-juveniles have a low ability to distribution of attention between stimulus of a different modality and high ability to concentration on visual stimulus. There are following tendencies: Hearst's index (H) of I gr. is more than one of II gr. (this index shows the effectiveness of working in fractals stream of stimulus), quantity of reactions which coincide with stimulus is more in I gr., than in II gr.; low-juveniles made more false starts, than highjuveniles females. The number of missed stimuli and erroneous presses on red stimulus in both groups were unaltered. Adult females had significant differences of sensori-motor integration which depend on the

constitutional factor- juvenile degree, and expressed in the greater reaction time on acoustic stimulus of high-juveniles in comparison with low-juveniles females. The high-juveniles females seem to perform more effectively in fractals stream of visual stimuli (than low-juveniles) because the acoustic stimuli were obstructive for them.

LONG-TERM CAFFEINE AND ETHANOL INTAKE INCREASES ALCOHOL PREFERENCE IN RATS: GENDER ASPECTS

E Kucher, A Egorov, E Filatova, K Kulagina, Sechenov Institute of Evolutionary Physiology and Biochemistry; Department of Psychiatry and Addictions, Medical School, St. Petersburg State University, St. Petersburg, Russia

INTRODUCTION: The intake of energy drinks (drinks containing caffeine and alcohol) both in young men and women is rapidly growing, while the role of gender differences remains unclear. The goal of the study was the investigation of ethanol and caffeine influence on the alcohol preference formation and behavior in male and female rats under the conditions of long-term experiment.
METHODS: The study was conducted on 30 male and 30 female Wistar rats. Alcohol preference was measured using a standard two bottle test before the experiment and each subsequent month during the whole experiment after a 24 hours deprivation. Behavior parameters were estimated before, every month and at the end of the experiment using Open field test. Suok test was carried out after six months consumption.
RESULTS: We found that a chronic 6-month intake of caffeine, ethanol and their combination increased alcohol preference both in male and female rats. Alcohol preference was formed earlier in rats receiving a combination of caffeine with ethanol, and delayed in rats receiving ethanol only. In animals consumed caffeine, the strong alcohol preference did not form till the end of the experiment. Behavioral activity significantly increased in female consumed caffeine and caffeine with ethanol, compared to animals received ethanol and controls. Similar tendency was observed in male rats. The anxiety level was significantly higher in females rats in all experimental groups compared to controls, while males did not demonstrate increased anxiety.

ALCOHOL PREFERENCE IN RATS UNDER FORCED ALCOHOL INTAKE WITH CAFFEINE AND PHENAZEPAM

EV Filatova, KO Kulagina, EO Kutcher, AY Egorov, Sechenov Institute of Evolutionary Physiology and Biochemistry, St. Petersburg, Russia

INTRODUCTION: The role or anxiety in forming ethanol preference remains poorly understood. The aim of the study was the investigation of rat individual characteristics influence on alcohol preference forming under forced consumption of ethanol with caffeine and phenazepam.
METHODS: The investigation was carried out on 60 Wistar male rats divided into four groups: 1. consumed 10% ethanol; 2. consumed 10% ethanol with 0,4 g/l caffeine; 3. 10% ethanol with 0,5 mg/l phenazepam; 4. water controls. Behavioral parameters were measured using the Open field test. Forced alcoholization continued during four months.

Alcohol preference was estimated by Two-bottle test before and every three weeks of the experiment.
RESULTS: In the 1st group the two-bottle test data have shown that the alcohol preference dynamics is progressive with maximum in the end of 4th month. The dynamics in 2d and 3rd groups was similar to 1st in the beginning of the experiment, then the plato of alcohol preference has been observed in the middle with sharp increase in the end of the experiment. Alcohol preference in all experimental groups was significantly higher compared to controls. According to the two-bottle test data after four months consumption all rats were divided into two groups with higher (more then 50% alcohol) and lower (less then 50%) alcohol preference. The Open field test results have shown that among ethanol+caffeine rats alcohol preference has formed in rats with initially high locomotor activity. In contrast, among rats consumed ethanol+phenazepam alcohol preference has formed in rats with initially low locomotor activity and low anxiety level. Pharmacological modulation of anxiety level and its influence on alcohol preference are discussed.

