**Agarwal, Yash[a]; Matt, Stephanie[a]; Mompho, Krisna[a]; Runner, Kaitlyn[a]; Gaskill, Peter J[a]**

## *(1) Mediators of inflammation alter HIV latency and re-activation in a human microglial cell line*

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Despite antiretroviral therapy (ART), persistent HIV reservoirs in tissue resident immune cells, such as central nervous system (CNS) macrophages and microglia, remain a major barrier to curing HIV. Not only does the CNS reservoir shelter virus from ART, it also promotes HIV-associated neuroinflammation. Our laboratory has shown that dopamine, produced in response to all substances of misuse, can modulate HIV infection and immune function, suggesting that dopamine-inducing substances could influence the progression of HIV-associated neuropathology. We examined the *in vitro* effects of pro-inflammatory mediators, dopamine, and antiretroviral drugs on HIV latency in an immortalized microglial cell line, HC69, which is transduced with an HIV carrying a green fluorescent protein (GFP) reporter. Dopamine receptor expression was defined by quantitative PCR (qPCR), and viral reactivation was assessed by flow cytometry. In decreasing order, HC69 microglia expressed D2, D5, and D1 dopamine receptors, while D3 and D4 receptors were not detected. HC69 microglia treated with the antiretroviral combination BIKTARVY showed a lower proportion of GFP-positive cells. Treatment with Poly(I:C), which induces the production of pro-inflammatory mediators, resulted in increased proportion of GFP-positive cells, indicating HIV re-activation. Co-treatment with Poly(I:C) and dopamine slightly reduced in GFP-positive cells compared to Poly(I:C) treatment alone, although this was not significant. Although no studies have examined the role of dopamine receptors on HIV latency, these results are consistent with previous findings that higher levels of D2 receptors are associated with anti-inflammatory effects in microglia. Future studies will continue to evaluate the effects of physiological dopamine exposure and ART on inflammation and transcriptional regulation in microglia.

**Allgire, Emily[a,b,c]; McAlees, Jaclyn[d]; Ajmani, Anisha[a]; McCullumsmith, Robert[b]; Lewkowich, Ian[d]; Sah, Renu[a,b,c]**

## *(2) Airway inflammation and fear: dissecting interleukin 17a (IL17a) mechanisms*

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Genetic and epidemiological evidence suggests that asthma is linked to posttraumatic stress disorder (PTSD), a disorder of emotional memory. Further, this relationship is stronger in severe asthma, which is facilitated by a mixed T helper 2 (Th2)/T helper 17 (Th17) phenotype while mild/moderate asthma is Th2-specific. We have previously found compromised fear extinction in a model of severe asthma, as well as increased IL17a in the brain. Our objective was to delineate the mechanisms and specificity of severe asthma vs. mild/moderate asthma in extinction fear learning. To achieve this, we used Balb/c mice, which typically only develop a Th2 phenotype following chronic intratracheal treatment of aeroallergen House Dust Mite (HDM) extract. C5aR1 treatment concurrent with HDM shifts these mice into a severe Th2/Th17 phenotype. Thus, Th2 vs Th2/Th17 animals underwent contextual fear conditioning. We also explored Th2 vs Th2/Th17 paradigms via protein and RNA analyses across brain regions relevant to immune trafficking and extinction learning, subfornical organ (SFO) and medial prefrontal cortex (mPFC), respectively. We found that only mice that exhibited the Th2/Th17 phenotype, not Th2 alone, developed a fear extinction deficit. Additionally, bulk RNAseq revealed recruitment of pathways involved in chemotaxis, T-cell recruitment, and Th17 pathways. Finally, protein analysis confirmed IL17a-dependent changes in immune mediators in the SFO and mPFC. Collectively, these data suggest that Th17/IL17a is involved in fear extinction deficits related to airway inflammation. Overall, our work provides novel mechanistic information on how airway inflammatory mediators can modulate PTSD-relevant behavior and is highly relevant for understanding PTSD-asthma relationship.

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**Alsaleh, Ala[a]; Hamidreza, Jamalabadi[a]**

## *(3) State-space model of depression: A reductionist framework*

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Understanding the dynamical change in mental states of psychological disorders like major depression enables the development of better diagnostic and interventional methodologies. Here, based on an elaborate literature review on depression within the framework of network control theory, we develop a reductionist state-space model of depression symptoms and underlying neural networks that maps control inputs (e.g., a therapeutic intervention) into possibly desired outputs such as remission from depression. Specifically, we established a 4-node depression symptom network comprised of avoidance, Low levels of Positive Reinforcement (LPR), Cognitive Distortions (CD), and dysphoria, and a corresponding 3-node neural network comprised of Reward Network (RN), Cognitive Control Network (CCN), and Affective Network (AN). This conceptual framework suggests that intervening with an explorative controller on the avoidance node of the depression network could potentially hold mitigatory effects on the rest of the network symptoms. Details on node relations in the state-space representation, a coarse investigational paradigm using different exploratory and exploitatory behavioural ratios, and limitations are discussed.

**Carrol, Danielle[a]; Hoel, Rachel[a]; Zetterberg, Henrik[b]; Heslegrave, Amanda[c]; Bendlin, Barbara[a]; Davidson, Richard[a]; Busse, William[d]; Rosenkranz, Melissa[a]**

## *(4) Neuroinflammation in asthma: evidence from brain structural alterations*

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Chronic systemic inflammation is associated with neuroinflammation, which impacts cognition, emotion, and brain health. Asthma, a highly prevalent inflammatory disease of the airways, often has comorbid depression and anxiety, and may increase risks for dementia. Few studies have explored links between airway inflammation, neuroinflammation, and brain structure. Here, we examine regional brain structure in asthmatic participants and investigate interactions with a plasma marker of astrocyte reactivity and disease severity. T1-weighted magnetic resonance images (MRI) were acquired from asthmatic participants (n=128, 18-69 years). Plasma glial fibrillary acidic protein (GFAP), a marker of astrocyte reactivity, was measured at baseline. A composite asthma severity score comprised the Asthma Control Questionnaire, forced expiratory volume in one second, and medication burden. Volume, cortical thickness, or surface area associations with GFAP and asthma severity were examined in the hippocampus, insula, striatum, pallidum, thalamus, and nucleus accumbens, based on previous literature linking these structures with systemic inflammation. Higher plasma GFAP concentration was associated with reduced right insula surface area (p=0.01). Assessment of interactions between GFAP and asthma severity found that those with greater asthma severity had a stronger negative association between GFAP and left insula thickness (p=0.009). In contrast, higher concentration of plasma GFAP was associated with increased left thalamus volume (p=0.027).These results implicate astrocyte reactivity as a potential link between airway and central nervous system inflammation. While MRI cannot delineate cellular substrates underlying the opposite associations between GFAP concentration and volumetric measures in the insula versus thalamus, the differences could reflect the cellular organizations of these regions. The thalamus is among the structures with the highest glial density in the human brain, and volume increases may reflect glial influx or increased cell body size of activated glia, while changes in insula thickness may reflect neuronal cell loss or reduced dendritic arborizations due to neurotoxic effects of chronic neuroinflammation.

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**Dimitroff, Stephanie[a]; Würfel, Lisa[a]; Meier, Maria[a]; Faig, Kelly[b]; Benz, Annika[a]; Denk, Bernadette[a,c]; Bentele, Ulrike [a]; Unternaehrer, Eva[a,d]; Pruessner, Jens[a,c]**

## *(5) Prediction of antibody levels after COVD-19 vaccination: evidence for immune interoception*

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How protected is one against COVID-19 after vaccination? IgG antibodies are an important part of the artillery for the immune system's defense against the SARS-CoV-2 virus, and its levels are predictive of protection against infection. The amount of antibodies produced by some individuals is exponentially higher than by others. This difference represents important variance in the future susceptibility to COVID-19 infection. The current study was conducted to determine whether individuals were able to estimate how many antibodies they produced after their COVID-19 vaccinations. 166 participants (18-60 years old, 103 female) were recruited to the laboratory 14-60 days post-vaccination, and a blood sample was taken for analysis. Participants were asked to estimate on a scale from 0-10 how many antibodies they had produced, and were also asked how protected they felt from COVID-19 due to vaccination. Both self-predicted antibody levels ($r(162) = 0.17$, $p = 0.028$), and feelings of protection against COVID-19 ($r(162) = 0.20$, $p = 0.009$) were significantly related to their actual IgG spike antibody titers. Results from this study suggest that individuals are able to predict their IgG titers after COVID-19 vaccination. These results hold relevance in two domains. Firstly, they suggest individuals who sense they have low protection, probably do. Such information can help individuals make informed choices about self-protective behaviors. Secondly, results provide empirical evidence for the transmission of immune information through humoral pathways of interoception. These findings open the door for future work in the intriguing domain of immune interoception.

