14th GEBIN Conference 2022
and AKNEI-DGFI Satellite Meeting

Final Program

Conference Schedule

	Tuesday, 29.03.2022	Wednesday, 30.03.2022	Thursday, 31.03.2022	Friday, 01.04.2022
09:00		GEBIN	Keynote 2	Keynote 3
09:15		Educational	Prof. Dr. Carsten Watzl	Prof. Dr. Luciana Besedovsky
09:30		Short	Chair: Eva M. J. Peters	Chair: Tanja Lange
09:45		Course		
10:00			Paper Session 3	Paper Session 5
10:15		Prof. Dr.		
10:30		Adriana del Rey	PAIN	PERIPHERY
10:45			Chair: Ulrike Gimsa	Chair: Rainer Straub
11:00				
11:15				
11:30			Paper Session 4	Closing Ceremony & Awards
11:45				
12:00			INFLAMMATION	
12:15			Chair: Christoph Rummel	
12:30				
12:45				
13:00	GEBIN	Lunch Break	Lunch Break	
13:15	Educational			
13:30	Short		(Steering Committee Meeting)	
13:45	Course			
14:00		Welcome and Opening		
14:15	Prof. Dr.	Keynote 1	GEBIN Outreach	
14:30	Adriana del Rey	Chair: Judith Alferink		
14:45		Prof. Dr. Josef Priller		
15:00				
15:15		Paper Session 1		
15:30			Poster Session	
15:45		PSYCHIATRY		
16:00		Chair: Harald Engler		
16:15				
16:30				
16:45		Paper Session 2		
17:00				
17:15		STRESS		
17:30		Chair: Silvia Capellino		
17:45				
18:00				

Tuesday, 29.03.2022

13:00 to 18:00 Educational Short Course
Adriana del Rey

Wednesday, 30.03.2022

09:00 to 13:00 Educational Short Course
Adriana del Rey

14:00 **Welcome and Opening**
Chairs: Nicolas Rohleder, Silvia Capellino, Harald Engler

14:15 to 15:00 **Keynote 1: Josef Priller "CNS immune reactions to neuropsychiatric diseases"**
Chair: Judith Alferink

15:15 to 16:30 **Paper Session 1 "Psychiatry"**
Chair: Harald Engler

11	Chemokine Receptor 4 Expression on Blood T Lymphocytes Predicts Severity of Major Depressive Disorder	Freff, Jana; Beins, Eva; Bröker, Lisa; Schwarte, Kathrin; Leite Dantas, Rafael; Maj, Carlo; Arolt, Volker; Dannlowski, Udo; Nöthen, Markus M.; Baune, Bernhard T.; Forstne...
44	Efficacy of sertraline versus celecoxib in Major depressive disorder: Macrophage migration inhibitory factor for patient stratification	Simon, Maria Susanne; Burger, Bianka; Weidinger, Elif; Arteaga-Henríquez, Gara; Zill, Peter; Musil, Richard; Drexhage, Hemmo; Müller, Norbert
12	Altered mitochondrial immunometabolism in major depressive disorder	Gamradt, Stefanie; Hasselmann, Helge; Taenzer, Aline; Brasanac, Jelena; Stiglbauer, Victoria; Sattler, Arne; Sejitz-Hermstein, Max; Kierszniowska, Sylwia; Ramien...
6	The steroid hormone dehydroepiandrosterone (DHEA) counteracts the consequences of psychological trauma on immunocellular ageing and mitochondrial bioenergetics	de Punder, Karin; Salinas-Manrique, Juan; Kolassa, Iris-Tatjana; Dietrich, Detlef E; Karabatsiakis, Alexander
19	Investigating the effects of antidepressive treatment on mitochondrial bioenergetic functioning and mitochondrial density in peripheral blood mononuclear cells	Karabatsiakis, Alexander; Woike, Kathrin; de Punder, Karin; Behnke, Alexander; Kolassa, Iris; Schönfeldt-Lecuona, Carlos; Kiefer, Markus; Sim, Eun-Jin

16:45 to 18:00 **Paper Session 2 "Stress"**
Chair: Silvia Capellino

14	Early-life maternal deprivation affects the coping behavior and neuroendocrine development of domestic pigs	Gimsa, Ulrike; Brückmann, Roberto; Tuchscherer, Margret; Tuchscherer, Armin; Kanitz, Ellen
25	Longitudinal and intergenerational effects of childhood maltreatment on leukocyte telomere length of mother-newborn dyads	Mavioglu, R. Nehir; Behnke, Alexander; Matits, Lynn; Mack, Matthias; Kolassa, Iris-Tatjana
1	Mental and physical health in informal caregiving and associations with relationship quality between caregiver and care recipient – a pilot study	Becker, Linda; Pendergrass, Anna; Gräßel, Elmar; Rohleder, Nicolas
23	Investigating the immunoregulatory potential of Mycobacterium vaccae (ATCC 15483) and closely related rapid-growing Mycobacteria species	Langgartner, Dominik; Noschka, Reiner; Mazzari, Giulia; Braun, Tirza; Kempter, Elena; Lowry, Christopher A.; Strauss, Gudrun; Stenger, Steffen; Reber, Stefan O.
9	The burden of overweight: Higher body mass index, but not vital exhaustion, is associated with higher DNA damage and lower DNA repair capacity	Fieres, Judy; Fischer, Marvin; Sauter, Christine; Moreno-Villanueva, Maria; Bürkle, Alexander; Wirtz, Petra H.
35	The cholinergic system takes center stage in the skin´s response to stress: Chrna7 at the switch between pro- and anti-inflammatory responses in allergic inflammation	Rommel, Frank Risto; Tumala, Susanne; Ertle, Christoph; Peters, Eva Milena Johanne

Thursday, 31.03.2022

09:00 to 13:00 **AKNEI-DGFI Satellite Meeting**

09:00 to 09:45 **Keynote 2: Carsten Watzl "What COVID-19 Vaccinations can teach us about the immune system"**
Chair: Eva Peters

10:00 to 11:15 **Paper Session 3 "Pain"**
Chair: Ulrike Gimsa

24	Pain research in a petri dish? Neuro-glial primary cell cultures of the rat dorsal root ganglia to study effects of inflammation on nociceptive signaling in vitro and ex vivo	Leisengang, Stephan; Nürnberger, Franz; Roth, Joachim
29	Altered Brain Structure in Chronic Visceral Pain: Specific Differences in Gray Matter Volume and Associations With Visceral Symptoms and Chronic Stress	Öhlmann, Hanna; Koenen, Laura Ricarda; Labrenz, Franziska; Engler, Harald; Theysohn, Nina; Langhorst, Jost; Elsenbruch, Sigrid
42	Pain and Inflammation in rheumatic diseases	Seifert, Olga; Baerwald, Christoph
20	Relationship between baseline pro-inflammatory cytokine levels and psychological inflexibility during behavioral treatment for chronic pain	Karshikoff, Bianka; Åström, Jenny; Kemani, Mike K.; Lekander, Mats; Holmström, Linda; Wicksell, Rikard K.
41	Impact of Fatigue on Rheumatic Diseases	Seifert, Olga; Baerwald, Christoph

