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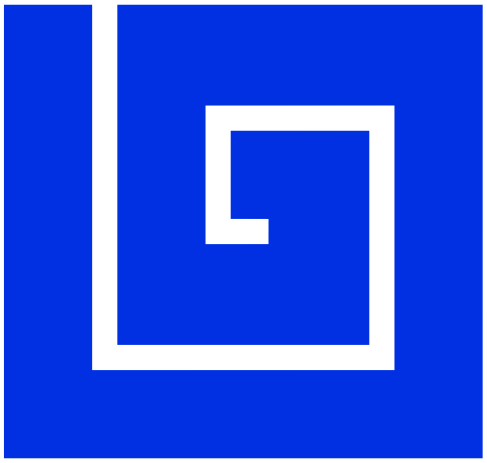
PSYCHIATRIA FENNICA



SUPPLEMENTUM 1

THE 5TH FINNISH SYMPOSIUM ON
BIOLOGICAL PSYCHIATRY

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ABSTRACT BOOKLET

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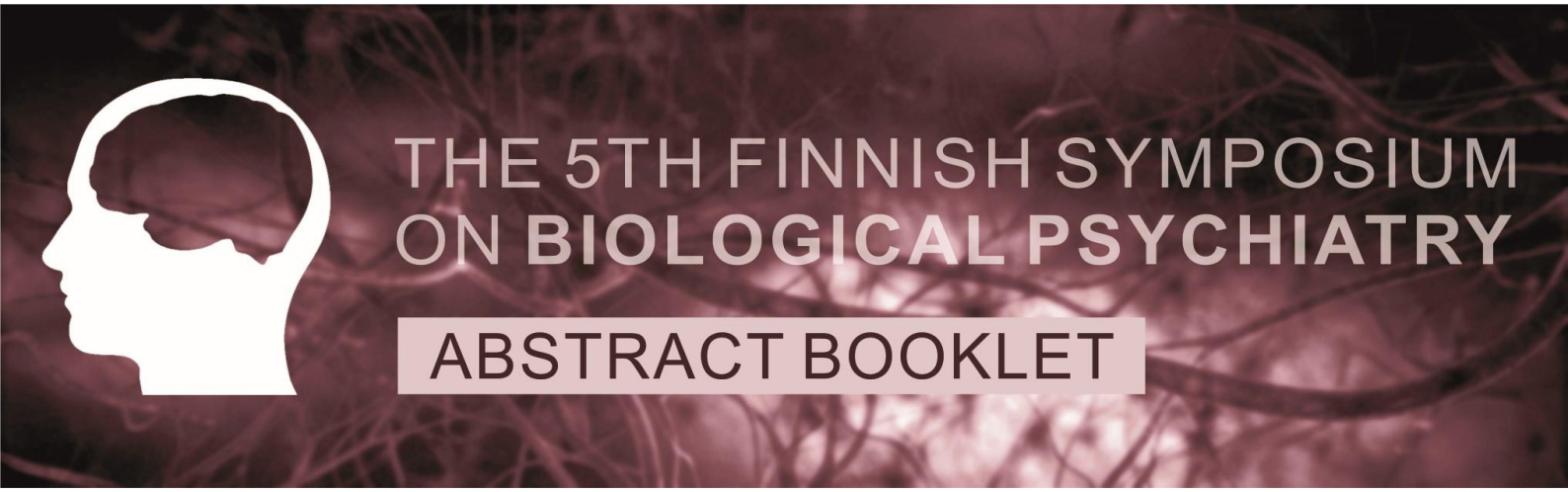

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The acute effects of LSD on goal-directed decision-making in mice

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Psychedelic drugs, such as LSD and psilocybin, have again become of great interest in neuroscience after several clinical studies have shown promising results in the treatment of psychiatric disorders with psychedelic therapies. In this study we explored the acute effects of serotonergic hallucinogens on goal-directed decision-making in mice using a rodent version of the human-validated Iowa Gambling Task modified to touchscreen operant chambers. In the test, the mice were first taught to press the touch-screen panels in order to get a sucrose reward. After this, the four different panels were given different reward contingencies: each of the panels gave out a certain amount of sugar combined with a certain fixed probability of a time-out punishment. The mice were then supposed to learn to optimize their choices in order to maximize the amount of sucrose and to minimize the amount of time-out punishment. After the mice had learned the optimal response strategy and the responses were stable, the effects of several drugs and doses were tested by acutely injecting the mice intraperitoneally with the drug immediately before the day's 30-minute test session. The drugs and doses tested in the experiment were as follows: saline (a negative control), a stimulant amphetamine (2.0 mg/kg, positive control), a classical psychedelic LSD (0.025, 0.1, 0.2 and 0.4 mg/kg), and a specific 5-HT2A agonist 25CN-NBOH (1.5 mg/kg). The results show that neither LSD nor 25CN-NBOH seem to have any effect on the overall performance nor on the decision-making of the mice whereas amphetamine greatly disrupts the performance of the mice, as described in literature. These results comply with the recently published data on humans where LSD did not acutely impair the participantsdecision-making in a similar test, implying a successful reverse-translation of the effects.