**Fleige, Leonie[a]; Wieber, Karolin[a]; Tsiami, Styliani[b]; Reinders, Jörg[c]; Braun, Jürgen[b]; Baraliakos, Xenofon[b]; Capellino, Silvia[a]**

## *(6) Influence of sex on the expression of dopamine receptor 1 pathway in B-cells as a potential influencing factor in rheumatoid arthritis*

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The neurotransmitter dopamine is suggested to regulate also the immune system but its concrete function is not clear. There is evidence that dopamine contributes to rheumatoid arthritis (RA) which occurs predominantly in women. However, the exact connection between dopamine, sex, and RA is poorly understood. For this study, 40/24 female/male healthy controls (HC) and 39/22 female/male RA patients were recruited. It was approved by the ethical committee and patients gave written consent. Basal expression of dopamine receptor 1 (DRD1) on B-cells and the amount of dopamine in peripheral blood mononuclear cells (PBMCs) were quantified via FACS and ELISA, respectively. Functional significance of dopaminergic activation was analyzed by B-cell specific DRD1 stimulation and cytokine quantification via ELISA. *In vitro* stimulation of sex hormone receptors (SHR) and subsequent DRD1 quantification was performed using "female" 721.221 and "male" JY B-cell lines. Higher DRD1 expression on B-cells ($p<0.001$) and dopamine levels in PBMCs ($p<0.05$) were found in RA women compared to HC; the opposite was observed in men with RA ($p<0.05$). Additionally, the profile of cytokines secreted was more pro-inflammatory for RA women and anti-inflammatory for RA men compared to HC. SHR stimulation resulted in

higher DRD1 expression on 721.221 ($p<0.01$) than on JY cells. Elevated DRD1 and dopamine levels in diseased women suggest that the dopaminergic pathway is overactivated in female RA patients. Together with changed cytokine levels, the DRD1 pathway seems to be pro-inflammatory in RA women and anti-inflammatory in RA men. The data point towards a regulation of the dopaminergic pathway by sex hormones, especially in women. However, the exact mechanism needs to be further investigated.

**Fuss, Anneke[a,b]; Tang, Stephan[a,b]; Culmsee, Carsten[a,b]**

## *(7) Drp1 knockout attenuates mitochondrial pathways of ferroptosis*

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Mitochondria are highly dynamic organelles that are essential in providing energy especially in neurons. A strict quality control system involving constant mitochondrial fusion and fission is necessary to recycle damaged mitochondria that are constantly exposed to reactive oxygen species and other harmful noxae. Mitochondrial fission is mediated by Fis1 and especially the GTPase Dynamin-related protein 1 (Drp1). Malfunction in this fusion and fission machinery and subsequent aberrant mitochondrial dynamics, integrity and function has been linked to neurodegenerative diseases but also cardiovascular diseases. Our previous data revealed excessive mitochondrial fragmentation and detrimental mitochondrial ROS formation in mouse hippocampal HT22 cells exposed to ferroptosis. In order to further elucidate the role of Drp1-mediated mitochondrial dynamics in ferroptosis, stable Drp1 CRISPR/Cas9 knockout (KO) cell lines were created. Analytical procedures for the determination of mitochondrial and metabolic parameters were performed. Mitochondria of Drp1 KO cells were significantly elongated, also showing reduced mitochondrial fragmentation after ferroptosis induction. Further, mitochondrial parameters such as mitochondrial membrane potential, mitochondrial ROS formation and mitochondrial respiration were rescued, and cell viability was enhanced in Drp1 KO cells exposed to Erastin and RSL3. Taken together, this study identified excessive mitochondrial fission mediated by Drp1 as a key process to execute cell death in ferroptosis. However, since the impact of Drp1 in mitochondrial pathways of ferroptosis has not yet been clarified, further research is required to understand related effects e.g. on antioxidant systems and proteome network regulation.

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**Gallucci, Georgina[a]; Imhoff, Matilde[a,b]; Diab, Magdalena[a]; Bongiovanni, Bettina[a]; Díaz, Ariana[a,b]; Santucci, Natalia[a,b]; Massa, Estefanía[a]; Derio, Marisa[a]; Bértola, Diego[b,c]; Bottasso, Oscar[a,b]; Baya, María, Luisa[b]; D'Attilio, Luciano[a,b]**

## *(8) Effect of circulating and local levels of cortisol on gene expression in mononuclear cells from patients with pulmonary or pleural tuberculosis*

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Tuberculosis (TB) constitutes one of the main global public health concerns. Its main manifestation is pulmonary TB (PTB), while pleural TB (PLTB) is the most common extrapulmonary form. Since the cellular immune response (IR) is essential for the containment and resolution of the pathology, PLTB is a natural model to study defensive mechanisms at the site of infection, and the ensuing endocrine response. We have previously shown that patients with PLTB have a greater inflammatory and cellular response in the pleural compartment (increased IL-1β, IL-6, and IFN-ɣ together with low cortisol levels) as compared to the systemic compartment. The aim of this study was to analyze by RT-qPCR the transcription profile of genes regulated by the Glucocorticoid Receptor (GR), such as ANXA1, GILZ, FKBP5, NFKBIA, NFKBIB, IL1-β, IL-6, and IFNɣ, in peripheral blood mononuclear cells (PBMC) from patients with PTB and PLTB, as well as from healthy controls (Co). We also examined the expression of these genes in pleural exudate cells (PEMC) from PLTB patients. TB and PLTB patients displayed increased mRNA levels of ANXA1, GILZ, and NFKBIA compared to values determined in PEMC and in cells from Co. No between-group differences in transcripts for FKBP5, NFkB1, and NFKBIB were observed. Within PTB patients, such increased expression was related to disease severity. mRNA levels of IL1-β were augmented in PBMC from PTB (vs. Co), whereas IL-6 and IFNɣ transcripts were elevated in PEMC (vs. PBMC). Collectively, PBMC from both groups of TB patients had an increased expression of GR-regulated anti-inflammatory genes with respect to Co and PEMC counterparts.

**Gebhardt, Kristina[a]; Reichel, Thomas[a]; Honekamp, Celine[b]; Nolte, Svenja[a]; Keck, Johannes[b]; Krüger, Britta[b]; Krüger, Karsten[a]**

## *(9) Different regulation of inflammation after a concentric and an eccentric running intervention*

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It is well known that exercise induces a systemic immune response. We tested if downhill running represents an experimental human model of systemic low-grade inflammation. 15 healthy male participants (age: 24 ± 4; VO2max: 52.6 ± 5.7 ml/min/kg) were recruited. In a randomized, cross-over design each participant performed a downhill (DR) (12% gradient) and a treadmill run on level (LR) for 45-minutes at an intensity of 70% of their individual VO2max. Intensity was controlled by adjusting the running speed via VO2. Received perception of exertion (RPE) and heart rate were recorded. Before and 3 hours after running, blood samples were taken to analyze leukocyte numbers and calculate inflammation indices. Plasma enzymes and cytokines were analyzed by LUMINEX assays. By nearly identical RPE (DR: 15 ± 1; LR: 15 ± 2), relative heart rate (DR: 159 ± 11 bpm, LR: 171 ± 11 bpm, $p < .001$), and oxygen uptake (DR: 81 ± 10 %; LR: 102 ± 7%; $p < .001$) were significant lower during DR whereas running speed was significant higher ($p < .001$). Both exercise tests were followed by a significant increase of the systemic-inflammation-index over time (DR: $p < .05$; LR: $p < .05$). Levels of myoglobin ($p < .05$), IL-6 ($p < .05$), and TNF-alpha ($p = .059$) were higher after DR. In conclusion, DR leads to a lower cardiovascular response but tends to induce a higher muscle damage following by a systemic pro-inflammatory environment. DR might be a suitable model for inducing low-grade inflammation without cardiovascular exhaustion.

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**González, Florencia B.[a]; Pacini, Antonella[a]; Villar, Silvina[a]; Leiva, Rodolfo[b]; Bottasso, Oscar[a]; Pérez, Ana Rosa[a]**

## *(10) Human chronic Chagas cardiomyopathy is associated to a disrupted activation of the hypothalamus-pituitary-adrenal axis and a systemic inflammatory state*

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[b] Cardiology Service, Chagas Section of the Centennial Provincial Hospital, Rosario, Argentina

Chronic Chagas cardiomyopathy (CCC) is a disease caused by *Trypanosoma cruzi*. CCC pathogenesis is not completely understood, but the balance between host immune response and parasite persistence seems crucial for its establishment and progression. Accordingly, we investigated the immuno-endocrine response in chagasic patients and their possible influence on CCC pathogenesis. CCC patients and T. cruzi-seronegative individuals were recruited. The concentration of cortisol, DHEA-S, TNF-alpha, IL-6, and adipocytokines was determined in serum. The expression of glucocorticoid receptors (GR-alpha is the functional receptor while GR-beta acts as an inhibitor of GR-alpha), 11beta-HSD1 (which regulates cortisol bioavailability) and genes regulated by cortisol and involved in the inflammatory response (IL-6, IFN-gamma, IL-1beta, and tristetraprolin) was evaluated by RT-qPCR in peripheral blood mononuclear cells (PBMCs). A systemic inflammatory state was evident (as judged by IL-6 and leptin levels) in CCC individuals paralleled by a disrupted activation of the hypothalamus-pituitary-adrenal axis, characterized by decreased DHEA-S and cortisol levels together with an unbalanced cortisol/DHEA-S ratio. RG-alpha expression in CCC patients did not differ from the control group, 11beta-HSD1 expression was increased in patients, and RG-beta expression was not detectable. mRNA levels of IL-6, IFN-gamma, and IL-1beta tended to increase in the CCC group, in presence of decreased tristetraprolin transcripts. Both tristetraprolin/IFN-gamma and tristetraprolin/IL-1beta ratios were decreased in CCC patients. The present results do not indicate a mechanism of cortisol resistance in PBMCs from CCC patients, but the adverse systemic endocrine milieu observed may favor the establishment of an immunometabolic pro-inflammatory state that promotes further myocardial tissue damage.