11:30 to 13:00 **Paper Session 4 "Inflammation"**
Chair: Christoph Rummel

30	Effects of acute inflammation on the acquisition and extinction of conditioned visceral pain-related fear in healthy humans	Pawlik, Robert Jan; Petrakova, Liubov; Cueillette, Alexandra; Krawczyk, Katharina; Theysohn, Nina; Elsenbruch, Sigrid; Engler, Harald
39	Effects of anti-inflammatory drug treatment on psychological and bodily sickness symptoms during experimental endotoxemia: A randomized controlled study in healthy volunteers	Schmidt, Justine; Reinold, Johanna; Witzke, Oliver; Schedlowski, Manfred; Engler, Harald; Benson, Sven
33	A role for n3 fatty acids in the modulation of LPS-induced fever or hypothermia: combined lipidomics in a multimodal pathway analysis of brain lipid mediators	Pflieger, Fabian Johannes; Garikapati, Vannuruswamy; Bhandari, Dhaka Ram; Bredehöft, Janne; Peek, Verena; Roeb, Elke; Roderfeld, Martin; Hernandez, Jessica; Schulz
8	Temporal dynamics of cytokine changes in blood, cerebrospinal fluid and brain tissue of endotoxemic rats	Dombrowski, Kirsten; Trautmann, Lisa; Schedlowski, Manfred; Barthel, Lennart; Hetze, Susann; Engler, Harald
48	The effect of LPS and ketoprofen on stress and immune responses, central monoamines and social behaviour in pigs	Veit, Christina; Janczak, Andrew M.; Ranheim, Birgit; Vas, Judit; Foister, Simone; Sali, Virpi; Valros, Anna; Sandercock, Dale A.; Nordgreen, Janicke
47	Baseline and inflammation-induced state fatigue impact motivated behavior in the context of a SARS-CoV-2 vaccination model	Stolz, David Sören; Luebber, Finn; Lange, Tanja; Lasselin, Julie; Ziemann, Malte; Riemekasten, Gabriela; Rupp, Jan; Krach, Sören; Paulus, Frieder Michel

13:00 to 14:15 Lunch Break
(**GEBIN Steering Committee Meeting**)

14:15 to 15:15 **GEBIN Outreach Session**

Rainer Straub: Neuroimmunomodulation (NIM) – A Journal for the People of GEBIN

Christoph Rummel: European Psychoneuroimmunology Network (EPN)

Eva M. J. Peters: Arbeitskreis NeuroEndokrinoImmunologie (AKNEI) der Deutschen Gesellschaft für Immunologie

15:30 to 18:00 **Poster Session**
(see poster abstracts below)

Friday, 01.04.2022

09:00 to 9:45 **Keynote 3: Luciana Besedovsky "Why sleeping in is not a waste of time: on the importance of sleep for our immune system"**
Chair: Tanja Lange

10:00 to 11:15 **Paper Session 5 "Periphery / Catecholamines"**
Chair: Rainer Straub

34	Adrenaline, noradrenaline, and cortisol alter immune cell numbers and promote innate immune functionality of domestic pigs in an intravenous infusion model	Reiske, Lena; Schmucker, Sonja; Pfaffinger, Birgit; Weiler, Ulrike; Steuber, Julia; Stefanski, Volker
28	Regulation of Natural Killer Cell Functions by Catecholamines	Obholzer, Martin; Claus, Maren; Wingert, Sabine; Klaschik, Nicole; Hennes, Elisabeth; Capellino, Silvia; Watzl, Carsten
22	Alpha-adrenergic receptors in individuals with primary Raynaud's phenomenon	Lange, Tanja; Frahm, Catharina; Lübber, Finn; Grasshoff, Hanna; Hackel, Alexander; Klapa, Sebastian; Müller, Antje; Kerstein-Stähle, Anja; Heidecke, Harald; Riemekasten...
40	Dopamine affects bone formation in arthritis patients	Schwendich, Elena; Salinas Tejedor, Laura; Rickert, Markus; Steinmeyer, Jürgen; Rehart, Stefan; Reinders, Jörg; Neumann, Elena; Müller-Ladner, Ulf; Capellino, Silvia
10	Dopamine receptor 1 pathway as a potential proinflammatory factor in female patients with rheumatoid arthritis	Fleige, Leonie; Wieber, Karolin; Tsiami, Styliani; Reinders, Jörg; Braun, Jürgen; Baraliakos, Xenofon; Capellino, Silvia

11:30 to 12:30 **Closing Ceremony & Awards**
Chairs: Nicolas Rohleder, Silvia Capellino, Harald Engler

