



Poster Session 4: Physiological and pathophysiological influences

WEDNESDAY

PI - 4-1

Ameliorative effects of *Pelargonium roseum* oil on spatial working memory and anxiety-like behavior induced by methomyl pesticide exposure in Wistar rats.

*K. M'hammed Amine^{1,2}, C. Kahina², H. Nawel³, Z. Faiza², O. Mohamed El Fadel², T. Mohamed², G. Jean⁴, B. Ahsene²

¹University of Ghardaia, Algeria, Department of Life and Natural Sciences, Ghardaia, Algeria

²ENS Kouba, Laboratory of biology and animal physiology, Algiers, Algeria

³Mustapha Pacha Hospital, Department of neurosurgery, Algiers, Algeria

⁴ University of Montpellier, UMR Qualisud- Faculty of Pharmacy, Montpellier, France

This study was carried out to evaluate the adverse effects of exposure to methomyl on neurocognitive and behavioral deficits and the protective role of *Pelargonium roseum* essential oil (EO) in the rat. 32 Male rats were separated into 4 groups of 8 rats each: group I received only vehicle (5 ml/kg of 10% Tween-20), group II received *pelargonium roseum* oil (67 mg/kg) in tween-20 daily via oral gavage for 28 days, group III treated with methomyl (1/8 LD50), group IV treated with methomyl and *pelargonium roseum* oil daily via oral gavage for 28 days. Spatial working memory was evaluated in the Y maze and Anxiety-related behavior was evaluated using the elevated plus maze. We observed a significant decreased of anxiety-like behavior and significant improvement of spatial working memory in the group of rats treated with *pelargonium roseum* essential oil compared to rats treated with methomyl only. We can conclude that methomyl caused neurocognitive and behavioral deficits in male rat and co-administration of *pelargonium roseum* essential oil exhibited protective effect by inhibiting MET-induced toxicity.

PI - 4-2

PLCG1 is required to ensure proper chemoattraction of netrin-1/DCC signaling in developing mouse brain

*D. S. Kang¹, A. H. Park¹, B. Park², D. Kim¹, H. Cho¹, A. Suzuki³, C. Lucio¹, P. G. Suh²

¹University of Bologna, Bologna, Italy

²UNIST, Lifesciences, Ulsan, South Korea

³Kyushu University, Fukuoka, Japan

Understanding the underlying mechanism of neural circuit formation provide us with key insights into potentially important means of research for nerve reconnection. Here, we reveal that phospholipase C gamma1 (PLCg1), a signal transducer of receptor tyrosine kinases, mediates axonal guidance of midbrain dopaminergic (mDA) neurons through netrin-1/DCC receptor signaling. Previous studies showed that receptor tyrosine kinases (RTKs)-mediated activation of PLCg1 plays a specific part in neuronal cell morphology and motility *in vitro*; however, several questions remain regarding which extracellular stimulus trigger PLCg1 signaling, and what role the PLCg1 plays in nervous system development. Recently, several *In vitro* studies have suggested a possibility that the netrin-1/DCC, a guidance cue, may be linked to PLCg1 signaling; however, there is no direct evidence that relationship between the receptor DCC and the PLCg1, because receptor DCC does not contain an intracellular catalytic domain therefore, DCC has not been proposed as a receptor tyrosine kinase. In this study, we identified a molecular mechanism of how netrin-1/DCC induce the lipase activity of PLCg1 by means of proteomic study. In addition, our data show that a role of PLCg1 in mDA axon extension and guidance by mediating netrin-1/DCC signaling and disruption of the PLCg1 signaling adversely affects mDA development and is associated with physiological and behavioral features of a range of dopamine-related neurodevelopmental disorders. Our diffusion tractography data show a strong negative correlation between the rate of diffusion of axon fibers and the hyper-locomotor activity. Treatment with methylphenidate, a drug for ADHD, remarkably attenuated the hyper-locomotor activity and improved the inattentive behavior in *Plcg1* cKO mice. These results suggest that PLCg1 plays an essential role for the faithful development of mDA system by mediating netrin-1/DCC signaling. Our study makes significant advances in understanding of the mDA pathway development by revealing a



mechanism of how the netrin-1/DCC could elicit the activity of PLCg1 and a physiological role of PLCg1 in nervous system development.