**Gotelli, Emanuele[a]; Cutolo, Maurizio[a]**

## *(11) SARS-CoV-2 infection, lung involvement and vitamin D-driven immune endocrine reactivity*

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Vitamin D is a hormone rather than a vitamin in the strict sense. In fact, the active form 1,25 dihydroxyvitamin $D_3$ [$1,25(OH)_2D_3$] exerts several effects on the inflammatory response of autoimmune rheumatic and infectious diseases. Low serum concentrations (less than 20 ng/ml) of 25-hydroxyvitamin $D_3$ [$25(OH)D_3$], the precursor of $1,25(OH)_2D_3$, are common in COVID-19 patients and are associated with an impairment of the innate (neutrophils, monocytes/macrophages, dendritic cells) and adaptive (T and B lymphocytes, antibodies production) immune responses. Respiratory parameters (partial pressure of arterial oxygen - $PaO_2$, partial pressure of arterial carbon dioxide - $PaCO_2$, pressure of arterial oxygen to fractional inspired oxygen concentration - $PaO_2/FiO_2$), radiological pulmonary involvement, and serum concentrations of $25(OH)D_3$ were evaluated in sixty-five hospitalized COVID-19 patients (mean age 76 ± 13 years) and sixty-five sex- and age-matched control subjects (CNT). COVID-19 patients showed significant lower $25(OH)D_3$ serum concentrations than CNT (median 8 ng/ml vs 16 ng/ml, p=0.001). $25(OH)D_3$ serum concentrations correlated positively with $PaO_2$ (p=0.03) and $PaO_2/FiO_2$ (p=0.02). Moreover, $25(OH)D_3$ serum concentrations were significantly lower in COVID-19 patients with diffuse/severe radiological lung involvement (p=0.05) or multiple lung consolidations (p=0.0001) than in those with mild radiological lung involvement. Finally, significantly lower $25(OH)D_3$ serum concentrations were found in COVID-19 patients who died during hospitalization, compared to those who survived (p=0.05). In conclusion, vitamin D deficiency is associated with a more severe lung involvement and a higher risk of death in old COVID-19 patients.

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## *(12) In-depth immunophenotyping of multiple cytokines reveals two subgroups of patients with immune-related depression*

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In the last years, it has been shown that a group of depressed patients has low grade inflammation. Recently, the concept of "immunometabolic depression" emerged, associating low grade inflammation with weight gain and hypersomnia. However, studies with deep phenotyping, an extensive cytokine panel and multiomic measurements to better characterize subgroups are missing. 224 probands from inhouse studies with a DSM-IV diagnosis were selected. A cytokine panel including 40 cytokines was measured in blood. The probands were clustered with High Dimensional Supervised Classification (HDclassif) based on the cytokine data. A four-cluster solution reveals two groups with immune-related depression patterns. The first group is the one with the highest median CRP level (6.7 mg/L). It has a higher average Beck Depression Inventory (BDI-II) score compared to the group with the lowest CRP level (p=.004) as well as a higher average BMI (p=.009) compared to all other groups. This group also reported increased sleep and food-intake in the single BDI-II items compared to the other groups (n.s.), in line with the immunometabolic depression. The second inflamed group (median CRP of 4.9 mg/L) does not show significantly higher BDI-II sum scores than the other groups. It reveals a different pattern of immune cell counts compared to the other groups (n.s.), decreased sleep according to the BDI-II (n.s.), a lower polygenic risk score for sleep duration (p=.019) and high levels of vascular endothelial growth factor (VEGF)-A, VEGF-C, CC chemokine ligand 17 and IL-7. Our results replicate the finding of an immunometabolic subgroup and allow the characterization of an additional immune-depression subtype with a VEGF signature and a trend to decreased sleep.

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**Hansson, Lina S.[a,b,c]; Lasselin, Julie [a,b,c]; Tognetti, Arnaud[b]; Axelsson, John[a,b]; Olsson, Mats J.[b]; Sundelin, Tina [a,b]; Lekander, Mats [a,b,c]**

## *(13) Pointing out sickness: detection of sickness from biological motion*

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The ability to detect sick individuals is crucial for survival, by allowing avoidance of contagion. We have shown that humans can detect sick individuals from facial cues and body odors, but perception of these cues requires close proximity to the infectious person. Given that gait patterns can be detected from a distance and are altered during sickness, it would be beneficial to detect sickness from biological motion. We collected videos and point-light displays of walking individuals who were either made sick experimentally with an injection of lipopolysaccharide, or who were healthy (placebo). In study 1, 106 naive subjects watched these displays and rated them as coming from someone sick or healthy. In study 2, 106 other subjects rated health, sadness, and tiredness of the displays on a visual analogue scale. In study 1, the sensitivity was 59% for videos and 57% for point-light displays, while the specificity was 74% for videos and 61% for point-light displays. In study 2, sick walkers were rated as having worse health compared to the same walkers when healthy, both in videos and point-light displays. This study indicates that sickness can be detected from biological motion, possibly adding to immune defensive behaviors by facilitating avoidance of contagious peers.

**Hedley, Kateleen E.[a,b]; Vanka, Swaroop[b,c]; Carroll, Olivia R.[a,b]; Horvat, Jay C.[a,b]; Tadros, Melissa A.[a,b]**

## *(14) Neonatal respiratory infection shows sex-specific long-term effects in both the lungs and brainstem*

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Evidence indicates that altered respiratory physiology, as a result of airway or lung inflammation, is partially dependent on changes within brainstem circuits driving respiration. Little is known about the development of these circuits and the role of early life events in disrupting normal developmental trajectory. To address this, we investigated the effects of a well-established model of early life respiratory infection on the lung and brainstem. Neonatal Balb/c mice were infected within 24-hours of birth with either Chlamydia muridarum (CMU) or sham-infected. At 6-weeks old, lung function was performed and the mice were then sacrificed. Following this, brainstems were dissected and processed for Iba1 immunoreactivity, to identify microglia. The dorsal motor nucleus of the vagus (DMV), a driver of respiration, was isolated and run through a custom MATLAB script for microglia tracing. CMU-infected mice had significantly reduced gas diffusion compared to sham-infected controls. Interestingly, infected female mice had more pronounced reductions in gas diffusion than males. Microglia in the DMV showed that infected mice had a significant increase in cell number and soma area, and a significant decrease in cell branching and cell radius compared to sham-infected mice. These differences were only observed in females. We show that significant changes in lung physiology following early life lung infection are associated with significant sex-dependent changes in microglia responses within respiratory brainstem circuits. This model represents an ideal tool for assessing whether changes in microglia and other neurobiological responses in the brainstem following early life infection can drive life-long modifications of the respiratory system and its central control.

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**Hernandez, Jessica[a]; Schäffer, Julia[b]; Herden, Christiane[c]; Pflieger, Fabian[a]; Kitagawa, Hiromo[d]; Welter, Joelle[a]; Culmsee, Carsten[e]; Sommer, Natascha[b]; Hecker, Matthias[b]; Mayer, Konstatin[f]; Rummel, Christoph[a]**

## *(15) n-3 fatty acids modulate LPS-induced local lung inflammation and the lung-brain axis in wild type versus Fat-1 mice genetically modified for leukotriene B4 receptor 1 or chemerin receptor 23 knock-out.*

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Emerging evidence has shown a level of communication between the lung and brain, where inflammation in the lung can influence immune reactivity in the brain. Additionally, omega 3 (n-3) fatty acids (FA) and their lipid mediator derivative resolvin E1 (RvE1) have demonstrated anti-inflammatory properties. Interestingly, since systemic inflammatory insults can exacerbate ongoing brain pathologies via immune cell trafficking, modulation of leukocyte trafficking might be a contributor to the therapeutic potential of n-3 FA. Here, we aimed at investigating the role of n-3 FA and RvE1 on brain inflammation and immune-to-brain communication via neutrophil granulocytes (NG) during local lung inflammation (LLI) in wild type (WT) and Fat-1 mice, which endogenously produce n-3 FAs, with combined knockouts (KO) for one of two RvE1 receptors (LTB4R or ChemR23). LLI was achieved by intra-tracheal instillation of LPS (10 µg/mouse), while brains and tissues were collected to characterize differences between groups as well as potential beneficial effects of n-3 FA and RvE1. Immunohistochemical analysis of the Organum vasculosum lamina terminalis (OVLT) and bifurcation (BIF) revealed minor effects of LTB4R and ChemR23 as well as Fat-1 on NG recruitment to the brain and expression of the inflammatory transcription factor NF-IL6. Moreover, analysis of lung, liver, and hypothalamus showed alterations in inflammatory marker profiles between groups. Overall, our data suggest that n-3 FA and RvE1 can alter the pro-inflammatory response and brain reactivity while NG are involved in transferring inflammatory information from the lung to the brain to potentially alter brain function during LLI.