From stress to depression: Development of extracellular matrix-dependent cognitive impairment following social stress

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Stress can predispose to depressive episodes, yet the molecular mechanisms regulating the transition from the initial stress response to a persistent pathological depressive state remain poorly understood. To shed light on this stress-to-depression transition process, we profiled the development of an enduring depressive-like state in rat by assessing affective behavior and hippocampal function >2 months following social defeat stress. In addition, we measured remodeling of hippocampal extracellular matrix (ECM) during this period, as we recently identified ECM changes to mediate cognitive impairment during a sustained depressive-like state. We found affective disturbance and cognitive impairment to develop disparately after social stress. While affective deficits emerged gradually, spatial memory impairment was present both early after stress and during the late-emerging chronic depressive-like state. Surprisingly, these phases were separated by a period of normalized hippocampal function. The SDPS paradigm induced a biphasic regulation of the hippocampal ECM coinciding with hippocampus-dependent memory deficits. Early after stress, synaptic ECM proteins and the number of perineuronal nets enwrapping parvalbumin-expressing interneurons were decreased. This was followed by a recovery period with no ECM dysregulation, before subsequent ECM build-up, previously shown to impair memory. This suggests that intact hippocampal function requires unaltered ECM levels. Together our data 1) reveal a dichotomy between affective and cognitive impairments similar to that observed in patients, 2) indicate different molecular processes taking place during early stress and the chronic depressive-like state, and 3) support a role of the ECM in mediating long-lasting memory-effects of social stress.

DNA methylation pattern associated with insufficient sleep

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Insufficient sleep may lead to an increased risk of various psychiatric and cardio-metabolic disorders. Since DNA methylation is known to regulate gene expression, study of differentially methylated positions (DMPs) might be valuable for understanding the mechanism underlying insufficient sleep. We performed a cross-sectional genome-wide analysis of DNA methylation in relation to self-reported insufficient sleep in a population-based sample of 517 men and in relation to shift-work disorder in an occupational cohort of 26 men. The analysis of DNA methylation data showed that genes corresponding to selected DMPs form a distinctive pathway: Nervous System Development (FDR P value < 0.05). We observed that 78% of the DMPs were hypomethylated in cases in both cohorts, suggesting that loss of sleep may be associated with a loss of DNA methylation. A karyoplot revealed DMP clusters at various chromosomal regions, including 12 DMPs on chromosome 17, associated with Smith-Magenis syndrome - a rare condition comprising inverse circadian rhythm and disturbed sleep. Our findings shed light on the biological changes associated with sleep loss, possibly modifying processes related to neurodegeneration and neuroplasticity. Future prospective studies are needed to explore the observed findings.

Strain-dependent differences in the structure of nodes of Ranvier and paranodes in mice following chronic psychosocial stress

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We and others have previously shown brain region-dependent differences in myelin thickness and myelin-related gene expression in mice exposed to chronic stress, a predisposing factor for anxiety disorders. As a model of chronic stress, we used the well-validated chronic social defeat stress (CSDS) paradigm, after which the mice can be phenotyped as either stress-resilient or -susceptible based on their social interaction behaviour. To understand whether chronic stress impacts other myelin parameters, such as the nodes of Ranvier, we exposed mice from B6 (C57BL6/NCrl) and D2 (DBA2/NCrl) strains to CSDS. We performed immunohistochemical staining of paranodal protein CASPR (CNTNAP1) and voltage-gated sodium channel Nav1.6 (SCN8A) in layer IV/V of the medial prefrontal cortex. Node and paranodal length were calculated using a novel automated 3D segmentation technique, which allowed for accurate measurement of over 1000 nodes as volumetric structures with varying alignments. We found that resilient and susceptible D2 mice had longer paranodes than controls (9.4% and 10.7% respectively). By contrast, B6 susceptible mice had shorter nodes (space between two paranodes) than controls (6.6%). To investigate whether these morphological differences associated with differences in expression of node component genes, we analysed our previously published RNA-seq data of the same mouse phenotypes for gene set enrichment. We found significant enrichment of nodal genes (e.g. Ank2, Scn8a and Cntn2) specifically among genes differentially expressed between susceptible and control D2 mice. We propose that chronic stress involves subtle alterations in myelin features such as nodes of Ranvier, which depend on resilience/susceptibility and genetic background. Longer paranodes may indicate loosening of the axonal contact, which is also reported in neuropathological conditions. Loosened axonal contact and shortened nodes both may impact conduction velocity and circuit function. Myelin may thus contribute to both adaptive and maladaptive stress responses, an important consideration in the study of psychopathology.