Posters

43	Influence of Real-Life Psychosocial Stressors on Immune System Dynamics: A Time Series Analysis Approach	Seizer, Lennart; Fritsche, Kurt; Burbaum, Christina; Chamson, Emil; Fuchs, Dietmar; Bliem, Harald R.; Schubert, Christian
7	Prediction of Antibody Levels After COVD-19 Vaccination: Evidence for Immune Interoception	Dimitroff, Stephanie; Würfel, Lisa; Meier, Maria; Faig, Kelly; Benz, Annika; Denk, Bernadette; Bentele, Ulrike; Unternaehrer, Eva; Pruessner, Jens
37	From Chronic Stress to Systemic Inflammation to Cortical Thickness: Pathways in Healthy, Mid-aged Adults?	Schaefer, Julia Katharina; Puhlmann, Lara; Valk, Sofie; Singer, Tania; Engert, Veronika
26	How to induce chronic psychosocial stress and reliably measure social deficits in female mice	Mazzari, Giulia; Langgartner, Dominik; Reber, Stefan O.
38	Sex-specific effects of early life adversity in combination or not with chronic psychosocial stress during adulthood on physiological parameters in C57BL/6N mice	Schiele, Jessica; Mazzari, Giulia; Langgartner, Dominik; Reber, Stefan O.
21	The MDSC – a key player in glucocorticoid resistance following combined physical and psychosocial trauma	Kempter, Elena; Amoroso, Mattia; Kustermann, Monika; Scheurer, Jasmin; Lupu, Ludmila; Baumann, Bernd; Straub, Rainer H.; Strauß, Gudrun; Huber-Lang, Markus; Langgartner...
17	Taste-Immune Conditioning with Fingolimod (FTY720) as Unconditioned Stimulus	Jakobs, Marie; Hörbelt-Grünheidt, Tina; Salem, Yasmin; Hadamitzky, Martin; Schedlowski, Manfred; Heiß-Lückemann, Laura
4	Immune age correlates with cardiorespiratory fitness, but not with general intelligence	Bröde, Peter; Claus, Maren; Genç, Erhan; Digutsch, Jan; Capellino, Silvia; Gajewski, Patrick D.; Getzmann, Stephan; Golka, Klaus; Hengstler, Jan G.; Nitsche, Michael...
15	Beta2-adrenergic receptor expression and signaling is profoundly changed in B lymphocytes during collagen-induced arthritis	Honke, Nadine; Wiest, Clemens; Pongratz, Georg
16	The regulatory function of TLR9-activated B cells is improved by endogenously produced catecholamines	Honke, Nadine; Pongratz, Georg
32	The role of estrous cycle induced cytokine expression on neuroinflammation in NF-kB p50 knock out mice and its impact on learning and behavior	Petrou, Christina Konstantina; Kobald, Sven Oliver; Getzmann, Stephan; Capellino, Silvia
5	Investigation of the relationship between Immune Age and Vaccination against SARS-CoV-2	Claus, Maren; Bröde, Peter; Urlaub, Doris; Wolfsdorff, Natalie; Watzl, Carsten
27	Systemic and local adipokines in rheumatoid arthritis and osteoarthritis mouse models	Neumann, Elena; Sauermilch, Hani Manfred; Hülser, Marie-Lisa; Luo, Yubin; Bozec, Aline; Schett, Georg; Müller-Ladner, Ulf
18	Adherence and beliefs about medication in patients with rheumatoid arthritis	Jugel, Corinna; Baerwald, Christoph; Seifert, Olga
13	Biological and psychological stress responses after miscarriage: Cross-sectional results from the MALT randomized controlled trial.	Gerber, Luis; Braun, Alexandra; Müller, Markus; Rohleder, Nicolas; Stein, Barbara; Radermacher, Peter; Waller, Christiane
3	Characterisation of circulating dendritic cells in major depressive disorder	Boller, Anna-Lena; Freff, Jana; Schwarte, Kathrin; Leite Dantas, Rafael; Arolt, Volker; Dannlowski, Udo; Baune, Bernhard T.; Scheu, Stefanie; Alferink, Judith
45	The alpha7 nicotinic acetylcholine receptor – a protective factor against endothelial to mesenchymal transition (EMT) in fibrosis?	Stegemann, Agatha; Pethö, Zoltan; Schwab, Albrecht; Raker, Verena; Steinbrink, Kerstin; Böhm, Markus
46	Fibroblast function in vitro modulated by the melanocortin tripeptide derivatives KdPT and WOL074-029	Stegemann, Agatha; Soeberdt, Michael; Abels, Christoph; Steinbrink, Kerstin; Böhm, Markus
31	Stress is not always stress: a comparison of cortisol and Brain Derived Neurotrophic Factor (BDNF) in hair after natural disaster stress and academic stress	Peters, Eva Milena Johanne; González-de-la-Vara, Marcela; Tumala, Susanne
2	Immune-mediated early endocrine response during tumorigenesis	Besedovsky, Hugo; Schardt, Martin; del Rey, Adriana
36	Stress reactions and test performance in a Zoom session with and without the camera running	Schade, Ursula

Abstracts

1

Mental and physical health in informal caregiving and associations with relationship quality between caregiver and care recipient – a pilot study

Linda Becker[1], Anna Pendergrass[2], Elmar Gräßel[2], Nicolas Rohleder[1]

[1] Department of Psychology, Chair of Health Psychology, Friedrich-Alexander Universität Erlangen-Nürnberg, Germany; [2] Department of Medical Psychology and Medical Sociology, University Hospital Erlangen, Erlangen, Germany

Background: Caregiving can be a long-term stressor, which is associated with mental and physical health complaints. Understanding protective factors is crucial. Here, we investigated the associations between relationship quality between caregiver (CG) and care recipient (CR) and CG's depression and perceived stress, and physiological stress markers such as C-reactive protein (CRP) and cortisol levels.

Methods: N = 36 (11 male; 61.7 ± 11.4 years) informal caregivers participated. CRP was measured in Dried Blood Spots. Cortisol levels were assessed from bedtime saliva samples as well as from hair samples. Relationship quality was assessed by means of a self-developed scale. Ratings were dichotomized as positive or neutral/negative. CG's depression and perceived stress were assessed by means of standardized questionnaires (PHQ-9 and PSS-10).

Results: A positive relationship was associated with less perceived stress as well as with lower depression (both $p < .003$, Cohen's $d > 4.5$). No significant differences were found for the physiological markers (all $p > .05$, Cohen's $d > 0.56$). However, CRP levels were related with perceived stress ($r = .48$, $p = .012$).

Conclusion: Our pilot study shows that relationship quality is associated with CG's mental health and perceived stress. More research with larger sample sizes is needed to investigate whether this is also associated with CG's physical health. Inflammatory markers such as CRP levels are promising measures.

2

Immune-mediated early endocrine response during tumorigenesis

Hugo Besedovsky[1], Martin Schardt[2], Adriana del Rey[1]

[1] Medical Faculty, Philipps University, Marburg, Germany; [2] Swiss Research Institute, Medical Department, Davos, Switzerland

Background: Endocrine host responses are detected during early stages of growth of different types of tumors. Although similar endocrine responses can be triggered by immune-derived cytokines, there is scarce evidence that immune cells are involved in this response. This would be clearly suggested if tumor-host histocompatibility would be required for such endocrine responses, since T cells recognize neoantigens and other antigens presented in the context of self MHC.

Methods: EL-4 tumor cells were inoculated into H-2 incompatible Balb/c and B10.D2 mice (tumor rejection), into Balb/B and C57Bl/10ScSn mice, which share with the tumor only H-2 antigens (tumor development), and into C57Bl/6J mice, which are fully syngeneic with the tumor (tumor development). Corticosterone and insulin blood levels were evaluated 24 hours later. These hormones were chosen because of their known capacity to influence immune cells and tumor growth.

Results: More than a 10-fold increase in corticosterone and 50 percent decrease in insulin blood levels were observed in EL-4 injected C57Bl/6J mice. Although corticosterone levels were elevated in tumor-injected mice of the five strains, the magnitude of such increase was

significantly higher in H-2b mice. Furthermore, the decrease in insulin levels was only observed in fully syngeneic C57Bl6J mice. These changes were paralleled by a profound depression of host inflammatory responses.