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## *(16) Brain functional changes associated with asthma-related outcomes following mindfulness training*

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Psychological distress can negatively impact asthma control, airway inflammation, and treatment efficacy. Interventions targeting emotion reactivity and regulation, such as Mindfulness-Based Stress Reduction (MBSR), have shown benefit in improving asthma control. Brain networks involved in emotion-processing have been linked to both mindfulness and asthma-related immune modulation; however, whether regions within these networks mediate the impact of MBSR on disease-related outcomes is unknown. Adults with asthma were randomized to an 8-week MBSR training (n = 35) or wait-list control group (n = 34). At baseline, immediately post-intervention, and 4 months post-intervention, we collected clinically-relevant asthma and psychological outcomes, and functional magnetic resonance imaging to assess neural responses to emotionally-salient cues. Mindfulness training decreased amygdala and lateral prefrontal cortex responses to emotionally-salient cues relative to wait-list controls, which was correlated with MBSR-related increased mindfulness. Additionally, increased anterior cingulate cortex response was associated with MBSR-related asthma control improvements and decreased depressive symptoms, but also with decreased mindfulness and increased distress over time. For both groups, reduced insula responses to emotionally-salient cues correlated with decreased distress and inflammation. In asthmatic adults, MBSR training changed neural responses to emotionally-salient cues, which was associated with increased mindfulness and asthma control. This suggests that mindfulness training alters emotion reactivity and regulation in neural responses to salient cues, which predicts symptom improvements. In all participants, decreased neural responses in emotion-relevant regions correlated with reduced distress and inflammation, advancing understandings of the complex neural mechanisms linking emotion and asthma. Overall, our results highlight the importance of targeting mind-body relationships in asthma treatment.

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## *(17) Increased MMP-9 gene expression did not reflect in BDNF higher translation after six-weeks of aerobic training in obese young men*

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Aerobic exercise training is a non-pharmacological effective intervention to impose an anti-inflammatory profile that improves the immunometabolic disorders arising from obesity. However, few studies have shown how aerobic training impacts on brain-derived neurotrophic factor (BDNF) pathway in immunological cells, such as lymphocytes, which can be altered in individuals with obesity. This study aimed at verifying the impact of short-term aerobic training on transcription of proteins related to the BDNF pathway and BDNF translation in lymphocytes from obese men. Eight obese young men (~26.00 years; BMI ~33.20 kg/m2) were assessed pre- and post- six weeks of aerobic training (3x/week; 300Kcal/session; walk or run). Lymphocytes were separated from blood samples and stimulated with Concanavalin A (ConA), or ConA plus recombinant BDNF (ConA+BDNF). The supernatant and pellets of lymphocyte cultures were collected after 48h to evaluate

cytokine concentrations by ELISA, BDNF, NFkB, Furin, MMP-9, tPA, p75 and Sotilin gene expression by PCR Real Time, and intracellular BDNF by ELISA, respectively. After six weeks of aerobic training, there were no significant effects on IL-2, IL-4, IFN-gamma cytokines, BDNF, NFkB, furin, tPA and p75 gene expression, neither BDNF intracellular. MMP-9 ($F(1,7)=6.034$, p-value= 0.044) and sortilin ($F(1,7)=10.370$, p-value= 0.015) gene expression was increased after the training period (six-weeks) as compared to baseline. These results indicate that short-term aerobic training did not impact cytokine release, transcription and translation of BDNF, although the gene expression of the cleavage protein MMP-9 was increased in lymphocytes from obese men after training.

**Ivanovska, Mariya[a,b]; Murdjeva, Marianna[a,b]**

## *(18) Distress, immunological reactivity, and dopamine levels in physicians*

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Psycho-emotional distress, psychological overvoltage, conflicts, and extreme and prolonged work under stress conditions affect the immune system. The aim of this study was to investigate immunological reactivity and dopamine levels in physicians working under chronic stress. The study included 27 physicians working under chronic stress conditions (emergency units, intensive care clinics) compared with a control group (n=29). Informed consent was obtained and a questionnaire evaluating the stress (PSS-14) was performed. The absolute number and percentage of immune cells (T, B, and NK cells), humoral immune factors (IgG, IgM, IgA), serum cortisol, plasma noradrenaline, and dopamine levels were determined by flow cytometry, nephelometry, chemiluminescence, and ELISA. According to Cohen's PSS-14, doctors were under stress (34.70 ± 5.21 points). The correlation between the concentrations of hormones (dopamine and norepinephrine) and immune cellular factors showed that dopamine has a specific effect on the concentration of total B cells and NK cells, as there is a weak, negative correlation for total B cells (r= -0.238, p= 0.046) and strong, negative dependence for NK cells (r= -0.440, p= 0.001). Plasma noradrenaline levels were significantly increased (2017.06 ± 935.41 pg/ml) compared to the control group. There is a statistically significant negative correlation between cortisol and noradrenaline concentrations ($p<0.05$). The results showed that a small proportion of physicians working under chronic stress conditions had cellular and humoral immunity imbalances. As dopamine increases, it reflects to immunosuppression of total B-cell and NK-cell concentrations, possibly by binding to dopaminergic receptors located on the surface of immune cells. Increased plasma noradrenaline levels can be the main indicative parameter for chronic stress.

**Keller, Judith K.[a]; Wülfing, Clemens[b]; Wahl, Jannes[a]; Diekhof, Esther K.[a]**

## *(19) Disease-related disgust promotes antibody release in human saliva*

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The behavioral immune system (BIS) comprises mechanisms that aim at avoiding pathogens even before the organism is exposed to them. Thus, activation of the BIS may reduce the necessity to activate the physiological immune system (PIS). Previous studies that found evidence for interactions between these two systems were correlative and have not been replicated. Further, none of them examined whether disease stimuli indicating an enhanced airborne transmission risk may trigger a different response in comparison to stimuli evoking core disgust. In this study, we employed a video-priming

approach to get insight into the influence of disgust- and disease-related stimuli on the changes of secretory immunoglobulin A (S-IgA) in saliva. We created three video primers that varied in their contagion risk and disgust-evoking potential. A landscape video acted as control. We expected a higher S-IgA response in the videos indicating a heightened airborne contagion risk than in the core disgust video. We analyzed data of 107 participants in a between-subjects design and found a significant increase of S-IgA in response to both disease- and disgust-related videos (but no significant difference between the videos), which correlated positively with the perceived contagion risk of the situations. We also found that the increase in S-IgA concentration inversely correlates with the trait contamination disgust, which is a hint for a compensating relationship between the BIS and PIS. Our data show that visual perception of videos showing realistic, contagious situations, elicits a heightened release of salivary antibodies, readying the immune defense even before actual pathogen contact has been made.

**Kular, Lara[a]; Klose, Dennis[a]; Needhamsen, Maria[a]; Ringh, Mikael[a]; Hagemann-Jensen, Michael[b]; Jagodic, Maja[a]**

## *(20) Biological ageing of lung bronchoalveolar cells in multiple sclerosis*

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Multiple Sclerosis (MS) is a chronic autoimmune, demyelinating, and neurodegenerative disease of the central nervous system that affects young and middle-aged adults, predominantly women, and translates into various symptoms including fatigue, cognitive impairment, sensory and motor dysfunction. Although the exact cause of MS is unknown, a compelling body of evidence has implied cigarette smoking, and lung inflammation in general, in MS susceptibility and progression. However, the precise mechanisms underpinning such effect remain elusive. In this study, we investigated biological ageing of lung bronchoalveolar (BAL) cells in relation to MS disease and smoking. We exploited the potential of eight DNA methylation-based epigenetic clocks to estimate biological ageing using methylome data previously generated in BAL cells of female smoker and non-smoker MS patients (n=15) and healthy controls (n=22) with Illumina Infinium EPIC arrays. We found that both the predictive performance and the resulting age acceleration measures greatly vary depending on the epigenetic clock, particularly between pan-tissue and blood-based epigenetic clocks. Results from pan-tissue clocks revealed significant ageing differences between MS patients and controls and in relation to smoking, which withstand correction for potential confounders. Correlation of ageing predictions with gene expression may help decipher the biological processes captured by the clocks. Thus, our preliminary findings provide novel insights into the lung-related mechanisms underlying MS immunopathogenesis by supporting a link between MS, smoking, and biological ageing of BAL cells. Because epigenetic modifications are reversible by nature, this opens possibilities to alter biological ageing in MS via targeted epigenome editing.

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**Lara-Espinosa, Jacqueline V.[a]; Mata-Espinosa, Dulce[a]; Barrios-Payán, Jorge[a]; Hernández-Pando, Rogelio[a]**

## *(21) Experimental Pulmonary Tuberculosis in the Absence of Brain Infection Induces Neuroinflammation and Behavioural Abnormalities*

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Tuberculosis (TB) is a chronic infectious disease in which prolonged, non-resolutive inflammation of the lung may lead to metabolic and neuroendocrine dysfunction. Previous studies have reported that individuals coursing pulmonary TB experience cognitive or behavioral changes; however, the pathogenic substrate of such manifestations has remained unknown. Here, using a mouse model of progressive pulmonary TB, we report that, even in the absence of brain infection, TB is associated with marked increased synthesis of both inflammatory and anti-inflammatory cytokines in discrete brain areas such as the hypothalamus, the hippocampal formation and cerebellum accompanied by substantial changes in the synthesis of neurotransmitters. Moreover, histopathological findings of neurodegeneration and neuronal death were found as infection progressed with activation of p38, JNK and reduction of BDNF levels. Finally, we perform behavioral analysis in infected mice throughout the infection, and our data show that the cytokine and neurochemical changes were associated with a marked onset of cognitive impairment as well as depressive- and anxiety-like behavior. Altogether, our results suggest that besides pulmonary damage, TB is accompanied by an extensive neuroinflammatory and neurodegenerative state that explains some of the neuropsychiatric abnormalities found in TB patients.