PI - 4-3

Substrate elasticity induces quiescence and promotes neurogenesis of primary neural stem cells – an *in vitro* model of the physiological cerebral milieu

*S. Blaschke^{1,2}, S. U. Vay¹, N. Pallast¹, M. Rabenstein¹, J. A. Abraham³, C. Linnartz³, M. Hoffmann³, N. Hersch³, R. Merkel³, B. Hoffmann³, G. R. Fink^{1,2}, M. A. Rüger^{1,2}

¹University Hospital Cologne, Cologne, Germany, Department of Neurology, Köln, Germany

²Institute of Neuroscience and Medicine (INM-3), Research Centre Juelich, Juelich, Germany, Cognitive Neuroscience, Juelich, Germany

³Institute of Complex Systems (ICS-7), Research Centre Juelich, Juelich, Germany, Biomechanics Section, Juelich, Germany

In the brain, neural stem cells (NSC) are tightly regulated by external signals and biophysical cues mediated by the local microenvironment or "niche". The wealth of data depicting the effects of cytokines, chemokines, or cell-cell contact on stem cell function is contrasted by the dearth of data on the influence of the environment's mechanical properties on NSC. In particular, the influence of tissue elasticity, known to fundamentally affect the function of various cell types in the body, on NSC remains poorly understood. Notably, the brain is among the softest tissues in the human body, with an elasticity of 1 kPa and less. Thus, standard cell culture conditions on glass plates with elasticity in the GPa range, as often used in in-vitro studies of NSC functions, constitute a non-physiological microenvironment. We, accordingly, aimed to characterize the effects of elastic substrates on crucial NSC functions.

Primary rat NSC were grown as monolayers on polydimethylsiloxane- (PDMS-) based gels. PDMS-coated cell culture plates, simulating the physiological microenvironment of the living brain, were generated in various degrees of elasticity, ranging from 1 - 50 kPa; regular glass plates served as a control. Cell survival, proliferation, differentiation speed and fate as well as neurite outgrowth were characterized to assess essential NSC functions.

Survival of NSC on the PDMS-based substrates was unimpaired. The proliferation rate on 1 kPa PDMS decreased by 54% compared to glass ($p < 0.01$) while, at the same time, expression of cyclin-dependent kinase inhibitor 1B / p27Kip1 increased more than 4-fold ($p < 0.001$), suggesting NSC quiescence. Upon mitogen withdrawal, NSC differentiation was accelerated on softer substrates and favored the generation of neurons (42% neurons on 1 kPa PDMS vs. 17% on glass; $p < 0.01$). Neurons generated on 1 kPa PDMS showed 49% longer neurites compared to those on glass surfaces ($p < 0.05$), suggesting optimized neuronal maturation and an accelerated generation of neuronal networks.

Data show that primary NSC are significantly affected by the mechanical properties of their microenvironment. Culturing NSC on a substrate with brain-like elasticity keeps them in their physiological, quiescent state and increases their neurogenic potential. Thus, to optimally mimic the brain microenvironment in vitro for stem cell research, elastic substrates should be used for NSC cultivation.

PI - 4-4

Snack Food impacts Resting State Networks in Rodents and Humans

*A. Mendez-Torrijos¹, S. Kreitz¹, C. Ivan¹, L. Konerth¹, J. Rosch², M. Pischetsrieder³, G. Moll⁴, O. Kratz⁴, A. Dörfler², S. Horndasch⁴, A. Hess¹

¹Friedrich-Alexander-Universität Erlangen-Nürnberg, Institute of Experimental and Clinical Pharmacology and Toxicology, Erlangen, Germany

²Universitätsklinikum Erlangen, Department of Neuroradiology, Erlangen, Germany

³Friedrich-Alexander-Universität Erlangen-Nürnberg, Food Chemistry Division, Erlangen, Germany

⁴Universitätsklinikum Erlangen, Department of Child and Adolescent Mental Health, Erlangen, Germany



Question: First, we tested in rats the tendency to consume snack food (chips vs. standard chow, additionally controlling the fat/carbohydrates ratio). Following, human Resting State fMRI (RS-fMRI) was investigated after visually presenting different foods (high-caloric: chips and low-caloric: zucchini) followed by the ingestion of one of the foods presented to explore changes in RS networks of healthy individuals.