Conclusion: The data show that the type and magnitude of the endocrine response elicited by a tumor depend on tumor-host histocompatibility, which require immune recognition of neoplastic cells. This evidence indicates that immune-mediated endocrine responses contribute to tumor-host interactions.

3

Characterisation of circulating dendritic cells in major depressive disorder

Anna-Lena Boller[1,2], Jana Freff[1,2], Kathrin Schwarte[1], Rafael Leite Dantas[1,2], Volker Arolt[1], Udo Dannlowski[3], Bernhard T. Baune[1,4,5], Stefanie Scheu[6], Judith Alferink[1,2]

[1] Department of Mental Health, University of Münster, Münster, Germany; [2] Cluster of Excellence EXC 1003, Cells in Motion, University of Münster, Münster, Germany; [3] Institute for Translational Psychiatry, University of Münster, Münster, Germany; [4] The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Melbourne, Australia; [5] Department of Psychiatry, The University of Melbourne, Melbourne, Australia; [6] Institute of Medical Microbiology and Hospital Hygiene, University of Düsseldorf, Düsseldorf, Germany

Background: Major depressive disorder (MDD) is a severe mental disorder associated with alterations of the innate immune system. Changes in blood monocytes have been found in MDD, whereas knowledge of dendritic cells (DCs) in depression is limited. DCs are professional antigen-presenting cells comprising various subsets such as CD1c+ and CD141+ DCs and plasmacytoid DCs (pDCs). Here, we investigated the proportions of DC subsets in MDD and their association with depressive symptoms and severity of MDD.

Methods: To analyse DC subsets in MDD, blood samples from healthy controls (HC, n=37) and depressed patients (n=61) were analysed at baseline and after six weeks of therapy using multi-parameter flow cytometry. Additionally, patients were stratified according to MDD severity using Hamilton Rating Scale for Depression (HAM-D) and DC subset frequencies were assessed. Next, HAM-D, Beck's Depression Inventory (BDI-II) and Inventory for Depression Symptomatology – clinical interview (IDS-C) scores were tested for correlation with frequencies of DC subsets.

Results: Compared to HC, MDD patients displayed significantly decreased frequencies of CD1c+ DCs and pDCs in peripheral blood when compared to HC. Stratification of MDD patients revealed a negative association between CD141+ DC frequencies and mild depression and between pDC frequencies and moderate/severe MDD. Additionally, negative correlations between pDCs, CD1c+ DCs, CD141+ DCs and HAM-D, BDI-II and IDS-C scores were found.

Conclusion: This study found changes in DC subsets in peripheral blood between HC and MDD. It also shows that frequencies of certain DC subsets are related to severity of MDD.

4

Immune age correlates with cardiorespiratory fitness, but not with general intelligence

Peter Bröde[1], Maren Claus[1], Erhan Genç[1], Jan Digutsch[1], Silvia Capellino[1], Patrick D. Gajewski[1], Stephan Getzmann[1], Klaus Golka[1], Jan G. Hengstler[1], Michael A. Nitsche[1], Edmund Wascher[1], Carsten Watzl[1]

[1] Leibniz Research Centre for Working Environment and Human Factors (IfADo), Dortmund, Germany

Background: Considering the individually varying age-related decline of physical and cognitive capacity in relation to the functionality of the immune system, this study aimed to analyze the correlation of personal characteristics with cardiorespiratory fitness (CRF), and with markers summarizing the multivariate nature of 'immune age' and 'general intelligence'.

Methods: For the cross-sectional baseline examinations within the longitudinal 'Dortmund Vital Study' (DVS) comprising 355 females and 222 males (20-70 years of age, body-mass-index (BMI) 17-54 kg/m²), peripheral blood mononuclear cell frequencies were determined by flow cytometry. These measurements were submitted to principal component regression approximating 'IMM-AGE', an advanced immune age score. Likewise, multivariate analyses of fifteen neuropsychological tests produced the g factor operationalizing general intelligence adjusted for sex and age. CRF was assessed by the power output standardized for body weight while performing the bicycle ergometer test PWC130. Bivariate and partial Pearson correlations were calculated.

Results: While bivariate correlations indicated significantly lower CRF with increasing BMI, chronological and immune age, and for females compared to males, partial correlations adjusting for the other predictors remained significant for Sex, BMI and immune age, but not for chronological age. No significant correlations occurred between personal characteristics and the g factor; however, there was a small, but significant positive correlation between global intelligence and CRF.

Conclusion: In summary, our results indicate a potential role for the immune age in explaining the inter-individual variability in cardiorespiratory fitness, whereas predictors for general intelligence will require further study including the ongoing longitudinal examinations within the DVS cohort.

5

Investigation of the relationship between immune age and vaccination against SARS-CoV-2

Maren Claus[1], Peter Bröde[1], Doris Urlaub[1], Natalie Wolfsdorff[1], Carsten Watzl[1]

[1] Leibniz Research Centre for Working Environment and Human Factors - IfADo, Dortmund, Germany

Background: Due to aging of the immune system, vaccinations are often less effective in older persons. The construct 'immune age' tries to reflect age-related changes in the immune system, which vary between individuals and do not necessarily parallel age. Vaccination against SARS-CoV-2 results in the rare situation that individuals are vaccinated against a pathogen to which they are immunologically naive. Thus, the initial situation is identical for all individuals. Furthermore, it is currently unknown whether vaccination success is influenced by chronological or immunological age. Therefore, this study aims to investigate such a relationship.

Methods: We developed an immune age score integrating a minimal set of immune cell populations determined by flow cytometry. Immune age and SARS-CoV-2 spike-RBD-specific antibodies were quantified in peripheral blood of 724 vaccinated adults. In addition, epidemiological data were collected by questionnaire.

Results: Our results show a strong correlation of antibody titers with immunological and chronological age. However, the immune age scores of women matched those of men who were about 6 years older. Antibody titers were also higher in women, suggesting an additional influence of sex on immune function. Interestingly, the immune age score of a cohort of 97 male professional firefighters was lower than that of other men and comparable to that of women of the same age. This hints towards positive effects of physical fitness on immunological age independent of sex.

Conclusion: Overall, the immune age score is a valuable tool to study vaccination success as function of immunological aging and its correlation with sex and physical fitness.

6

The steroid hormone dehydroepiandrosterone (DHEA) counteracts the consequences of psychological trauma on immunocellular ageing and mitochondrial bioenergetics

Karin de Punder[1], Juan Salinas-Manrique[2], Iris-Tatjana Kolassa[3], Detlef E Dietrich[2,4], Alexander Karabatsiakis[1]

[1] Institute of Psychology, Department of Clinical Psychology II, University of Innsbruck, Innsbruck, Austria; [2] AMEOS Clinic for Psychiatry and Psychotherapy Hildesheim, Hildesheim, Germany; [3] Clinical & Biological Psychology, Ulm University, Ulm, Germany; [4] Center for Systems Neurosciences Hannover, Hannover, Germany

Background: We previously demonstrated associations between the presence of psychological trauma and Major Depressive Disorder (MDD) and immune cell telomere length (TL) and mitochondrial respiratory activity. Here, we investigated the proposed anti-ageing effects of endogenous circulating levels of the steroid hormone dehydroepiandrosterone (DHEA) on these associations.