GENETIC ASSOCIATION STUDY BETWEEN DOPAMINE D2 RECEPTOR POLYMORPHISMS AND TARDIVE DYSKINESIA

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INTRODUCTION: Tardive dyskinesia (TD) is an adverse effect of long-term or high-dose antipsychotic treatment. Dopaminergic activity in the nigrostriatal system have been proposed to be involved in development of TD, and dopamine D2 receptor (DRD2) has been regarded as a candidate gene for TD as antipsychotics have potent DRD2 antagonism. This study was aimed to find the relationship between DRD2 gene and antipsychotic-induced TD.
Methods: We evaluated whether five DRD2 single nucleotide polymorphisms (SNPs) (-141Cins>del/TaqID/NcoI/Ser311Cys/TaqIA) are associated with antipsychotic-induced TD in 263 Korean schizophrenia patients with (n=100) and without TD (n=163) who were matched for antipsychotic drug exposure and other relevant variables. Haplotype analyses were also performed.
RESULTS: None of the polymorphisms analyzed here were found to be significantly associated with TD or TD severity (as measured by AIMS: Abnormal Involuntary Movement Scale). Overall haplotype (-141Cins>del/TaqID/NcoI/Ser311Cys/TaqIA) frequency was also not significantly different between TD and non-TD groups, although one rare haplotype (I-D1-T-G-A1) showed significantly different frequency between TD and non-TD groups (2.7% vs. 8.5%, respectively, p=0.031). The present study does not support that DRD2 gene may be involved in TD pathogenesis in the Korean population, although further studies are warranted.

RELATIONSHIP BETWEEN PSYCHIATRIC DISORDERS AND ALOPECIA AREATA

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INTRODUCTION: Alopecia areata (AA) is heterogeneous disease characterized by nonsccaring hair loss. Recent studies suggest a higher prevalence of psychiatric sisorders in patients with AA. The aim of this study was to determine whether AA is statistically significantly associated with psychiatric diseases.
METHODS: We enrolled 60 patients with AA. The control group included 60 healthy adults recruited from the hospital staff and their relatives, who did not currently or previously have any psychiatric and dermatologic disorders. Sociodemographic, dermatologic and psychiatric variables were collected. The prevalence of psychiatric disorders was determined using diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IIIR).
RESULTS: Generalized anxiety disorder, depressive episodes and social phobia were all present in patients with AA at rates significantly higher than in the control group. There is a high psychiatric comorbidity in alopecia areata requiring systematic psychiatrc evaluation of these patients.

STRESS CHANGES ASSOCIATED WITH ALTERATION OF SMOKING STATUS

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INTRODUCTION: Though the hazardous effect of cigarette smoking is well known, many smokers don't quit smoking and many former-smokers relapse, making excuse with heavy psychological stress due to ordinary life affairs. Recent researches support that smoking itself induces stress; a higher rate with failure of smoking cessation is associated with inappropriate coping strategies for stressful events; and smoking cessation is associated with less perceived stress in ischemic heart disease patients. This research is aimed to evaluate perceived stress levels associated with changes of smoking status in the general population.
METHODS: A total of 8690 subjects who visited a health promotion center more than twice were enrolled with a self-administered questionnaire encoding general characteristics with smoking status and perceived stress scores (Brief Encounter Psychosocial Instrument, BEPSI). The first two questionnaire results were used to make groups with smoking status as Non-(and former-) smokers, Smokers, Re-smokers, Smoking quitters. The amount of stress score changes were evaluated with Analysis of Variance (ANOVA) and multiple regression methods with four groups.
RESULTS: At baseline, stress scores were higher in smokers (8.99 vs 8.40, $P<0.001$). The amount of stress score changes did not show statistical difference between four groups ($P=0.281$) with ANOVA (Non-smokers: -0.02±0.031, Smokers: -0.08±0.054, Re-smokers: -0.01±0.164, Smoking quitters: -0.23±0.115). When sex, age, drinking, regular exercise, marital status, income, education level, and existence of metabolic disease were included as covariates with multiple regression, no association was found between smoking status and perceived stress score changes ($\beta=-0.021$, $P=0.715$).

HIPPOCAMPAL VOLUME AND EARLY LIFE STRESS IN ADULTS WITH MAJOR DEPRESSIVE DISORDER

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INTRODUCTION: We aimed to assess the hippocampal volume in major depressive disorder (MDD) and its relationship with the experience of traumatic stressors during childhood.