Method: Manganese-enhanced magnetic resonance imaging (MEMRI) was used for mapping the whole rat brain activity related to standard chow and chips intake over one week. Following, 17 healthy human subjects with BMI 19 to 27 underwent two different fMRI sessions where an initial resting state scan was acquired, followed by visual presentation of different potato chips and zucchini images. There was then a 5 minutes pause to ingest food (day 1=chips, day 3=zucchini), followed by a second resting state scan. Human FMRI data was further analyzed using graph theory analysis and support vector machine techniques.

Results: Results in rats showed that the intake of potato chips manganese accumulation increased in certain areas related to the reward system as well as to locomotor activity, indicating higher neural activity in these areas. Furthermore a specific mixture of 35% fat and 50% carbohydrate in food but not the pure energy content leads to this hedonic hyperphagia and activates similar brain areas as the ones found with chips stimulation [5, 6]. In humans, chips vs. zucchini stimulation lead to significant connectivity changes. The support vector machine was able to accurately categorize the two types of food stimuli with 100% accuracy. Visual, auditory and somatosensory structures, as well as, thalamus, insula and basal ganglia were found to be important for food classification. After chips consumption, the BMI was positively correlated with the path length and degree in nucleus accumbens, middle temporal gyrus and thalamus.

Conclusions: Our human study showed that high vs. low caloric food in healthy individuals can induce significant changes in RS which are detectable by graph theory and support vector machine. Nucleus accumbens connectivity changes in humans directly relate to changes in the rats. However, some human connectivity differences (e.g. visual cortex) cannot be found in rats, as no visual stimulation occurred. Furthermore, our results in humans involve higher order brain functions such as semantic reasoning not present in rats. However, our human RS-fMRI study nicely translated results from rats MEMRI studies.

PI - 4-5

Impact of recurrent hypoglycemia exposure on hippocampal metabolism

*K. Dave¹, N. Dewan¹, V. Shukla¹, A. Rehni¹, K. Koronowski¹, H. Stradecki¹, T. Garrett¹, M. Perez-Pinzon¹

¹University of Miami Miller School of Medicine, Neurology, Miami, United States

Questions: Recurrent hypoglycemia (RH) is common in diabetic patients receiving glucose-lowering therapies¹. Exposure to RH leads to cognitive impairments². Despite the significant effect of RH on hippocampal function, the underlying mechanisms are unknown. Our goal was to determine the effect of RH on hippocampal metabolism. In an earlier metabolomics study, we observed a profound effect of exposure to RH on the hippocampal metabolome in diabetic rats. We have extended our previous study by evaluating the impact of RH exposure on the substrate kinetics of key glycolytic enzymes in the hippocampus, to determine if changes in metabolites are due to altered enzyme functions.

Methods: Hyperglycemia in streptozotocin-diabetic rats was corrected by insulin-pellet implantation. These animals were considered as "insulin-treated-diabetic" (ITD) rats. ITD rats were randomly divided into ITD+RH (diabetics on insulin therapy experiencing RH), and ITD+RH+Glucose (co-infusion of insulin and dextrose to control for the effect of exogenous insulin used in the RH group) groups. Mild/moderate RH was induced once a day (for 3 hours) for 5 consecutive days. Substrate kinetics of key glycolytic enzymes (hexokinase³, phosphofructokinase⁴, and pyruvate kinase⁵) in the hippocampus were evaluated.

Results: Several statistically significant differences in metabolite levels belonging to major metabolic pathways (e.g., Krebs cycle, gluconeogenesis, and amino acid metabolism) were noticed in the ITD+RH group (n=9) compared to the ITD+RH+Glucose group (n=10). We observed a severe impact of RH exposure on substrate



kinetic properties of these enzymes. For hexokinase, K_m values for both glucose and ATP were not altered by RH exposure. For phosphofructokinase, a higher K_m of ATP and lower V_{max} for fructose-6-phosphate were observed. For pyruvate kinase, we observed higher K_m for phosphoenolpyruvate, lower V_{max} for ADP, a potentially compensatory lower K_m for ADP, and higher V_{max} for phosphoenolpyruvate. To a large extent, an association between substrate kinetics data and metabolomics data was observed.

Conclusions: This is the first study evaluating the effect of RH on hippocampal biochemistry. Exposure to RH exhibits differential effects on kinetic properties of key glycolytic enzymes. Understanding how RH affects hippocampal biochemistry may help attenuate the adverse effects of RH on hippocampal function.