Methods: Blood samples were collected from n=22 inpatients with MDD and n=22 non-depressed controls. Lifetime traumatic events were assessed by self-report using the Essener Trauma Inventory. DHEA levels were measured by immunoassay. Immune cell TL was quantified in kilobases using qFISH and mitochondrial respiration was measured applying high-resolution respirometry.

Results: Higher trauma load was associated with lower DHEA concentration (r=-.25, p=.03) and lower DHEA concentration associated with more depression-related fatigue symptoms in MDD patients (r=-.45, p=.01). In addition, we observed that DHEA levels positively associated with TL in memory CD4+ T-cells (r=.39, p=.01) as well as in naïve and memory CD8+ T cells (r=.46, p=.002 and r=.47, p=.002, respectively). DHEA concentration also related to routine (r=.31, p=.04) and uncoupled respiration (r=.34, p=.04) in leukocytes. Mediational analysis (path analyses with bootstrapping) suggested that the effect of trauma load on memory CD8+ T-cell TL was mediated by DHEA concentration (ab=-.11, CI95%: -.22 to -.01). Finally, in MDD patients, DHEA concentration mediated the effect of trauma load on depression-related fatigue (ab=.10, CI95%: .02 to .21).

Conclusion: The current findings highlight the role of DHEA as an endogenous biological resilience factor that was demonstrated here to attenuate the adverse immunocellular consequences of trauma exposure.

7

Prediction of antibody levels after COVD-19 vaccination: evidence for immune interoception

Stephanie Dimitroff[1], Lisa Würfel[1], Maria Meier[1], Kelly Faig[2], Annika Benz[1], Bernadette Denk[1,3], Ulrike Bentele[1], Eva Unternaehrer[1,4], Jens Pruessner[1,3]

[1] Department of Psychology, Division of Neuropsychology, University of Konstanz, Germany; [2] Department of Psychology, Hamilton College, USA; [3] Centre for Advanced Study of Collective Behavior, University of Konstanz, Germany; [4] Child and Adolescent Research Department, Psychiatric Hospital Basel, University of Basel, Switzerland

Background: 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 number of antibodies produced by some individuals is exponentially higher than 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.

Methods: 166 participants (18-60 years old, 103 female) were recruited to the lab 14-60 days post-vaccination, where a blood sample was taken for analysis. Participants were asked to estimate on a scale from 0-10 how many antibodies they produced, and were also asked how protected they felt from COVID-19 due to vaccination.

Results: 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.

Conclusion: 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.

8

Temporal dynamics of cytokine changes in blood, cerebrospinal fluid and brain tissue of endotoxemic rats

Kirsten Dombrowski[1], Lisa Trautmann[1], Manfred Schedlowski[1], Lennart Barthel[2], Susann Hetze[2], Harald Engler[1]

[1] Institute of Medical Psychology and Behavioral Immunobiology, Center for Translational and Behavioral Neurosciences, University Hospital Essen, University of Duisburg-Essen, Essen, Germany; [2] Department of Neurosurgery, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

Background: Experimental endotoxemia is a translational model of systemic inflammation that is widely used to study the mechanisms underlying inflammation-induced changes in mood and behavior. In humans, we recently found a strong association between endotoxin-induced cytokine alterations in the cerebrospinal fluid (CSF) and the severity of affective symptoms. However, it remains open to what extent changes in the CSF reflect cytokine alterations within the brain. Against this background, we analyzed the temporal relationship between cytokine changes in the peripheral blood, the CSF and brain tissue of endotoxemic rats.

Methods: Adult Wistar rats received intraperitoneal injections of either 100 µg/kg lipopolysaccharide (LPS) or vehicle, and blood, CSF and brain samples were collected at 1, 2, 3, 4 or 6 h post-injection. Blood was obtained from the tail vein, and uncontaminated CSF was collected from the cisterna magna under isoflurane anaesthesia. Brains were harvested immediately after CSF collection and stored at -80°C. Frozen brains were sectioned on a cryostat and tissue from various brain regions was obtained by micropunches. Cytokine concentrations were quantified by multiplex immunoassays.

Results: LPS administration induced a rapid increase of cytokine levels in the blood, peaking between 2 to 3 h post-injection. Cytokine changes in the CSF were much lower in magnitude and time-delayed relative to the circulation. The pattern of cytokine expression in the brain was overall comparable to the CSF, with differences between brain regions.

Conclusion: The assessment of cytokines in the CSF during LPS-induced inflammation provides a representative picture of cytokine changes within the brain.

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The burden of overweight: Higher body mass index, but not vital exhaustion, is associated with higher DNA damage and lower DNA repair capacity

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Background: DNA damage and the capacity to repair damaged DNA has been associated with the pathogenesis of several diseases such as cancer. While it is well known that external mutagenic agents can induce DNA damage, less is known about endogenous contributors to genomic instability. The aim of this study was to investigate whether excess body weight as a physiological factor and vital exhaustion as a psychological factor would be associated with basal levels of DNA damage as well as DNA repair capacity.

Methods: In a cross-sectional between-subject design we recruited 53 apparently healthy men within the normal to non-obese overweight range (mean BMI: 25.2±.5) who were either vitally exhausted (VE) (VE-score≥10) or non-exhausted (VE-score≤3). Vital exhaustion was assessed using the Maastricht Vital Exhaustion Questionnaire. We assessed DNA damage and repair in terms of strand breaks in PBMCs by means of the automated Fluorimetric Detection of Alkaline Unwinding (FADU) assay. DNA repair capacity was assessed by repeatedly measuring the amount of intact DNA up to 90 minutes after standardized X-irradiation of the cells.

Results: General linear models revealed that elevated levels of basal DNA damage (β=-.34,p=.013,f=0.33) as well as impaired capacity to repair damaged DNA (F(1/50)=5.40,p=.024,f=.33) with increasing BMI, but not with vital exhaustion (p's≥.63).

Conclusion: Our findings point to DNA integrity impairments with increasing BMI, already in the overweight range, and suggest impaired DNA repair as a potential underlying molecular mechanism. In contrast, the psychological factor vital exhaustion was not associated with DNA damage or DNA repair capacity.