**Laubacher, Claire[a,b]; Davidson, Richard[a,c]; Rosenkranz, Melissa[a,c]**

## *(22) Resting State Functional Connectivity Changes Associated with Mindfulness-Based Stress Reduction Intervention in Patients with Asthma*

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Clinical trials show that Mindfulness-Based Stress Reduction (MBSR) improves asthma control, but the neural mechanisms underlying these effects are unknown. In healthy adults, MBSR modulates brain activity in regions that regulate attention towards emotionally relevant cues called the salience network (SAL). In patients with asthma, SAL activity contributes to lung inflammation in response to psychosocial stress. Thus, modulating SAL function may contribute to the clinical benefit of MBSR for asthma patients. This is the first randomized clinical trial in adults with asthma to examine the impact of 8 weeks of MBSR (n=24) compared to a waitlist control group (n=22) and associated changes in inflammatory biomarkers on resting state functional connectivity. Changes in functional connectivity were calculated by generating whole brain maps from key SAL seed regions (anterior insula, dorsal anterior cingulate (dACC), bilateral amygdala). The MBSR group showed greater increases in functional connectivity between the insula seed and dACC relative to the waitlist group. Improvements in asthma symptom control correlated with increased functional connectivity between the dACC seed and the left dorsal lateral prefrontal cortex, an important area for emotion regulation. However, decreases in asthma-related biomarkers were related to decreased functional connectivity with SAL seeds. The results suggest that the benefits of MBSR for asthma relate to increased resting SAL coherence and improved emotion regulation, but the neural correlates may be distinct from the correlates of inflammatory biomarker changes. This increases the evidence that MBSR may be most useful for augmenting asthma management in patients with dysfunctional emotion regulation .

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**Liljebo, Therese[a,b]; Jonsjö, Martin[c] ; Andreasson, Anna[b,d]**

## *(23) Comparison of energy- and macronutrient intake in patient with Myalgic encephalomyelitis/Chronic fatigue syndrome and healthy controls -a pilot study*

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Myalgic Encephalomyelitis/Chronic fatigue syndrome (ME/CFS) is a chronic disabling disorder. The pathophysiology is still unknown but we hypothesized that poor dietary intake of energy and macronutrients may contribute to the persistent fatigue in these patients. We compared energy and macronutrient intake from calculated 3-day food diaries from 18 patients with ME/CFS participating in a longitudinal study on persistent fatigue and 117 healthy individuals from the general Swedish population. Patients with ME/CFS had a significantly lower energy intake (mean 1670 kcal/day) than healthy individuals (mean 1934 kcal/day), p=0.04 (one sided t-test) and eight patients with ME/CFS had an energy intake below their estimated basal metabolic rate. This was due to a lower intake of proteins (65 g and 76 g, respectively, p=0.03) and carbohydrates (180 g and 210 g, respectively, p=0.03) while no difference was seen in fat intake (70 g versus 75 g, p=0.24). Patients with ME/CFS had a significantly higher fluid intake (2280 ml versus 1640 ml, p<0.001). No differences were seen in energy percent (E%; the proportion of energy in food that derives from protein, fat, and carbohydrate) between patients with ME/CFS and controls: 16 versus 17 fat E% (p=0.8), 34 versus 36 protein E% (p=0.3) and 47 E% from carbohydrates in both groups (p=0.9). In conclusion, the patients with ME/CFS reported a lower energy intake than healthy individuals from the general Swedish population, and had a lower intake of proteins and carbohydrates. Further studies on a larger patient population are needed to further compare dietary patterns and micronutrient intake between patients with ME/CFS and healthy individuals.

**Louie, Allison Y.[a]; Drnevich, Jenny[b]; Steelman, Andrew J.[c,d,e]**

## *(24) Influenza infection suppresses myelin transcripts during remyelination in the cuprizone mouse model*

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A hallmark feature of multiple sclerosis is the partial but incomplete regeneration of myelin following inflammatory demyelination. We previously found that influenza infection downregulated genes associated with myelination in an otherwise healthy adult mouse. Here, we hypothesized that infection would induce alterations to oligodendrocyte-specific transcripts during remyelination. C57BL/6J mice were fed 0.2% cuprizone diet for 5 weeks and inoculated at 4.5 weeks with saline or influenza A virus. Brains were harvested, bisected, and immediately frozen at time points corresponding to complete demyelination and partial remyelination. Sagittal sections were placed on slides containing spatially-barcoded oligonucleotide probes in a 6.5 x 6.5 mm area. Tissues were fixed and permeabilized on the slide, and cDNA libraries were synthesized from captured RNA, resulting in spatially-resolved brain transcriptomes of mice from four conditions (n=3): Normal (control diet), Demyelinated (complete demyelination), Saline (saline-inoculated, partial remyelination), and Flu

(influenza-inoculated, partial remyelination). Analysis resulted in eight clusters corresponding to specific brain regions of which we have identified hypothalamus, cortex, corpus callosum/fornix, thalamus, hippocampus, habenula, and choroid plexus. Within the corpus callosum/fornix, differentially expressed genes ($q < 0.05$) associated with the ontology terms immune system process and inflammatory response were increased in Demyelinated mice compared to Normal mice, whereas genes involved in myelination and cholesterol metabolic process were decreased. Genes associated with the terms myelination, tissue regeneration and oligodendrocyte development were increased in the corpus callosum/fornix of Saline mice undergoing remyelination compared to the Demyelinated group. However, genes involved in lipid metabolic process and myelination were decreased in Flu mice compared to Saline mice. These data confirm our previous findings that influenza infection affects oligodendrocyte homeostasis and suggest that infection impedes remyelination at the transcriptional level.

**Madison, Annelise A.[a]; Burd, Christin E.[b]; Andridge, Rebecca[c]; Wilson, Stephanie J.[d]; Bailey, Michael T.[e]; Malarkey, William[f]; Kiecolt-Glaser, Janice K.[g]**

## *(25) Lower gut microbiota complexity predicts accelerated T cell aging in healthy adults*

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[g] Department of Psychiatry and Behavioral Health, OSU, USA

Depressed individuals are at risk for accelerated immunological aging and reduced gut microbiota complexity (diversity and richness). Here we aim at investigating links between depressive symptoms, gut microbiota complexity, and T cell aging, and whether any observed effect depends on chronological age. Ninety healthy adults (aged 21-73) had blood drawn to assess markers of T cell aging (P16, ARF, B3GAT1, KLRG1) as well as DNA methylation. We calculated a T cell aging index and used the Horvath algorithm to calculate DNA methylation. Participants also reported their depressive symptoms on the Center for Epidemiological Studies-Depression Scale and collected a stool sample. The V4 region of the 16S rRNA gene was sequenced to derive the Shannon and Simpson diversity indices, and total count of observed operational taxonomic units (richness). Models controlled for BMI, comorbidities, sex, dietary quality, smoking status, physical activity, and sleep quality. Depressive symptoms were unrelated to T cell aging or DNA methylation ($p>.53$). Chronological age interacted with gut microbiota richness ($p=.033$), such that individuals with lower richness had a stronger positive relationship between chronological age and T cell age, and older individuals with lower microbiota richness had higher T cell ages. There were other notable trends: lower Shannon diversity ($p=.050$) and richness ($p=.071$) marginally tracked with higher Horvath DNAm ages. Gut microbiota complexity may correspond with the rate of T cell aging, especially in mid-to-late life. This study is the first to show this relationship among humans, and it warrants further experimental work.

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**Michels, Susanne[a,b]; Picard, Felix[c]; Braun, Moria[d]; Kisko, Theresa[d]; Schwarting, Rainer[b,d]; Wöhr, Markus[b,d,e,f]; Garn, Holger[c]; Culmsee, Carsten[a,b]**

## *(26) Effects of the psychiatric risk gene Cacna1c on neuroinflammatory responses in microglia*

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Psychiatric disorders such as major depression, bipolar disorder, schizophrenia, and autism are highly prevalent chronic diseases. However, their underlying pathophysiology is still largely unknown. Genomic studies have identified single nucleotide polymorphisms in the CACNA1C gene that are robustly associated with all of these major psychoses. Furthermore, immune alterations and the involvement of their primary mediators in the brain, the microglia, have also been reported for psychiatric disorders. In the present study, we investigated the effects of modified Cacna1c gene expression as well as pharmacological L-type calcium channel (LTCC) blockade on neuroinflammatory responses upon Lipopolysaccharide (LPS) stimulation in primary microglia cultures. The microglial cells were obtained from neonatal Cacna1c haploinsufficient Sprague Dawley rats and their wildtype littermates. LPS-triggered morphological alterations were studied in real-time via electrical impedance readout. Cellular bioenergetics were assessed using a XFe96-Analyzer. Nitric oxide (NO) and pro-inflammatory cytokine release were determined in the culture supernatants. In response to the pro-inflammatory stimulus LPS, primary microglial cells change their morphology from spindle-shaped to ameboid-like structures and we observed that the LPS-induced cell expansion was less pronounced in the heterozygous Cacna1c microglia. Moreover, both Cacna1c haploinsufficiency and treatment with the LTCC blocker nimodipine were associated with reduced glycolytic metabolism as well as diminished release of NO, IL-1 beta, IL-6, and TNF-$\alpha$ upon LPS stimulation. Overall, these results suggest that the psychiatric risk gene CACNA1C plays a significant role in the immune-metabolic activation of microglia, thereby adding to a better understanding of the neurobiological processes likely involved in the pathophysiology of CACNA1C-associated disorders.