The effect of LPS-induced neuroinflammation on intracranial self-stimulation reward in mice

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Neuroinflammation modulates emotional regulation. In preclinical animal models of depression, immune system activation has been shown to alter brain motivation and reward leading to increased helplessness and reduced feelings of pleasure (anhedonia). However, mechanisms how immune system activation modulates these functions and contributes to emotional regulation are not well understood. Our aim here was to elucidate how immune system activation induced by bacterial lipopolysaccharide (LPS) administration alters mouse reward-related behaviors. We used an operant intracranial self-stimulation (ICSS) method and adult C57Bl/6J and DBA2 (Charles River/Scanbur) male mice. A bipolar electrode was stereotaxically implanted into the lateral hypothalamus under isoflurane anesthesia. After recovery, the mice were trained to self-stimulate the brain reward pathway by turning an operant wheel. After reaching a stable baseline stimulation threshold, the mice were first treated with D-amphetamine sulphate (3 mg/kg, i.p.) and saline. After a washout period and reaching again a constant baseline stimulation level, the mice were treated with LPS (E.coli strain 0111:B4, Sigma; 0.5 mg/kg, i.p.) or saline and tested at different time points (4 h to 2 weeks). Several weeks later, the effect of a lower LPS dose (0.05 mg/kg, i.p.) was also tested. Our results indicate, that C57Bl/6J mice performed better in the ICSS procedure than DBA2 mice. More DBA2 mice were excluded from the study due to inability to reach a stable baseline threshold. Amphetamine significantly lowered the stimulation threshold. Both doses of LPS acutely increased the stimulation threshold, the lower 0.05-mg/kg dose only at a 4-h time point. In conclusion, C57Bl/6J mice appear to be suitable for ICSS studies by establishing a stable baseline stimulation threshold, showing sensitivity to rewarding properties of amphetamine and aversive properties of acute LPS treatment.

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MIM-Deficient Mice Exhibit Anatomical Changes in Dendritic Spines, Cortex Volume and Brain Ventricles, and Functional Changes in Motor Coordination and Learning.

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In this study, we performed a comprehensive behavioral and anatomical analysis of the Missing in Metastasis (Mtss1/MIM) knockout (KO) mouse brain. We also analyzed the expression of MIM in different brain regions at different ages. MIM is an I-BAR containing membrane curving protein, shown to be involved in dendritic spine initiation and dendritic branching in Purkinje cells in the cerebellum. Behavioral analysis of MIM KO mice revealed defects in both learning and reverse-learning, alterations in anxiety levels and reduced dominant behavior, and confirmed the previously described deficiency in motor coordination and pre-pulse inhibition. Anatomically, we observed enlarged brain ventricles and decreased cortical volume. Although MIM expression was relatively low in hippocampus after early development, hippocampal pyramidal neurons exhibited reduced density of thin and stubby dendritic spines. Learning deficiencies can be connected to all detected anatomical changes. Both behavioral and anatomical findings are typical for schizophrenia mouse models.

TrkB deletion from serotonergic neurons leads to impairment in memory and antidepressant efficacy