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Dopamine receptor 1 pathway as a potential proinflammatory factor in ~~female patients with~~ rheumatoid arthritis

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Background: Besides the widely known function of dopamine in the brain, the neurotransmitter is also described as a regulator of the immune system. There is evidence for a contribution of dopamine to rheumatoid arthritis (RA) which predominantly occurs in women. However, the exact connection between dopamine and RA is poorly understood.

Methods: Basal expression of dopamine receptor 1 (DRD1) on B cells and the amount of dopamine in PBMCs were quantified via FACS or ELISA for female RA patients and healthy controls (HC; n=23). In vitro stimulation with D1-like agonists SKF38393/A68930 was performed with RA and healthy immune cells. Subsequently, HLA-DR expression was analysed via FACS and CCL3 and IL-8 secretion via ELISA. The study was approved by the ethical committee and all patients gave written consent.

Results: Higher DRD1 expression on B cells ($p<0.001$) and dopamine levels in PBMCs ($p<0.05$) were found for RA women compared to HC. Positive correlations between DRD1 expression, disease duration ($p<0.01$) and Hannover Functional Questionnaire parameter FFbH ($p<0.05$) were obtained. D1-like stimulation resulted in higher HLA-DR expression on B cells ($p<0.05$), more proinflammatory and less antiinflammatory cytokine secretion ($p<0.01$) for RA compared to HC.

Conclusion: Elevated DRD1 and dopamine levels in diseased women suggest that the dopaminergic pathway is overactivated in RA. Along with present correlations with RA parameters a proinflammatory contribution is indicated. This is supported by an increased HLA-DR expression and a stronger proinflammatory cytokine profile after D1-like stimulation for RA than HC. However, the exact mechanism needs to be further investigated.

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Chemokine receptor 4 expression on blood T lymphocytes predicts severity of major depressive disorder

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Background: Chemokines and their receptors regulate inflammatory processes in major depressive disorder (MDD). Here, we characterize the expression pattern of the C-C chemokine receptor 4 (CCR4) and its ligands CCL17 and CCL22 in MDD and its clinical relevance in predicting disease severity.

Methods: Expression of CCR4 on peripheral blood lymphocytes and serum CCL17/CCL22 levels were measured using multiparameter flow cytometry and multiplex assays in 33 depressed inpatients at baseline (T0) and after 6-week multimodal treatment (T1) compared with 21 healthy controls (HC). Using stratified and correlation analysis, we examined the associations of CCR4-CCL17/CCL22 expression with depression severity and symptoms according to standard clinical rating scales and questionnaires. Additionally, we assessed whether polygenic risk score (PRS) for psychiatric disorders and chronotype are associated with disease status or CCR4-CCL17/CCL22 expression. Regression analysis was performed to assess the capacity of CCR4 and PRS in predicting disease severity.

Results: Compared with HC, MDD patients showed significantly decreased CCR4 expression on T cells (T0 and T1), whereas CCL17/CCL22 serum levels were increased. Stratified and correlation analysis revealed an association of CCR4 expression on CD4+ T cells with depression severity as well as Beck Depression Inventory-II items including loss of pleasure, agitation and cognitive deficits. CCR4 expression levels on CD4+ T cells together with cross-disorder and chronotype PRS significantly predicted disease severity.

Conclusion: This newly identified CCR4-CCL17/CCL22 signature and its predictive capacity for MDD severity suggest its potential functional involvement in the pathophysiology of MDD.

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Altered mitochondrial immunometabolism in major depressive disorder

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Background: Major depressive disorder (MDD) and metabolic disorders are highly prevalent diseases. Converging evidence indicates that MDD and metabolic disorders might be mediated by shared (patho)biological pathways. Moreover, animal studies suggest that impaired metabolic function in the immune system may be sufficient to induce depression-like behavior. However, it remains unknown if this can be translated to depression in humans.
Methods: We investigated metabolic dysfunction on a systemic, cellular, and molecular level in unmedicated MDD patients (n=28) compared to healthy controls (n=28), matched for age, sex, body mass index (BMI), and smoking status. We measured targeted (LDL and HDL) and metabolome-wide differences in systemic markers, cellular respiration, and glycolysis in T cells and monocytes, and cell-specific expression of key regulators of cellular metabolism. Immune phenotyping and anti-viral T cell frequency served as control read-outs.
Results: Despite comparable BMI scores and absence of cardiometabolic disease, patients with MDD showed significant dyslipidemia. On a cellular level, T cells obtained from MDD patients exhibited reduced respiratory and glycolytic capacity. However, metabolic dysfunction was not secondary to immune activation, senescence, or altered anti-viral immunity. Gene expression analysis revealed increased carnitine palmitoyltransferase I (CPT1) levels (but unaltered expression of glucose transporter GLUT1) in T cells, suggesting metabolic reprogramming with a shift towards fatty acid oxidation.
Conclusion: Metabolic dysfunction in unmedicated, non-overweight MDD patients can be detected on a systemic, cellular, and molecular level. Our results on mitochondrial dysfunction in T cells provide translation of previous animal studies regarding a putative pathogenetic role of altered immunometabolism in depression.

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Biological and psychological stress responses after miscarriage: cross-sectional results from the MALT randomized controlled trial.

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Background: Traumatic life events have a great impact on the individuals' lives and their mental and physical health. However, few studies target early interventions for the prevention of post-traumatic stress disorder (PTSD) and their psychological and biological impact. The aim of this study is to help understand the difference in psychological and biological stress responses associated with traumatic symptoms.

Methods: Women (N = 25, 18 to 50 years old) who experienced a miscarriage (< 3 months before study inclusion) were recruited in Nuremberg. They were exposed to the socially evaluated cold-pressor test (SECPT). We measured biological and psychological stress responses and various mental health constructs and compared the results to a healthy control cohort (N = 28).

Results: Recently traumatized women scored significantly higher on psychological symptoms, including traumatization, stress and depression. In all biological measurements a significant stress response was observed (time effects: sAmylase: F= 3,961 p= 0,014; Cortisol: F= 17,935 p> 0,001 Interleukin 6: F=30,246 p=0,001.) Both groups had a similar stress reactivity in all three measures (n.s.). Traumatized women showed lower overall cortisol (Group effect: F= 333,549 p= 0,031) levels.

Conclusion: The study shows the effect of recent traumatic experiences on biological and psychological stress markers shortly after the traumatizing event. In addition, it highlights that the SECPT is an option to induce a stress response in a clinical setting. Further research is needed to assess the early development of PTSD symptoms and the influence of stress reactivity on the development of these symptoms.

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Early-life maternal deprivation affects the coping behavior and neuroendocrine development of domestic pigs

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Background: Early-life adversity may have sustained effects on the behavior, stress-reactivity and immune competence. Here, we studied the effects of repeated maternal and littermate deprivation in domestic pigs.