METHODS: Forty-seven subjects with lifetime history of MDD (age 45.6±12.8; male/female=12/35) and 77 control subjects without any Axis-I psychiatric disorder (47.2± 12.0; male/female=28/49) participated in the current study. Axis-I psychiatric disorders, including MDD, were diagnosed by Structured Clinical Interview for DSM-IV (SCID-IV). Data on early life adverse events (before 18 years of age) were gathered using Early Adverse Event Scale (EAES). The volume of bilateral hippocampus was determined manually on T1 magnetic resonance image.

RESULTS: Subjects with MDD more commonly had the experience of early life adverse events on EAEA than control subjects (61.7% versus 31.2%, $p<0.001$). The volume of bilateral hippocampus of MDD subjects (Left: 3223.9±437.2; Right: 3080.9±441.7) were smaller compared to controls (Left: 3447.3±474.0; Right: 3273.0±426.4)(Left: $t=2.62$, $p<0.01$; Right: $t=2.40$, $p=0.02$). Furthermore, MDD subjects with early life adverse events (n=29) had smaller hippocampal volume (Left: 3119.3±358.3; Right: 2976.2±429.7) than subjects without early life adverse events (n=18) (Left: 3392.4±506.9; Right: 3249.7±418.2)(Left: $t=2.62$, $p=0.04$; Right: $t=2.40$, $p=0.04$). Among control subjects, early life adverse events did not significantly alter hippocampal volume. Our findings suggest that hippocampal volume reduction in MDD may be related to the experience of traumatic stressors during childhood.

RESEARCH SUPPORT: This work was supported by the National Research Foundation of Korea grant funded by the Korea government (MEST, 2010-0007738)

Day 4. May 19, 2011
Morning session

10.00-13.00 Symposium IV: Clinical Aspects of Biological Psychiatry
Chair: AV Kalueff (USA)

PECULIARITIES OF AXIAL MUSCLE TONUS AND BODY SCHEMA PERCEPTION IN PSYCHIATRIC PATIENTS

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INTRODUCTION: The goal of the present study was to investigate the influence of the proprioceptive input on the axial tonus and body schema perception in normal subjects and patients treated with antidepressants and neuroleptics.
METHODS: Fukuda stepping test for axial tonus asymmetry and the cognitive test for body schema mental perception were used to examine subjects. To modify the propriceptive input, all subjects were examined in three head positions: straight forward, turned to the left, and turned to the right.
RESULTS: For each group, the Pearson correlation matrix 3X48 was obtained (in 3 head positions: rotation angle in Fukuda test versus average reaction times to each of the 16 types of stimuli with different rotation amplitude in the cognitive task for body perception). The matrix showed that the asymmetry of axial muscle tonus relates differently to body schema perception within the three groups. There were no correlations in the control. In the group treated with neuroleptics, the correlations were strong and significant for the straight forward and the turned-right head positions. In the group treated with antidepressants, the only strong and significant correlation was found for the turned-left head position. All correlations found were negative, indicating that the more shift to the left in Fukuda test leads to slower body schema perception in the cognitive test, and vice versa. Our results confirm the literary data analyzing the changes in interhemispheric balance due to psychiatric pathology and neuropharmacological treatment. Relations found in the study between the axial tonus asymmetry and the reaction times of body schema perception task were unidirectional: the fewer left turn performed in Fukuda test related to faster reactions in the cognitive test. This data supports the notion that axial muscles tonus relates to hemispheric specialization, particularly to body schema perception function. As the head turn influences the Fukuda test more than the body schema perception test (correlation structure), we propose that the interhemispheric balance is modified more strongly due to axial tonus changes compared to changes in cognitive functions.