References: 1) Diabetes Metab. 2015;41:116-25; 2) Scientific World Journal. 2014 Mar 23;2014:616534; 3) Biochem Biophys Res Commun. 1991;177:1101-6; 4) J Biol Chem. 1994;269:3348-55; 5) Arch Biochem Biophys. 1985;236:703-713.

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PI - 4-6

Associations among inflammation, mental health, and quality of life in adults with metabolic syndrome

*J. R. Kim¹

¹College of Medicine, The Catholic University of Korea, Family medicine, Suwon-si, South Korea

Question: Metabolic syndrome (MetS), a pro-inflammatory state, has become increasingly common worldwide and is a major risk factor for type 2 diabetes mellitus and cardiovascular disease. Recently, studies on the relationships among inflammation, mental health, quality of life, and other diseases have been conducted. We investigated the relationship between serum high-sensitivity C-reactive protein (hs-CRP) levels, as an indicator of inflammation, and the quality of life and psychiatric symptoms of Korean adults with MetS.

Methods: The analysis used data from the Korean National Health and Nutrition Examination Survey, a cross-sectional survey of Korean civilians, conducted from January to December 2015. A total of 1,600 participants were analyzed in this study. We obtained the information from EQ-5D and a survey about four psychiatric symptoms. To analyze the data using a complex sampling design, we used the SAS PROC SURVEY module, considering strata, clusters, and weights. Characteristics of the study population according to serum hs-CRP quartile were analyzed.

Result: Mobility problem was associated with high serum hs-CRP levels in adults with and the positive association was more significant after adjusting for covariates (age and sex adjusted OR 1.71, 95% CI 1.10-2.72, $p = 0.018$; multivariate-adjusted OR 1.66, 95% CI 1.03-2.66, $p = 0.036$). EQ-5D index showed a significant inverse correlation with serum hs-CRP levels and suggested high serum hs-CRP levels were associated with poor overall quality of life. In additions, as serum hs-CRP levels increased, suicide ideation increased in adults with MetS ($p = 0.002$, p for trend = 0.002). Suicide ideation had positively associated with serum hs-CRP levels in adults with and the association remained significant after adjusting for covariates (age and sex adjusted OR 2.61, 95% CI 1.35-5.04, $p = 0.005$; multivariate-adjusted OR 2.48, 95% CI 1.23-4.99, $p = 0.011$).

Conclusion: These findings suggest that management of inflammation in MetS may have a positive impact on quality of life and suicide ideation as well as its disease course. Prospective studies and more stratified studies will be needed to assess the impact of inflammation on quality of life and mental health in the MetS.



P II - 4-7

Metabolic disorders and long-term cognitive decline : a preclinical approach

O. Petrault¹, M. Petrault¹, T. Ouk¹, R. Bordet¹, V. Berezowski¹, *M. Bastide¹

¹University of Lille, INSERM U1171 Degenerative and vascular cognitive disorders, Lille cedex, France

Introduction: Initially slow and progressive, cognitive decline is a multifactorial decline in cognitive functions that can lead to dementia, that is to say a more or less severe loss of autonomy in everyday activities. Several studies have suggested that cardiovascular risk factors, including the presence in the middle age of metabolic disorders, are associated with mild cognitive impairment and may predict late dementia. However, a multitude of associated variables such as lifestyle, age or pre-existing pathologies, prevents establishing this link univocally. We wanted to test whether metabolic disorders alone and settled in middle age, could induce a slight cognitive impairment in the long run. We have developed a non-transgenic preclinical model, free of any pre-existing pathology, mimicking the progressive onset of metabolic disorders over 12 months.

Methods: Male mice (C57Bl/6) aged of 8 weeks at the beginning of the protocol were fed ad libitum with an animal fat-enriched diet (HFD) and compared to standard-fed mice (ND). Metabolic parameters, behavioral status, histological integrity of brain tissue, tissue perfusion and functional integrity of the cerebrovascular bed (middle cerebral artery and intra-parenchymal microvessels) are checked at different time-points: D0 and after 3, 6, 9 and 12 months of fat-enriched or standard diet.