**Monroe, Sarah[a,b]; Bilbo, Staci D.[a,c,d]**

## *(27) Neuroimmune response to respiratory infection via the vagus nerve*

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Society faces increasing incidence of respiratory immune challenge including air pollution and novel respiratory virus. Understanding the impact of lung health on the brain is critical to anticipating shifts in the health needs of our changing society. Respiratory viral infection with influenza A strain PR8 causes local inflammation as well as a neuroinflammatory response in hippocampal neurons and microglia. Pulmonary neuroendocrine cells (PNECs) secrete mediators during respiratory challenge, recruiting immune cells to lung tissue. However, it is unknown whether PNEC signaling contributes to

the microglial response to influenza A infection. Interestingly, PNECs are innervated by neurons of the vagus nerve, sending afferent information to the brain. This project investigates potential rapid immune signaling mechanisms from PNECs to microglia through the vagus nerve during influenza A infection. Analysis of lung tissue by RT-qPCR indicated cytokine upregulation 72 hours post infection (hpi) with influenza A virus but not at 24 hpi. Region-specific analysis of cFos positive neurons from matched animals showed that several brain regions had altered neuronal activity at 24 hpi, prior to detection of an inflammatory response in lung tissue. By reactivating influenza infection responsive neurons, it is possible to examine whether this neural activity drives microglial changes. Future experiments will directly manipulate PNECs to determine the necessity of their signaling in early timepoint microglial response to influenza A infection.

**Müller, Jana[a]; Ebinger, Arnt[b]; Nobach, Daniel[a]; Höper, Dirk[c]; Pfaff, Florian[c]; Herden, Christiane[a]**

## *(28) Transcriptome analysis in a natural reservoir host of zoonotic Bornavirus infection: first insights into differentially regulated genes in the central nervous system*

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Borna Disease Virus-1 (BoDV-1, family *Bornaviridae*) is a neurotropic and zoonotic RNA virus. Typically, fatal neurological disease with severe non-purulent meningoencephalitis is seen in accidentally BoDV-1 infected spill-over hosts, like horses and humans. To date, more than 35 lethal human cases were reported and curative therapy is not available yet. The bicolored, white-toothed shrew, *Crocidura leucodon*, is currently the only known natural reservoir of BoDV-1. Conversely to dead-end hosts, *C. leucodon* displays neither clinical symptoms nor histological lesions despite widespread viral persistence in the central nervous system and nearly all organ systems. Numerous bornavirus-host interactions, such as modulation of neuronal functions or interaction with the interferon system, have already been described experimentally in dead-end host species. Currently, there are no *in vivo* or *in vitro* data in the reservoir species. Hence, RNA sequencing and differential gene expression analysis was performed on brain tissue of naturally persistently BoDV-1 infected and non-infected captive-bred *C. leucodon*. As reference-based transcriptome analysis was not possible, *de novo* assembly was performed. Expression of viral transcripts, the majority of reads from the N gene, and thus, persistent infection, was confirmed and few genes were shown to be differentially expressed in initial analyses. RT-PCR and Sanger sequencing was pursued to confirm selected genes and to establish RT-qPCRs for validation. Interpretation of differential gene expression of sampled *in vivo* tissue is challenging, but preliminary data on potentially differentially regulated genes possibly associated with the reservoir status was gained and methods are refined for further studies with this species.

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**Pott, Hendrik[a]; Gaffron, Swetlana[b]; Vogelmeier, Claus F.[c,d]; Schmeck, Bernd[a,d]**

## *(29) Psychological conditions associate with patient subgroups in chronic inflammatory lung disease*

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[d] Member of the German Center for Lung Research (DZL)

Chronic obstructive pulmonary disease (COPD) is a leading cause of death worldwide. Treatment is complicated by a considerable range of comorbidities, among them psychiatric comorbidities including depression, which gravely affects individual prognosis, success of smoking cessation programs, and healthcare utilization. In this study we investigated 1,377 patients from the German longitudinal, multi-center COSYCONET-cohort by means of self-organizing maps (SOM), in which data-points are ordered based on their similarity using a machine learning algorithm (Viscovery SOMine 7.2, Viscovery Software Gmbh). We included clinical data assessed at baseline and 4.5 years of follow-up (V5). Depression was assessed by completion of the patient's health questionnaire (PHQ-9). We generated a 13-cluster SOM for COSYCONET-patients. Patients were segregated by having died or dropped for clinical worsening within follow-up. Patients who completed the last visit after 4.5 years were ordered by decline of lung function parameters (FEV1 % predicted), increase of self-reported symptoms (SGRQ-score), and acute worsenings (exacerbation grade) during the last year (0 = no exacerbation, 1 = exacerbation not requiring hospital admission, 2 = exacerbation requiring hospital admission). We found a significantly higher mean PHQ-9 Score and a significantly higher percentage of patients with a diagnosis of depression in cluster C6 (which consisted of patients with an exacerbation grade of two, who curiously improved in FEV1 and SGRQ). FEV1 and/or SGRQ deterioration solely were not significantly associated with either PHQ-9 score or a diagnosis of depression. Further studies are required to delineate the crosstalk between pulmonary inflammation and depression.

**Pradhan, Sahar H.[a]; Gibb, Matthew[b]; Kramer, Alec T.[a]; Sayes, Christie M.[a]**

## *(30) Inhalation of combustion products leads to systemic neuroinflammation*

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Combustion-derived air pollution is a multi-layered environmental toxin that is becoming a global health concern due to rapid urbanization in the United States. These pollutants contain mixtures of pro-inflammatory stimulants such as fine particulate matter (PM<2.5), gases, and metals. Inhalation of these compounds are linked to systemic inflammation through the peripheral circulatory system from respiration. Systemic circulation of these stimulants can cause reactive mechanisms that implicate the central nervous system. Chronic respiration of these pollutants can lead to prolonged neuroinflammation and eventual degenerative damage. This specific study looks at an *in vitro* model of an inhalation exposure to diesel particulate matter (DPM) on alveolar macrophages and collecting the post-exposure serum to induce activation of microglia. U-937 macrophages were incubated with DPM for acute exposure and the expression of MCP-1, IL-8, IL-6, and TNF-α was evaluated. Post-exposure serum was collected from the activated macrophages, added to a healthy culture of microglial (HMC-3) over 48-hours, and tested for activation (HLA-DR, TLR-4 and CD-14). Lipopolysaccharide (LPS; 10 ng/mL) was used as a positive control to stimulate activation. Generation of ROS and cytokine expression was measured. Macrophages indicated active inflammation via MCP-1 and significant expression of IL-8, IL-6, and TNF-α. Post-exposure serum indicated elevated ROS and moderate expression of cytokines. CD-14 expression indicated that indirect exposure to pollutants is a potent cell activator and HLA-DR expression confirmed activation of microglia. This *in vitro* model of microglia activation implicates peripheral pathway exposure as a potent and more specific method to induce systemic neuroinflammation versus a direct exposure to the microglia.

**Privitera, Lucia[a,b]; Morè, Lorenzo[a,c] ; Arthur, Simon J[d] ; Frenguelli, Bruno G[a]**

## *(31) Mitogen- and Stress-activated protein Kinase-1 as a gatekeeper of experience-induced expansion of the dynamic range of the synapses*

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Environmental enrichment (EE), through a combination of physical, cognitive, and social stimulation, enhances synaptic plasticity. However, the mechanisms underlying this enhancement remain to be elucidated, but likely involve BDNF. We have shown that mice carrying an inactivating kinase-dead (KD) mutation of the BDNF-activated enzyme MSK1 failed to show an enhancement of miniature excitatory post synaptic currents (mEPSCs) in response to EE and a blunted increase in the density of dendritic spines. We subsequently investigated whether EE also influenced hippocampal synaptic plasticity in an MSK1-dependent manner. Wild-type (WT) and MSK1 KD mice were kept in standard housing conditions (SH) or in EE from birth to 2.5-5 months of age. Field excitatory postsynaptic potentials (fEPSPs) were recorded in the CA1 region of hippocampal slices for the measurement of basal synaptic transmission, paired-pulse facilitation (PPF), long-term potentiation (LTP) and long- term depression (LTD). We show that MSK1 is required for the full extent of experience-induced expansion of the dynamic range of synapses, demonstrated by the enhancement of both LTP and LTD. Positive experiences promote brain development and support learning and memory and resistance to mood disorders such as anxiety. While this has been known for many years, our observations reveal how this may occur. Using male mice with a mutation in MSK1, we show that MSK1 is necessary for molecular mechanisms underlying the changes associated with experience, extending the range over which the communication between neurons occurs, and for both the persistence of memory and the ability to learn new task rules.

