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Learning deficit and altered *Mmp9* and *Timp1* gene expression in adult rats exposed to bacterial endotoxin during early postnatal development

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Introduction

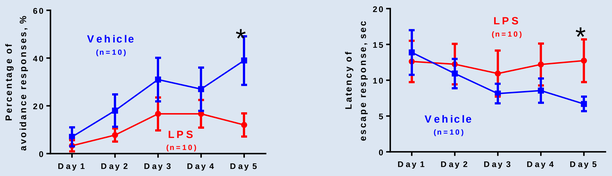
- Perinatal brain pathologies are known to impair the development of CNS functioning and are involved in the etiology of chronic cognitive dysfunction [3, 7, 10].
- These conditions are associated with high production of pro-inflammatory cytokines by the cells of the immune and nervous systems [11].
- It is well established that neurons express receptors for pro-inflammatory cytokines, which provides evidence for the functioning of cytokines as neuromodulators [4].
- Pro-inflammatory cytokines are capable to influence the expression of neuroplasticity related genes [8].
- Matrix metalloproteinase 9 (MMP-9) and tissue inhibitor of metalloproteinase 1 (TIMP-1) are expressed in many cell types, including neurons and glia and help regulate neuronal re-modelling and cell-to-cell interactions by modifying the extracellular matrix [1, 2, 5, 6].
- While MMP-9 levels are lower in the adult brain, its activity has been shown to increase in response to synaptic activity [9].

Goal

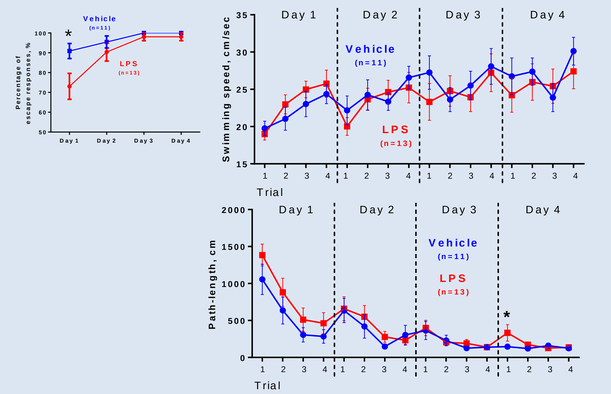
to study the expression patterns of *Mmp9* and *Timp1* genes in the medial prefrontal cortex and dorsal/ventral hippocampus of rat pups and adult rats after early inflammatory process

Results

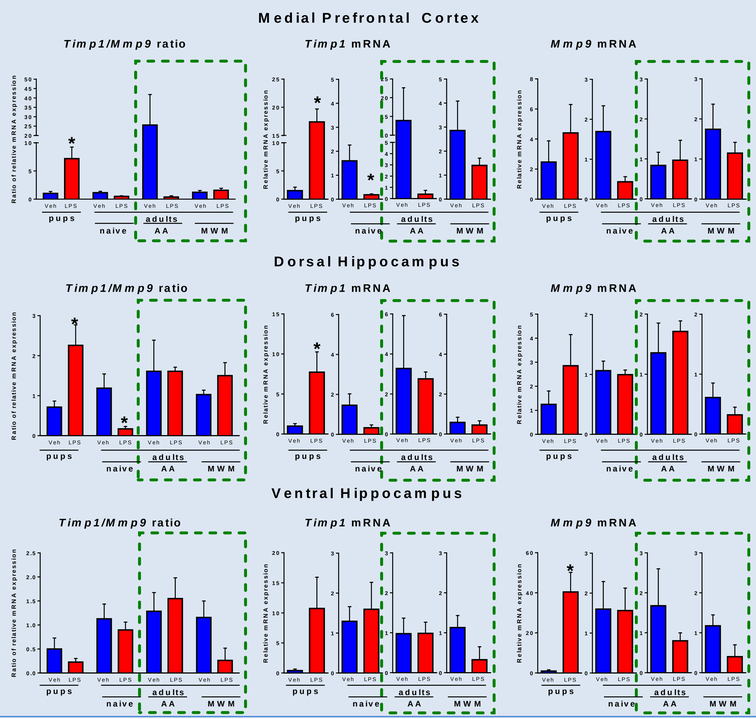
Early life LPS treatment impaired Active avoidance learning



Early life LPS treatment impaired spatial navigation in Morris water maze



Early life LPS treatment differentially altered of *Mmp9* and *Timp1* expression in the cortex and hippocampus of pups vs. adult untrained rats



Gene expression of *Mmp9* and *Timp1* remained unchanged in rats trained in either learning task

Study outline

Birth

Equalization of number of Wistar rat pups in the litters

3rd week

Formation of rat groups

LPS (i.p. 25 μg/kg moderately pyrogenic dose, P15, P18, P21 – equivalent of perinatal period in human)

Control (i.p. saline, same period)

2.5-3 months

Behavioral tests

AA
5 consequent days
20 trials per day
CS – light,
US – footshock
Number of avoidances

MWM
4 consequent days
4 trials per day
Inter-trial – 90-180 sec
Time on platform – 30 sec
Distance passed to the platform

No test

Gene expression analysis

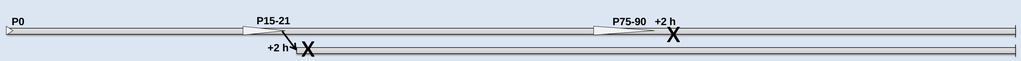
- Extraction of mPFC and hippocampus using microtome-cryostat
- RNA isolation by TRI-reagent
- qRT-PCR using Taqman system (reference gene - *Gapdh*)

Statistical analysis

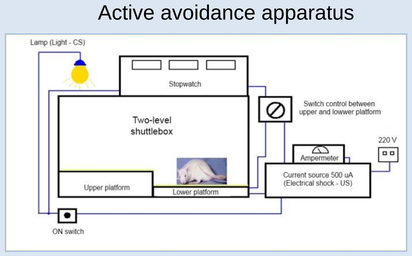
Normality Kolmogorov-Smirnov

Pairwise comparisons Mann-Whitney U-test

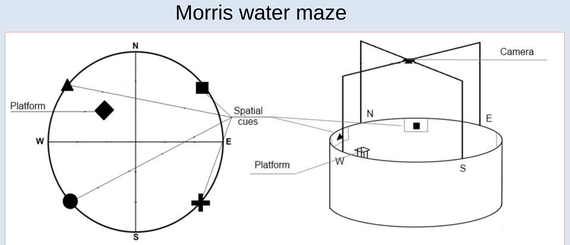
p<0.05



Active avoidance apparatus



Morris water maze



Conclusions

1. LPS treatment during the 3rd week of life impaired the learning process of adult rats in the Active avoidance and Morris water maze paradigms
2. These impairments were accompanied by changed *Mmp9* and *Timp1* expression in the medial prefrontal cortex and hippocampus of rat pups and adult rats which were not exposed to a cognitive training
3. After training in the AA and MWM tests, adult LPS treated rats had the same level of *Mmp9* and *Timp1* expression in the brain structures as in control
4. These results suggest that an increase in cognitive stimulation might be an effective approach to reduce the negative effects of neonatal immune challenges on brain functioning

Our new paper

Trofimov A., Strekalova T., Mortimer N., Zubareva O., Schwarz A., Svirin E., Umriukhin A., Svistunov A., Lesch K.-P., Klimenko V. ***Postnatal LPS Challenge Impacts Escape Learning and Expression of Plasticity Factors Mmp9 and Timp1 in Rats: Effects of Repeated Training.*** **2017. Neurotoxicity Research.**

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