EMOTIONAL STRESS AS PROVOKING FACTOR IN CHILDHOOD PSORIASIS

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INTRODUCTION: Psoriasis is a common chronic disease in childhood of yet unclear etiology.
The first signs of psoriatic lesions occur from birth to 18 years of age, and both genetic and environmental factors interact to precipitate the development of psoriasis. Population studies indicate that besides streptococcal infection, emotional stress is important in the early onset or exacerbation of psoriasis in the pediatric age group. The aims of our study were to determine the incidence of emotional stress as the provoking factors in the onset of the disease and to correlate the clinical type of psoriasis with emotional stress.
METHODS: In this retrospective epidemiologic study, the data from 67 children (less than 16 years) with psoriasis treated at Dermatovenerology Clinic between 1991 and 2009 were included.
RESULTS: The 67 children accounted for 8.2 % of all children in whom a diagnosis was made. Girls outnumbered boys 67 % to 33 %. The mean age of onset was 8.2 years, whereas the peak age of onset was in 6-10 age group. The most common clinical types of psoriasis were psoriasis vulgaris (71.7%) and psoriasis guttata (19.4%). Precipitating factors that brought about the onset of the psoriasis or were associated with exacerbation could be recalled in 48 (71.7%) children, the most frequent being emotional stress (54.1 %) and focus (infectious disease) (41.7%). The incidence of stress as provoking factor in psoriasis vulgaris was 80 % and in psoriasis guttata 20 %.To conclude, our data indicate that emotional stress is more likely to be associated with onset or exacerbation of psoriasis in childhood and more common associated with psoriasis vulgaris than other clinical types of psoriasis.

REGRESSION OF PML IN PATIENT WITH VASCULITIS: MR AND MRS FEATURES

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INTRODUCTION: The aim of this report is to show MR and MRS features of progressive multifocal leucoencephalopathy (PML) during active and regressive stages in patient with lupus vasculitis.
METHODS: We analyzed a case study of a 39-year-old woman with a histoty of lupus vasculitis presented with developing progressive left-sided weakness over two weeks. MRI and MRS were performed initially and 7 months after discontinuation of immunosupressive treatment. PCR analysis was performed after the first MR/MRS study.
RESULTS: A huge right frontoparietal lesion respecting the integrity of cortex was evident, associated with a huge peak of lactate and markedly reduced N-acetyl-aspartate. Several white matter lesions were also present in the contralateral supratentorial white matter, most compatible with PML. Seven months later, a control MR/MRS examination, that followed excellent clinical improvement after halting immunosupressive therapy, revealed marked regression of the volume of PML lesion,

significant increase of N-acetyl-aspartate concentration and regression of the lactate peak. Our data suggests that: 1) compared to HIV positive patients, PML could be a treatable disorder if correct and prompt imaging recognition in patients under immunosuppressive treatment is done; 2) the presence of huge lactate peak in white matter processes could be additional supporting information to include PML in differential diagnosis; and 3) Increase of N-acetyl-aspartate peak after clinical improvement additionally confirms the fact that reduction of this neuronal marker could be consistent not only with destruction of neurons but also with a reversible neuronal dysfunction.

DEPRESSION AND ITS ASSOCIATION TO NEGATIVE AUTOMATIC THOUGHTS AMONG UNDERGRADUATE MEDICAL AND HEALTH SCIENCES STUDENTS IN MALAYSIA

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INTRODUCTION: Depression is currently one of the leading causes of disability among medical doctors and health related workers. However, few related studies have been reported on negative automatic thoughts and their relationship to symptoms of depression among medical and health science students in Malaysia. Thus, the objectives of this study are to determine the prevalence and relationship of negative automatic thoughts and depression.
METHODS: A cross sectional study was conducted among 281 first-year students from Faculty Medicine and Health Sciences (FMHS), University Putra Malaysia. Health sciences programs consist of four groups: Biomedical Science, Environmental and Occupational Health, Nutrition and Community Health and Dietetic. Two sets of validated questionnaires: Automatic Thoughts Questionnaire-Malay (ATQ-Malay) and Beck Depression Inventory-Malay (BDI-Malay) were administered. Data were analysed using SPSS (version 17.0), including descriptive, Pearson correlation and 2-sample T-test.
RESULTS: The prevalence for negative automatic thoughts and depression were higher among medical than health sciences students. Overall, there is a significant relationship between negative automatic thoughts and depression ($r = 0.622$). However, there was no effect of ethnicity on negative automatic thought, as well as no significant difference for gender or ethnicity on depression among medical and health sciences students.
RESEARCH SUPPORT: The study was not been funded by any authority or grant. It is part of research requirement by the university and the ethical approval is sought from the University Putra Malaysia with absolute voluntarily consent from the participants.