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Antidepressants mainly the selective serotonin reuptake inhibitors (SSRI) drugs activate neurotrophin signaling and neuronal plasticity. Brain derived neurotrophic factor (BDNF) together with its high-affinity cognate receptor, tyrosine kinase B (TrkB) plays a significant role in neuronal survival, synaptic plasticity and have been concomitantly related with serotonin (5-HT) in a myriad of neurochemical and behavioral responses. The mechanism of this interplay between BDNF/TrkB with 5-HT is limited. To investigate the interaction between the signaling molecules, we have produced a conditional knockout mice for TrkB receptors using a Tph2 (tryptophan hydroxylase 2) promoter cre line. The knockouts were produced by injecting tamoxifen to six weeks aged mice. These knockout mice have been characterized in a series of behavior tests related to depression and anxiety. These transgenics have been found to be hyperactive. We further investigated the antidepressant efficacy of fluoxetine an SSRI in the knockouts using ocular dominance plasticity. Furthermore, we assessed the learning and memory in these mice by contextual fear conditioning. At the cellular and molecular levels, serotonin levels in different brain regions have been measured and were found to be augmented. A substantial increase in neurogenesis was observed, while the survival rates of the newborn neurons were unchanged. The results from this study suggest functional deficits in the serotonin-TrkB pathway contributes to blunted memory consolidation and response to SSRI. Further characterization of the downstream signaling cascades and serotonin receptors could possibly resolve the critical balance between the two systems that are indispensable for neuronal development, synapse formation, and plasticity.

The effect of insufficient sleep on microglial morphology

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Aims: Sleep deficiency is a common problem in modern society. Insufficient sleep leads to an immune response and many molecular immune mediators are crucially involved in sleep regulation. The brain's main immune cells, microglia, take part in maintaining tissue homeostasis in highly ramified steady-state, and upon immune challenge they transform into a reactive state with increased soma size and de-ramification. However, as little is known about the effects of insufficient sleep on microglia, wherefore we investigated how they are affected by acute sleep deprivation (SD) and chronic sleep fragmentation (SF). **Methods:** Acute 9h SD was performed with the gentle handling method and the 14d chronic SF by housing the mice (C57BL/6JR) in a Sleep Fragmentation Chamber (Lafayette), in which sleep is automatically interrupted in 2min intervals during the 12 lights-on period. After the treatments the animals were deeply anesthetized and perfused, brain tissue was immunostained for microglia (anti-IBA1, Synaptic Systems) and imaged with a confocal microscope (TCS SPX, Leica). Morphometric analyses of the 3-dimensional microglia reconstructions from the somatosensory cortex (SSC), the hippocampus (HC) and the basal forebrain (BF) were accomplished using Fiji (ImageJ, NIH). Results: Preliminary results show that cortical microglia are affected by both: acute and chronic sleep disruption (Ncells =20, $P<0.005$, Nmice=8) in a way that does not equal the classical response to immune stimuli (Ncells =10, $P<0.005$, Nmice=4). Microglia in the basal forebrain and hippocampus are not affected by sleep disruption. **Conclusions:** Cortical microglia are differently affected by insufficient sleep than microglia in basal forebrain and hippocampus.

Maternal MTHFR rs1801131 polymorphism modifies the association between maternal prenatal folate levels and developmental delay in the offspring

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Background: Micronutrient folate is crucial in neural development. Folate metabolism is affected by genomic variation in methylenetetrahydrofolate reductase (MTHRF) gene. We set out to study the effects of prenatal maternal folate levels and genomic variation in the MTHFR on offspring developmental delay (DD), and whether candidate maternal single nucleotide polymorphisms (SNPs) modify the effect of folate on the risk of DD in the offspring. **Methods**: The mother-child dyads in this study (n1= 456, n2 = 415, n3= 184, n4 = 192) are part of the Prediction and Prevention of Pre-eclampsia and Intrauterine Growth Restriction (PREDO) -cohort. Folate levels were measured from the plasma maximum of three times during pregnancy. Maternal MTHFR SNPs (rs1801131, rs1801133, rs1999594) were genotyped with Illumina Global Screening Array. Developmental milestones were assessed by Ages and Stages Questionnaire Third edition (ASQ-3) completed by mothers between the years 2 to 5. **Results**: Maternal folate levels during pregnancy did not associate with the risk of DD in the offspring. Any C-alleles in the maternal rs1801131 associated with both higher folate levels during pregnancy in the mother and lower risk of DD in the offspring. Moreover, maternal rs1801131 modified the association between the early pregnancy folate levels and the risk of DD in the offspring (p-value for interaction < .05). With low early pregnancy folate levels, the risk of DD in the offspring was lower if mother carried any C-alleles compared to AA genotype. While CC genotype in the rs1801133 associated with higher folate levels during pregnancy in the mother, we found no associations between maternal rs1801133 or rs1999594 and the risk of DD in the offspring. **Conclusions**: The current findings suggest that C-alleles in the MTHFR SNP rs1801131 may protect early neurodevelopment in the offspring when maternal folate levels during pregnancy are low.

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