Results: We have evidenced over the 12-months diet some metabolic disorders (plasma lipid imbalance, visceral fat deposition, glucose intolerance, steatosis) in HFD-fed mice. Spontaneous locomotor activity and different types of memory (visual recognition, spatial memory, flexibility, working memory) are tested. A specific cognitive impairment of visual recognition memory progressively takes place in HF mice, whereas spatial memory and working memory did not. The vessels assessment revealed progressive and significant alterations in HF mice. The resting cerebral blood flow is decreased after 9 months of HF diet. The endothelial-dependent responses of pial artery and hippocampus arterioles are impaired after 9 and 12 months of high-fat diet with a concomitant decrease of the perfusion in entorhinal cortex and hippocampus.

Conclusions: These results highlight the long-term detrimental effect of metabolic disorders on cerebral vasculature properties associated to a specific cognitive decline. However, the cascade mechanisms, triggering cognitive decline in the long term or rendering the brain more likely to, needs to be elucidated. Beyond the nature of the diet, the cognitive and vascular deficits are going to be analyzed according to the metabolic disturbances evidenced in HF-fed mice but also in some of the ND-fed mice group.

P II - 4-8

Expression of neurogenesis, angiogenesis and inflammatory markers in brain beyond the subacute phase after experimental stroke in female rats

*M. Mostajeran¹, L. Edvinsson^{1,2}, H. Ahnstedt³, K. Arkelius¹, S. Ansar¹

¹Lund University, Department of Clinical Sciences, Lund, Sweden

²Glostrup Research Institute, Department of Clinical Experimental Research, Glostrup, Denmark

³University of Texas Health Science, Department of Neurology, Houston, United States

Question: Stroke is a disease with well documented sex differences. However, the majority of pre-clinical studies are performed in young healthy male rodents, a clear discrepancy when considering the clinical population affected by stroke. The underlying mechanisms in the recovery processes are not well studied in females. Therefore, the present study aimed to evaluate neurological deficits, infarct size and expression of neurogenesis, angiogenesis and inflammatory markers in ipsilateral and contralateral side of the brain two weeks after experimental stroke in female rats.



Method: Transient middle cerebral artery occlusion (tMCAO, 120 min) was induced in female Wistar rats (12-week old, n=8) during the low influence of estrogen in their estrus cycle by using the intraluminal suture model. Neurological functions were evaluated by 28-point and 6-point neuroscore tests at day 1, 2, 5, 8 and 14 post stroke. Infarct size was determined at day 14 post-stroke by using silver staining. Protein expression of interleukin 10 (IL-10), transforming growth factor (TGF)-b, NeuN, Nestin, Tie-2, extracellular signal-regulated kinase (ERK) 1/2 and protein kinase B (Akt) was evaluated in the peri-infarct and ischemic core compared to contralateral side of the brain by western blot. Two-tailed Wilcoxon signed rank test using SPSS (Version 25) was performed for statistical analysis. $p < 0.05$ was considered significant.

Results: Spontaneous recovery from neurological deficits after stroke was observed from day 2 to day 14 in female rats (15 (12.25-20) vs 21.5 (17.5-24) respectively, $p < 0.01$ for 28-point test and 3.5 (3-4) vs 2.5 (2-3) respectively, $p < 0.05$ for 6-point test). However, neurological deficits still significantly differed at day 14 compared to the day before stroke. The infarct area was $17.51 \pm 7.33\%$ of the ipsilateral side. It was observed that the two pathways Akt and ERK1/2 were affected in peri-infarct and ischemic core compared to contralateral side. Moreover, the expression of nestin and TGF-b were significantly increased in ischemic region compared to control side. However, the expression of NeuN significantly decreased in the ischemic region compared to control side. Expression of Tie-2 and IL-10 did not differ significantly between the two sides.

Conclusion: We showed that neurological deficits spontaneously recovered from day 2 to day 14 after ischemic stroke in female rats, Moreover, there was a difference observed in the expression of markers involved in the recovery phase after stroke. These markers changes might be of importance to address for future therapeutic strategies in female rats.

P II - 4-9

Cardiovascular disease risk, menopause and uric acid level

*S. H. Kim¹, S. H. Lee¹

¹The Catholic University of Korea, Daejeon ST. Mary's Hospital, Family medicine, Daejeon, South Korea

Question: Recently, many studies have shown a link between serum uric acid (sUA) and Cardiovascular disease (CVD) risk, so uric acid is attracting attention as one of the risk factors of CVD.