Methods: Piglets from ten sows were exposed to daily 2-h maternal deprivation on postnatal days 2-15 either alone (DA) or in a group of littermates (DG). Control piglets (C) from ten sows were not deprived. We studied cortisol and oxytocin concentrations of sow milk and cortisol, IgA and neutrophil/lymphocyte (N/L) ratios in piglets' blood. Coping behavior was tested during open-field/novel-object (OF/NO) tests on days 16 and 40. Two piglets from each group and sow were euthanized on day 20 and stress-related gene expression in hypothalamus, hippocampus, amygdala and prefrontal cortex (PFC) was examined by qRT-PCR.

Results: Milk cortisol increased during separation of dam and offspring on day 2 of lactation, whereas oxytocin did not change. The increase in cortisol by the OF/NO test on day 16 was greater in C piglets than in DA and DG piglets. Furthermore, DA piglets showed less aroused behavior than DG and C piglets in the OF/NO test on day 16, which was partly reversed on day 40. The deprivation resulted in a reduction of GR, MR, and CRHR1 expression in the PFC. Neither plasma IgA nor N/L ratios were affected by deprivation.

Conclusion: Repeated maternal deprivation has lasting effects on stress reactivity and behavior in domestic pigs. Some of these were buffered by the presence of littermates.

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Beta2-adrenergic receptor expression and signaling is profoundly changed in B lymphocytes during collagen-induced arthritis

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Background: The sympathetic nervous system is pro-inflammatory at the beginning and anti-inflammatory in established arthritis by, e.g. promoting the generation of regulatory B cells (Bregs). As previously shown, ß2-adrenergic receptor (ß2-ADR) signaling is involved in the modulation of Bregs. We investigated whether B cells exhibit a change in ß2-ADR expression or signaling during collagen-induced arthritis (CIA).

Methods: The expression and receptor density of ß2-ADRs on B cells, intracellular ADR downstream molecules (GRK-2, ß-Arrestin2, p38 MAPK, ERK1/2, CREB) and IL-10 expression were analyzed in naïve and arthritic B cells by flow cytometry.

Results: ß2-ADR-expressing B cells increase during CIA (d55, p***<0.001) without a change in receptor density. Moreover, we observed a profound downregulation of GRK-2 shortly after induction (d3, p**= 0,0029) and an increase in ß-Arrestin2 only at late stage arthritis (d55, p**=0,005). The second messengers studied (pp38, pERK and pCREB) followed a biphasic course, characterized by a reduction at onset and an increase in established arthritis (d55: pp38: p*= 0,0270; pCREB: p***=0,0001). Stimulation of CIA B cells with terbutaline, a ß2-ADR-agonist, increased pp38 MAPK independent of the timepoint (d18 p**=0,0031, d55, p**=0,0062), while pERK and pCREB were enhanced only in the late phase of arthritis (d55, pERK: p*=0,0454; pCREB: p*=0,0358). The phosphorylation of p38, ERK and CREB in the late phase of arthritis was associated with increased IL-10 produced by Bregs (d48, p****<0.0001).

Conclusion: The change of ß2-ADR expression and signaling during sustained inflammation might be an integral part of the switch from pro- to anti-inflammatory action of sympathetic mechanisms in late arthritis.

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The regulatory function of TLR9-activated B cells is improved by endogenously produced catecholamines

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Background: Catecholamines released by the sympathetic nervous system (SNS) contributes to immune balance by promoting regulatory B cells (Bregs). In this study we investigated, whether B cells produce their own catecholamines and possess a self-regulating mechanism to modulate their regulatory function.

Methods: Catecholamines were analyzed by ELISA and FACS. The expression of IL-10 was determined by qRT-PCR, ELISA and FACS and, suppression of CD4 T cell proliferation was investigated by FACS.

Results: We found that TLR9-activated B cells have the ability to synthesize and release their own catecholamines independently from the SNS in a time and stimulus-dependent manner. Analysis of anti-IgM/CpG-activated B cell showed increased levels of intracellular catecholamines (dopamine: p**= 0,0066; norepinephrine: p*= 0,0357; epinephrine: p****<0,0001), while most of produced catecholamines were released into the supernatant 24h after activation (dopamine: n.s.; norepinephrine: p****<0,0001; epinephrine: p***=0,0001). Moreover, anti-IgM/CpG-activated B cells produce IL-10 as determined by ELISA (p***<0,0001) and FACS (p****<0,0001). B cells analyzed by qRT-PCR reveal that ß-ADR stimulation enhanced CpG-induced IL-10 levels and is able to increase IL-10 production independently of CpG activation (CpG vs. CpG+NE: p** = 0.0100; C vs. NE: p*** =0,0002). Furthermore, we showed that ß-ADR enhanced suppression of CD4 T cell proliferation by activated B cells was mediated by IL-10 (CpG vs. CpG/Isopr.: WT: p**=0.0075; IL-10-/-: n.s).

Conclusion: Our data show that B cells possess an autonomous mechanism to modulate their regulatory function. These findings help to better understand the function of B cells in the regulation of autoimmune diseases and the interplay of SNS.

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Taste-immune conditioning with fingolimod (FTY720) as unconditioned stimulus

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Background: During taste-immune associative learning, a novel taste (conditioned stimulus, CS) is administered together with an immunmodulating drug (unconditioned stimulus, US). After the individual has learned to associate CS and US, conditioned effects similar to the pharmacological effects of the US can be retrieved by the sole presentation of the CS. Applying a taste-immune conditioning paradigm in rats by using the immunosuppressive drugs cyclosporin A or rapamycin as US, a diminished T cell proliferation and cytokine production upon CS re-exposure has already been shown. The present approach aims at examining whether this phenomenon generalizes across immunosuppressive drugs with different underlying mechanisms.

Methods: We performed taste-immune conditioning in rats using the immunosuppressive drug fingolimod (FTY720, US) and a sweet tastant (CS). FTY720 acts as a functional antagonist of the S1PR1 receptor and is widely applied in multiple sclerosis therapy. On the one hand, the development of a conditioned taste avoidance (CTA) was assessed and on the other hand, blood immune cell subsets, splenic cytokine secretion and splenic S1PR1 receptor expression were analyzed by flow cytometry, ELISA, MSD and Western Blotting.

Results: In contrast to the pharmacological effect of FTY720, conditioned immunomodulation did not diminish the number of leukocytes in the blood. However, CS re-exposure resulted in a learned suppression of cytokine production.

Conclusion: Overall, our results underline the need to further investigate the mechanisms underlying taste-immune conditioning. To assess the clinical relevance of the conditioning paradigm as a supplementary therapy, future studies will implement this paradigm in an experimental autoimmune encephalomyelitis (EAE) disease model.