**Rendina, Danielle[a]; Smith, Caroline[a]; Kingsbury, Marcy[a]; Keziah, Virginia[a]; Nguyen, Dang[a]; Bilbo, Staci D.[a]**

## *(32) Prenatal environmental stressors induce social deficits and alter gut cytoarchitecture, microbiome, and immune landscape*

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Gastrointestinal (GI) dysfunction is prevalent in individuals with neurodevelopmental disorders, such as autism spectrum disorder (ASD). Prenatal exposure to air pollution is known to impact gut function and its microbiome and has been implicated in the etiology of ASD. The mechanisms by which air pollution alters the development of the gut-brain axis and contributes to ASD pathogenesis are unknown. However, research suggests that modification of macrophage (Mϕ) populations in the gut wall may act as an intermediary. Using a mouse model that combines exposure to diesel exhaust particles (DEP) and maternal stress (MS) during gestation, we induce ASD-like behavior deficits in juvenile male, but not female, offspring, recapitulating the male-bias in ASD. Juvenile DEP/MS-exposed males were found to have alterations in the cytoarchitecture of the small intestine and gut microbiome composition. Interestingly, our data indicate that DEP/MS-induced shifts in the gut microbiome are not inherited from the mother and may be preceded by changes in gut structure. Thus, we are currently working to test the hypothesis that DEP/MS impacts Mϕ phagocytosis of apoptotic intestinal cells, thereby impacting the cytoarchitecture and microbial colonization of the gut, and indirectly contributing to DEP/MS-induced gut dysfunction, microbiome dysbiosis, and behavior deficits. Our preliminary data indicate that during

the postnatal period, when the gut microbiome is highly labile, DEP/MS-exposed male offspring do exhibit alterations in developmental patterns of Mϕ gene expression localized to the small intestine, suggesting modification of the abundance or phenotype of intestinal Mϕ populations. These findings are intriguing as our lab has previously reported that DEP/MS diminishes phagocytic capacity in microglia, a population of brain resident Mϕ. Moreover, despite no evidence of shifts in gut motility, the small and large intestines are heavier and longer in juvenile offspring exposed to DEP/MS, which may impact other gut functions such as nutrient absorption. This research will advance understanding of the role of the enteric immune system in the developmental organization of the gut-brain axis.

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## *(33) Exploring changes in the brain microenvironment caused by systemic hypoxia*

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Chronic lung diseases are common in humans and can lead to systemic hypoxia. Importantly, the central nervous system is particularly sensitive to acute chronic respiratory insufficiency. In this study, we aim at detecting systemic hypoxia-induced changes in the brain microenvironment using a model of pulmonary hypertension (PH) and analyze the activity of the hypoxia-inducible factor (HIF) pathway in different brain regions, focusing on the brain stem and the hippocampus. Further, we aim at uncovering whether these alterations are connected to inflammatory pathways and sensitive to treatment with anti-inflammatory omega-3 fatty acids. BL6/J mice were exposed to 10% oxygen for 28 days or kept at normoxia. At the endpoint of the experiment, pimonidazole (hypoxyprobe), a standard immunohistochemical hypoxia marker to detect hypoxia *in vivo*, was injected prior to cardiac perfusion. Lung, liver, spleen, brain, and plasma were collected approximately 10 min after perfusion. Tissues were fixed with formalin and paraffin-embedded for immunostaining, and additional lung, liver, and spleen fresh frozen samples were prepared for immunostaining and RNA analyses. The hypoxyprobe staining for detecting hypoxic regions with <10 mmHg partial oxygen tension was validated on liver sections. HIF1α and CAIX immunostaining protocols are being developed to more comprehensively monitor HIF-pathway activation in the brain samples. Our preliminary results show that the mapping of HIF-pathway activation is feasible with the proposed approach. In conclusion, our work provides the basis for an extended characterization of hypoxia and inflammatory pathway crosstalk in the lung-brain axis and its effect on brain function in a mouse model of chronic lung disease.

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## *(34) The therapeutic potential of Resolvin E1 in pulmonary hypertension*

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Pulmonary hypertension (PH) is characterized by pulmonary vascular remodeling, which is promoted by perivascular inflammatory cell infiltration and leads to right heart insufficiency. Resolvin E1 (5S,12R,18R-trihydroxyeicosapentaenoic acid; RvE1), derived from omega-3 fatty acid (n-3 FA), is a pro-resolving lipid mediator and has also been suggested to inhibit proliferation of pulmonary arterial smooth muscle cells (PASMC). PH was either initiated by exposure of wildtype (WT) and transgenic fat-1 mice (which generate n-3 FA from omega-6 FA) to hypoxia or by injection of WT rats with monocrotaline (MCT). WT rodents were treated with RvE1, its precursor 18-hydroxyeicosapentaenoic acid (18-HEPE) or placebo after induction of PH. Development of PH was quantified by echocardiography, hemodynamic *in vivo* measurements and histological analysis. Proliferation of mouse and human PASMC was determined by BrdU incorporation and hypoxic pulmonary vasoconstriction (HPV) was measured in isolated, ventilated, and perfused mouse lungs. WT mice exposed to hypoxia and treated with RvE1 or 18-HEPE showed significantly lower right ventricular systolic pressure (RVSP) and pulmonary vascular remodeling compared to placebo treated mice, while fat-1 mice only showed attenuated RVSP. Rats injected with MCT and treated with RvE1 also showed reduced RVSP, better right heart function, and less CD68+ cell infiltration. RvE1 treatment did not affect HPV of isolated mouse lungs or proliferation of murine PASMC but inhibited in human cells of patients with PH, macrophage-induced enhancement of PASMC proliferation. Therapeutic treatment with RvE1 (and its precursor 18-HEPE) attenuated PH in different rodent models, most probably by affecting inflammatory cell infiltration. Further studies to investigate the underlying protective mechanism of RvE1 in PH and the contribution of perivascular inflammation need to be performed.

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## *(35) The role of wounding in stress-induced glucocorticoid resistance*

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Clinical data indicate that some severely traumatized patients on intensive care develop resistance to immunosuppressive glucocorticoids (GCs), resulting in an overshooting inflammatory response, uncontrollable sepsis and, consequently, multi-organ failure (MOF). The underlying mechanisms are not yet understood. However, as preclinical data from our group indicate that chronic psychosocial stress promotes development of splenic functional in vitro GC resistance when accompanied by significant bite wounds or surgery-induced wounding, it is likely that a history of chronic psychosocial stress in physically traumatized patients on intensive care predisposes them for development of GC resistance and subsequent MOF. The aim of this study is to employ the chronic subordinate colony housing (CSC) paradigm, a preclinical mouse model for chronic psychosocial stress, to investigate the interplay between psychosocial stress and wounding in the development

of GC resistance. CSC is based on chronic subordination (20 days) of four male mice towards a dominant male conspecific and has been shown earlier to cause general and social anxiety, hyperactivity, spontaneous colitis, and an aggravated dextran-sulphate-sodium (DSS)-induced colitis compared with single-housed control (SHC) mice. CSC exposure, if accompanied by significant bite wounding, is further associated with increased percentages of activated and GC insensitive CD11b+ cells in the spleen as well as splenomegaly. However, first results from the present study indicate that CSC in combination with an experimental skin excisional wound did not promote functional splenic GC resistance in the absence of bite wounds. Future studies will address whether laparotomy prior to CSC is able to cause GC resistance.

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## *(36) Emotional States Explain Cellular Immune System Activity Under Real-Life Conditions: A Multivariate Time-Series Analysis Approach*

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The relation between emotional states and immune activity is characterized by bidirectional influences that lead to strong dynamic interdependencies. We argue that these psycho-immunological interdependencies cannot be investigated by a nomothetic research approach that assumes relative between-subject homogeneity and time-invariance. Instead, an idiographic approach is required that can properly handle within- and between-subject variability. In this integrative single-case study, a 27-year-old healthy woman collected her entire urine over a period of 63 days in 12-h intervals (8 a.m.–8 p.m., 8 p.m.–8 a.m.), resulting in a total of 126 consecutive measurements. In addition, the subject completed a questionnaire on emotional states (EWL-60-S) each morning and evening. To determine levels of cellular immune activity, neopterin/creatinine concentrations were measured in the urine samples (HPLC). The dynamic relations between the time series of the six emotional states (mental energy levels, general lethargy, extraversion/introversion, well-being, irritation, anxiousness/depressiveness) and urinary neopterin levels were estimated in a vector autoregressive model and evaluated using granger-causality tests, forecast error variance decomposition, and impulse response functions. Emotional states were found to explain 33.24% of the variance in neopterin/creatinine levels, whereby most of the effects were manifested for a period of three days. The strongest predictor of neopterin variance was anxiousness/depressiveness (13%), followed by extraversion and mental activity (7% each). Specifically, rises in anxiousness/depressiveness and extraversion led to increases in urinary neopterin levels, while mental activity led to decreases in neopterin. These results highlight the reactive nature of the immune system and the importance of psychosocial (environmental) influences.