Methods: We conducted a retrospective cohort study using the medical records of a hospital screening center to analyze the relationship between sUA and CVD risk and menopause. The subjects were 11240 adults with no CVD from May 2015 to April 2017 at the Health Checkup Center in Daejeon St. Mary's Hospital, and those aged 40 to 79, total cholesterol 130-320mg / dL, HDL cholesterol 20-100mg / dL, systolic blood pressure(SBP) 90-200 mmHg. We identified their sex, age, total cholesterol, HDL cholesterol, SBP, current smoking status, whether he or she has DM and HTN, and current sUA levels. The probability of occurrence of CVD in individuals after 10 years was calculated and the relationship between sUA level and possibility of CVD was analyzed statistically.

We then collected data from 5285 women aged 40 or older. The relationship between the presence of menopause and the level of sUA was statistically analyzed.

Results: There was a significant correlation between sUA levels and CVD risk in all and women only subjects. The mean value of sUA was 5.14 ± 1.36 mg/dL and of probability of occurrence of CVD after 10 years was $5.3 \pm 6\%$ in all group (p -value < 0.0001). The mean value of sUA was 4.26 ± 0.96 (mean \pm SD) mg/dL and the mean value of probability of occurrence of CVD after 10 years was 2.37 ± 3.29 (mean \pm SD) % in women only group (p -value < 0.0001).

There was a significant correlation between menopausal status and sUA level. The mean value of sUA of premenopausal women was 4.1 ± 0.9 mg/dL and of postmenopausal women was 4.3 ± 1.0 mg/dL (p -value < 0.0001).



Conclusions: In women only group and all group, there is a significant positive correlation between sUA levels and CVD risk, and there is a significant correlation between menopause and sUA levels in women.

P II - 4-10

Sex Differences in Spatial Frame of Reference Switching Using the Octagon Navigation Task

*K. Chua¹, M. Fida¹, R. Sutherland¹

¹University of Lethbridge, Neuroscience, Lethbridge, Canada

Questions: Sex differences literature analyzing spatial performance has consistently reported male advantage in spatial ability. The Morris Water Task (MWT) is commonly used to test spatial memory and hippocampal-dependent learning in animals. Two frames of reference exist in the literature of spatial navigation. Egocentric spatial frame of reference depends on internal cues such as body axis and position, whereas allocentric frame of reference depends on external cues such as environmental cues. We investigated whether sex differences in spatial navigation are due to spatial ability or strategy selection by using a novel tabletop version of the MWT, called the Octagon Navigation Task (ONT) in humans. We found that the men outperformed women in the allocentric condition, the women outperformed men in the egocentric. There were no sex differences found in the neutral condition where they could use either strategy to solve the task. The purpose of this study was to investigate whether a sex difference would be found if subjects are first exposed to an experimental condition that allows them to use any spatial frame of reference to navigate and then switched to either an allocentric or egocentric spatial frame of reference. Based on our previous study, our prediction was that men will be able to adapt more easily in the allocentric switch and that women will excel in the egocentric switch.

Methods: In our lab, we designed a tabletop version of the MWT with consistent environmental cues and conditions. The goal of the experiments was to locate a hidden target by navigating on the octagonal board using different spatial frame of references. There were a total of ten trials where the first five trials had the target location in the center of the board (neutral) and the remaining either in relation to external environmental cues (allocentric) or in relation to body axis and position (egocentric). The neutral to allocentric switch had 33 subjects (16 women) ages 18-25 and the neutral to egocentric switch had 53 (20 women) ages 18-25. Results were analyzed using a t-test in SPSS IBM Statistics.

Results: Results revealed statistically significant ($p < 0.05$) sex differences in both neutral-to-egocentric switch and neutral-to-allocentric switch experiments, with women outperforming men and men outperforming women, respectively.

Conclusions: Our findings suggest that men easily adapt to using an allocentric spatial frame of reference whereas women adapt better than men to egocentric spatial frame reference.

P II - 4-11

Sex differences in Allocentric vs. Egocentric spatial frame of reference preference in resting state fMRI activity in Men and Women using a novel Octagon Navigation Task

*M. Fida¹, K. McCreary¹, K. Chua¹, R. Sutherland¹

¹Canadian Centre of Behavioural Neuroscience, University of Lethbridge, Neuroscience, LETHBRIDGE, Canada

Question: The Morris water task (MWT) is a test of spatial learning and memory commonly used in research on spatial cognition in rodents. From this research it is clear that the hippocampus is necessary for accurate navigation and that males and females sometimes perform differently. Most often, a computer-based, virtual MWT is used with humans. To further examine the sex difference, we designed a real-world version of the MWT and found that men, by default, use an allocentric spatial frame of reference to guide locomotion, but women by default use an egocentric spatial frame of reference. Based on these findings, we designed allocentric and



egocentric tabletop versions of the MWT, called the Octagon Navigation Task to study the use of these spatial frameworks.