LEARNING IMPAIRMENT IN AMYLOID-BETA RAT MODEL OF ALZHEIMER DISEASE

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INTRODUCTION: Amyloid-beta peptide is a part of the physiological mechanism of memory. On the other hand, accumulation of this peptide in the form of plaques is a principal attribute of Alzheimer's disease. Moreover, it is considered that amyloid-beta is involved in pathogenesis of Alzheimer's disease. In line with this, injections of amyloid-

beta in different sites of the animal brain cause memory deficits. For this reason such injections could be animal models of Alzheimer disease for applied studies. However, there is not clarity of what kind of learning impairment should be observed depending on the kind of amyloid-beta peptide (fragment and solubility), injection site, and time between injection and testing. The aim of this study was to investigate behavioral markers of memory deficits in rats due to intracerebroventricular injection of the soluble form of amyloid-beta peptide.
METHODS: Three groups of adult Wistar rats (220 +- 20 g) were used in this study: experimental group, saline solution control group and intact group. Amyloid-beta fragment 25-35 was dissolved in water and injected into the right brain ventricle (5 µl, 1.2 µl/min) of the experimental group. After 14 days behavioral testing of learning and memory started, in which rats were subjected to passive avoidance test and learning in the TSE PhenoMaster system.
RESULTS: Complex cognitive impairments in rats, including impairment of long-term memory and confusion-like loss of behavioral certainty were discovered. These results confirmed the pathogenetic significance of amyloid-beta 25-35, and made it possible to discriminate amyloid-beta rats with behavioral testing.

DO WOMEN WITH SHOULDER AND NECK PAIN PRESENT A DYSREGULATION OF THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS WITH INCREASED RISK OF DEVELOPING FIBROMYALGIA?

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INTRODUCTION: Shoulder and neck pain (SNP) and fibromyalgia syndrome (FMS), two musculoskeletal conditions of unknown pathogenesis, share common features in terms of altered neuroendocrine responses, pain and stress perception. However, the pain distribution in SNP is localized, whereas FMS is more widespread. To investigate whether SNP showed a dysregulated hypothalamic-pituitary-adrenal (HPA) axis and represent an intermediate stage between FMS and pain free conditions, we compared free salivary cortisol levels in women with SNP, FMS patients, and healthy controls (HC) in a controlled hospital-hotel setting, in which the participants' compliance was high and a number of potential confounders were analyzed.
METHODS: We recruited 22 women with SNP, 29 female FMS patients, and 29 female HC. Cortisol samples were collected to measure the cortisol waking response: upon waking, 30 and 60 minutes later. Questionnaires measuring pain levels, sleeping problems, perceived stress and personality were administered to the participants.
RESULTS: Compared with HC, women with SNP had a tendency towards higher cortisol levels, whereas FMS had lower cortisol levels. The potential confounders analyzed did not influence the results. Women with SNP and FMS patients reported more health complaints, pain, and perceived stress than the HC, but women with SNP were less affected than the FMS patients. Women with SNP showed a tendency towards an elevated HPA axis activity compared with HC. Overall, our data on circulating cortisol

levels suggests that women with SNP might represent an intermediate stage between FMS patients and HC.
RESEARCH SUPPORT: This research was supported by grants to Professor Ulf Lundberg from the Swedish Research Council and the Swedish Council for Working Life and Social Research.

Special Abstracts

HYPOTHALAMIC VASOTICIN- AND DOPAMINE-IMMUNOREACTIVE STRUCTURES UNDER STRESS IN RATS

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INTRODUCTION: Nonapeptide hormones, such as vasopressin, play an active role in stress regulation and adaptation. In vertibrates, central dopaminergic system plays a more active role in the regulation of vasotocin-, vasopressinergic hypothalamic centers functional activity, compared to lower animals. These systems are involved in the regulation of locomotion, which changes during sleep-weakness cycle.
METHODS AND RESULTS: Hypothalamic vasotocin- and dopamine structures functional activity was assessed during the sleep-deprivation stress. Immunohistochemical assays of vasotocin and thyrosine hydrohylase (the main enzyme in dopamine synthesis) were performed in the slices of frog brain. Sleep deprivation stress causes the increase of dopamine synthesis in hypothalamic structures, but also causes the secretion block, msuggesting that changes in the vasotocin system activity during sleep after deprivation contributes to the dopaminergic cells functional activity regulation.

17th "Stress and Behavior" ISBS Conference, St. Petersburg, Russia, May 16-19, 2012

18th "Stress and Behavior" North America Conference, New Orleans, LA, USA, June 22-24, 2012

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