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## *(37) Influenza infection promotes relapse and exacerbates CNS pathology in a murine model of relapsing-remitting multiple sclerosis*

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Multiple sclerosis (MS) is an inflammatory demyelinating disease of the CNS, where respiratory viral infections increase the risk of relapse. Influenza infection is one of the pathogens associated with this phenomenon. We previously found that influenza-A virus triggered disease in myelin-specific T cell receptor transgenic mice. However, whether influenza infection can cause relapse in mice undergoing relapsing experimental autoimmune encephalomyelitis (R-EAE), an animal model of MS, is not known. R-EAE was induced by immunizing SJL/JCrHsd mice with PLP139-151. At the peak of disease, mice were randomized into treatment groups, and two days later inoculated with saline or mouse-adapted human influenza-A virus. Weights and scores were recorded daily. Mice were euthanized either at relapse or 40 days post immunization. Histopathological analysis of luxol fast blue/periodic acid-Schiff stained sections from brains and spinal cords was performed. Inflammatory foci were defined as a cluster of at least 5 cells while inflammatory area was manually traced using Image J. Analysis of the brain was performed in the cerebellum, hippocampus, midbrain, medulla, pons, diencephalon, corpus callosum, cortex, olfactory bulb/cortex, and ventricles. In the spinal cord thoracic, lumbar and sacral sections were analyzed. Finally, serum neurofilament light chain (NfL) levels were measured by ELISA. Infection increased the number of relapses and exacerbated disease. Infection increased inflammation in the cerebellum, hippocampus, diencephalon, corpus callosum and cortex at both time-points, in the subependymal zone during relapse, and in the midbrain, 3rd ventricle, and lateral ventricle at day 40. In the spinal cord, infection increased inflammation in the grey matter only at the relapse time-point. Infection did not alter serum NfL levels at the relapse time-point but tended to increase levels at the end time-point ($p=0.057$). Influenza infection promoted relapse in mice with R-EAE and appeared to trigger inflammation in a region-specific manner within the CNS.

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## *(38) Neuronal plasticity of vagal sensory neurons in allergic inflammation*

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Recurrent activation of vagal sensory neurons and second order neurons of the solitary tract induces neuronal plasticity and subsequently contributes to altered reflexes. In patients with airway inflammation, this is associated with e.g. cough and airway constriction. In previous transcriptome studies, we were able to detect TLR4 receptor and MyD88 expression as well as the functional relevant expression of several cytokine receptors in vagal sensory neurons. Since airway infections can induce exacerbation of an existing airway inflammation in asthma, the aim of our study is to elucidate the cellular mechanisms of pathogen-induced neuronal alterations in sensory neurons during allergic airway inflammation. Even though validation of the transcriptome data by single-cell RT-PCR studies has not been fully completed, we performed homo- and heterologous challenges of primary vagal sensory neurons by (co-) incubation with LPS and Th2 cytokines, Contrary to our expectation, our preliminary data demonstrate that in contrast to IL-3 and IL-5, the Th2 cytokines IL-4 and IL-13 decrease the percentage of jugular C-fiber neurons responsive to cinnamaldehyde, a TRPA1 agonist. The number of cells analyzed

until now is too low to draw a final conclusion about a possible modulatory effect of LPS. The first experiments studying the effects on axonal outgrowth and $Ca^{2+}$-influx are being analyzed at present.

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## *(39) Effects of G-protein-coupled receptor 55 (GPR55) on neuroinflammation and depression*

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Anti-neuroinflammatory treatment has gained importance in the search for pharmacological treatments of different neurological and psychiatric diseases. Clinical studies demonstrate a reduction of the mentioned diseases; symptoms after administration of anti-inflammatory drugs. G-protein-coupled receptor 55 (GPR55) is an orphan G-protein-coupled receptor highly expressed in the central nervous system (CNS), but also in peripheral tissues. Expression of GPR55 has been demonstrated in areas of the brain involved in mood, cognition, and perception, like the medial orbitofrontal cortex, prefrontal cortex, and hippocampus. However, the anti-inflammatory effects mediated by GPR55 need to be further investigated. We intend to study the expression of GPR55 in IL-1beta-treated SK-N-SH cells, the effects of antagonists/agonists of GPR55 on inflammatory mediators and signaling molecules in IL-1beta stimulated SK-N-SH cells and LPS-stimulated microglia. For our preliminary study, the synthesized antagonist of GPR55 significantly inhibited release of different cytokines and chemokines (such as Interleukin-1β (IL1 β) and tumor necrosis factor-α (TNF-α) in BV2 microglia (LPS-induced) and in human neuronal SK-N-SH cells (IL1 β induced), and had effects on the COX-2/PGE2 pathway. We hypothesize that GPR55 plays an important role in neuroinflammation involved in the pathophysiology of depression and that targeting GPR55 might be a novel and innovative therapeutic approach for the treatment of depression.

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## *(40) Sex differences in the effect of social isolation on brain circuits and neuroendocrine-immune status in rats*

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Social isolation (SI) is a risk factor for malignancy, morbidity, and mortality, and is associated with immune suppression, accelerated cancer progression, and neuroendocrine perturbations. Here we investigated the effects of SI on genes expression in the Nucleus Accumbens (NAc), the Bed Nucleus of the Stria Terminalis (BNST), and on peripheral neuroendocrine immune responses. Female and male Fischer-344 rats, 4-6 months-old, were assigned to control versus six weeks SI. Brain and plasma samples were collected. Relative expression levels of oxytocin receptor (OXTR), corticotropin-releasing factor receptor 1 (CRFR1), corticotropin-releasing factor-binding protein (CRF-BP), serotonin/5-HT receptor (5-HTRa1), and dopamine receptor (D1R) genes were assessed. Plasma levels of corticosterone (CORT), IL-6, and TNFα were quantified by ELISA. In the NAc, SI females showed increased levels of OXTR and 5HTR mRNAs (p=0.02; p=0.01, respectively), whereas SI males showed decreased levels of 5HTR (p=0.03) and increased levels of D1R mRNAs (p=0.04). In the BNST, female rats showed a significant increase of CRFR1 (p=0.001) and a marginal increase in CRFBP (p=0.07) expression, whereas males showed no significant differences. In the periphery, both sexes exhibited higher levels of plasma IL-6 in isolated rats (p=0.03). Plasma TNFα levels were significantly higher (p=0.002) in isolated females, but significantly lower (p=0.006) in isolated males, and CORT levels were significantly increased only in isolated females (p=0.004). SI affected expression of key genes related to social neurocircuits in the NAc and the BNST. SI also altered peripheral cytokines and CORT levels. These neuronal and immune alterations were sex-dependent, and associated with a pro-inflammatory state in females. Our ongoing studies address the influence of social environment on neuro-immune pathways.

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## *(41) Alterations of pericapillary microglia in psychiatric patients who committed suicide*

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The role of microglia in neuropsychiatric disorders is an area of research that has become increasingly important in recent years. Microglia interactions with neurons, glial cells, and the blood-brain-barrier are thought to be part of the pathophysiology of psychiatric diseases. Previous postmortem studies revealed preliminary evidence of microglial activation in a subset of patients with schizophrenic and affective disorders and microglial activation (increased numerical density of HLA-DR expressing cells) as has been reported in patients who had committed suicide. Using a digital image machine learning-based analysis method, we differentiate between microglia (TMEM-119-positive) and capillaries (Factor-VIII-positive) in double-labelled human postmortem brain sections, identify microglia in the pericapillary corridor, and explore the changes in ramification of pericapillary microglia. The study was carried out in three cohorts: patients with psychiatric disorders who committed suicide, patients with psychiatric disorders who died from natural causes, and a control group without a history of neuropsychiatric diseases. Preliminary results already revealed that pericapillary microglia in the subgenual anterior cingulate cortex compared to microglia remote from the capillaries shows significantly higher (p=0.005) ramification parameters in the group of patients who committed suicide compared to patients who died from natural causes and healthy controls. These findings suggest that pericapillary microglia is altered in patients who committed suicide, but it remains unclear whether this activation is influenced by the severity of the underlying psychiatric illness or an independent neurobiology of suicidality. This question remains a topic for future research.

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## *(42) Olfaction and prejudice: a disease avoidance perspective*

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Research has shown that disease avoidance and odor-induced disgust are related to prejudice. Although this relation might seem surprising at first, it fits well with the disease avoidance theoretical framework that emphasizes psychological mechanisms - attitudes and behaviors - to recognize and evade pathogen threats, often by evoking disgust. Disease avoidance plays a main role in olfaction. Body odors are universal elicitors of disgust, and their quality changes with sickness. I will present overall evidence from two experimental and two survey studies. We used Bayesian modeling and parameter estimation in the experimental studies, and structural equation modeling (SEM) in survey studies. Three of the four studies were preregistered. We investigate the relation between disgust sensitivity to body odors prejudice (Study 1 and 2), and replicate the effect in 9 countries across all continents (Study 3). Lastly, we look at the relation between the self-reported body odor disgust and perception of real odors. Higher disgust sensitivity to body odors was related to higher levels of prejudice The standardized estimates for the relation was similar in all studies (Study 1: 0.16, 95% posterior credibility interval (PCI)=[0.08, 0.24], Study 2: 0.15, 95% PCI=[0.07, 0.23], Study 3: 0.19, 95% confidence interval=[0.16, 0.21]). This effect generalizes to different cultures and geographical locations. Moreover, individuals with higher body odor disgust

sensitivity (BODS) perceive smells as more highly valenced overall: unpleasant smells (potential cues of disease) were rated as more unpleasant (by -0.14 standard deviation, 94% PCI = [-0.23,-0.6]), and pleasant smells (potential cues of health and hygiene) were rated as more pleasant (by 0.15 standard deviation, 94% PCI = [0.09,0.21]), suggesting that disgust sensitivity is involved in both avoidance and approach reactions to olfactory cues. There is a link between olfactory disgust and prejudice, which can be explained by disease avoidance behaviors.