Method: In a first experiment, 40 subjects (20 women) ages 18-25, were initially exposed to either an allocentric spatial task in which the hidden goal had a fixed location relative to stable room cues or egocentric spatial task in which the hidden goal was in a fixed location relative to body position at the start of each trial. Subjects in the experiment were exposed to both allocentric and egocentric conditions in a 4x4x4 block design. The order of whether the subjects were first exposed to an allocentric or egocentric version of the spatial task was randomized. The second part of the experiment required the subjects to have their resting state fMRI activity measured. The resting state activity was then correlated with behavioural measures. Behavioural data was analyzed using MATLAB, SPSS and Prism, whereas fMRI data was analyzed using CONN.

Results: Men performed significantly better than women when using allocentric spatial frame of reference whereas women performed better when using an egocentric spatial frame of reference.

Conclusion: Together, these results suggest that sex differences in spatial navigation result from different prepotent spatial frameworks guiding performance.

P II - 4-12

Reproductive Age Affects Microbiome and Stroke Outcome in Female Rats

M. J. Park¹, *F. Sohrabji¹

¹Texas A&M University, Women's Health in Neuroscience Program, Dept. of Neuroscience and Experimental Therapeutics, Bryan, TX, United States

Question: Stroke is more prevalent in older population, and among this demographic, older women are at a higher risk for stroke, with worse outcomes and poorer recovery. Recent advances have suggested that intestinal bacteria affect stroke outcome and cardiovascular events. Recent studies reveal an important role for the gut microbiome in cardiovascular health, and a reciprocal regulation between intestinal bacteria and circulating estrogen levels. However, the mechanistic link between estrogen deficiency and gut microbiome among acute brain disorders has not been well established.

Methods: Fecal samples from adult (cyclic, 5 months old) and middle-aged (acyclic, 12 months old) Sprague-Dawley female rats at pre (0d) and post (5d) middle cerebral artery occlusion (MCAO) were analyzed by Illumina-sequencing of the 16S rRNA gene. Animals were tested for infarct volume and sensory motor performance pre and/or post stroke. Rats were sacrificed at the early (2d) or late (5d) acute phase after MCAO to collect serum and tissue samples for histological and biochemical analyses.

Results: Diversity of the gut microbiome was significantly decreased in estrogen-deficient middle-aged females at 0d (pre stroke) compared to estrogen-sufficient adult animals. Middle-aged rats at 5d post stroke had the most profound alterations in their microbiome, as significant separations were observed on PCoA plots of Unifrac distances. Middle-aged rats presented a larger infarct size as well as a significantly worse sensory motor function at 2d and 5d post MCAO as compared to adult female rats. Middle-aged rats had significantly increased gut leakiness (measured by serum endotoxin concentration) and blood brain barrier disruption (assayed by ELISA for glial fibrillary acidic protein, GFAP, as a surrogate marker of BBB permeability) at 5d post stroke compared to adult group. Moreover, the gut microbiome community was significantly altered by reproductive age, as evidenced by the decreased members of the genus *Akkermansia* and increased members of the genus *S24-7*, suggesting a role for these bacteria in estrogen deficiency and stroke severity. Prevotellaceae was significantly altered by stroke. Endogenously, short-chain fatty acids (SCFAs) are derived from gastrointestinal (GI) bacteria-dependent fermentation of fiber (produced primarily in the ileum/colon). We also found that butyrate levels were significantly lower after stroke in middle-aged females as compared to adults. Butyrate stimulates IGF-1 synthesis and decreased levels of this SCFA in middle aged females suggests that gut dysbiosis may be mechanistically linked to lower levels of IGF-1 levels in this group.



Conclusions: These data provide the first evidence that reproductive age induces microbiome dysbiosis and gut leakiness in middle-aged female rats and underscores the link between microbiota (and its metabolites, SCFAs) and stroke outcome and severity.

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