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Adherence and beliefs about medication in patients with rheumatoid arthritis

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Background: Consistent immunosuppressive treatment of rheumatoid arthritis (RA) with disease-modifying anti-rheumatic drugs (DMARDs) is crucial for reduced progression and improved long-term outcome of the disease. Therefore, drug adherence is a prerequisite, which is often insufficient according to literature. Our aim was to investigate the relationship between adherence and beliefs about medication in patients with RA.

Methods: The study included 137 RA patients. Medication adherence was measured with the Compliance-Questionnaire-Rheumatology (CQR). In addition, the specific part of the Beliefs about Medicines Questionnaire (BMQ) was used to assess patients' opinions about the necessity of their medication therapy and their concerns.

Results: Adherence was satisfactory in 93 RA patients (67.9 %) and insufficient in almost one-third (n = 44, 32.1 %). Analyses showed that adherence was significantly related to belief in necessity ($r = 0.46$; $p < 0.001$) and concerns about drug therapy ($r = -0.27$; $p = 0.001$). Belief in the necessity of therapy, medication concerns and patient age accounted for almost half of the patient-specific variability in adherence (each $p < 0.001$; $R2 = 42.9$ %), suggesting a strong dependence of adherence on these three factors.

Conclusion: Adherence is insufficient in about one-third of RA patients. Additionally, adherence appears to be strongly dependent on the patient's belief in the necessity of therapy, medication concerns and age. Physicians should strive for all RA patients to have sufficient

knowledge about their medication, strengthen the belief in the necessity of the therapy and be mindful of adherence when talking to patients.

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Investigating the effects of antidepressive treatment on mitochondrial bioenergetic functioning and mitochondrial density in peripheral blood mononuclear cells

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Background: Major depressive disorder (MDD) is characterized by both psychological and somatic symptoms and changes in immune-cell functioning. One conceptual approach links MDD to impairments in mitochondrial bioenergetics, including reduced adenosine triphosphate (ATP) production. We previously demonstrated impaired mitochondrial function in peripheral blood mononuclear cells (PBMC) from depressed patients, which negatively correlated with the clinical severity of MDD. Here, we aimed to replicate this finding in an independent cohort. In addition, we investigated the effects of antidepressive treatment on the possible recovery of mitochondrial bioenergetics.

Methods: Twenty-five depressed patients provided blood samples before and five weeks after receiving antidepressive treatment (antidepressants and add-on cognitive-behavioural therapy). Additionally, two blood samples, separated by five weeks, were also collected from non-depressed controls (n=35). PBMC were isolated and a bioenergetic profile was assessed using high-resolution O2K respirometry. After respirometry, citrate synthase activity was measured by spectrophotometry to determine mitochondrial density in PBMC for the normalization of respiration values.

Results: Compared to the control group, significantly lower oxygen consumption rates were observed in PBMC from depressed patients before treatment, which correlated significantly with the severity of depressive symptoms. Normalization of respiration by mitochondrial density revealed non-significant between-group differences. Leak respiration, a marker for membrane integrity, significantly improved in the MDD group with treatment, independently from mitochondrial density.

Conclusion: Based on our results, mitochondria in PBMC of depressed patients might not be dysfunctional, but functionally impaired due to their lower density. Leak respiration improved with clinical treatment. Future studies should test the robustness of our results.

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Relationship between baseline pro-inflammatory cytokine levels and psychological inflexibility during behavioral treatment for chronic pain

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Background: The medical and scientific communities are struggling to understand mechanisms underlying chronic pain and find effective treatment strategies. Multimodal

approaches are encouraging, but large individual differences call for a better understanding of factors influencing treatment success. We explore low-grade inflammatory activity as a factor influencing behavioral treatment for chronic pain.

Methods: 78 persons (56 women) with chronic pain received behavioral treatment (Acceptance and Commitment Therapy) and provided blood samples before and after treatment. With blood sampling, the participants completed surveys on pain intensity, psychological comorbidity, psychological inflexibility and pain interference. Blood plasma was analyzed for IL-6 and TNF-α levels with the Olink Inflammation Panel (Olink Bioscience Uppsala, Sweden). Treatment effects and moderating effects of low-grade inflammation on changes in outcomes were analysed using linear mixed models.

Results: Pain interference ($p < 0.001$), pain intensity ($p = 0.042$) and psychological inflexibility ($p < 0.001$) improved significantly during treatment. Cytokine levels did not change over the course of the treatment (IL-6/ TNF-α $p = 0.084/0.663$). Higher baseline levels of IL-6 and TNF-α moderated improvement in psychological inflexibility during the course of treatment ($p = 0.008$), but cytokine levels did not moderate changes in pain interference ($p = 0.058$) or pain intensity ($p= 0.748$).

Conclusion: Results suggest that higher levels of baseline inflammation are related to less improvement in psychological inflexibility. These findings are in line with two previous studies, supporting the validity of the findings. Low-grade inflammation may be one factor underlying the variability in behavioral treatment in chronic pain.

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The MDSC – a key player in glucocorticoid resistance following combined physical and psychosocial trauma

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Background: Stress-associated somatic and psychiatric disorders are often linked to non-resolving low-grade inflammation, which is promoted at least in part by glucocorticoid (GC) resistance of certain immune cell subpopulations. While the monocyte/macrophage compartment was in the focus of many clinical and preclinical studies, the role of myeloid-derived suppressor cells (MDSCs) in stress-associated pathologies and GC resistance is less understood. Despite GC resistance is also a risk factor for posttraumatic complications in patients on intensive care, the interplay of physical and psychosocial traumatization in the development of GC resistance needs to be further clarified.

Methods: In the current study we employ the chronic subordinate colony housing (CSC) paradigm, a pre-clinically validated mouse model of chronic psychosocial stress, to study the role of myeloid cells, in particular of MDSCs, in innate immune activation and GC resistance following combined physical and psychosocial trauma.

Results/Conclusion: Our findings support the hypothesis that stress-induced myeloid subpopulations get primed (i.e. upregulation of toll-like receptor (TLR)-2) and activated (i.e. increased basal and lipopolysaccharide (LPS)-induced in vitro cell viability) locally in the bone marrow. These primed and activated myeloid cells emigrate into the peripheral circulation (i.e.

also white blood cells (WBCs) show increased basal and LPS-induced in vitro cell viability) and, in a bite wound dependent manner, accumulate in the spleen. Here, MDSCs and monocytes upregulate TLR-4 expression, which in exclusively in MDSCs promotes excessive nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-kB) signaling following in vitro LPS-stimulation, exceeding the anti-inflammatory capacities of GCs on this cell type.

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Alpha-adrenergic receptors in individuals with primary Raynaud's phenomenon

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Background: Raynaud's phenomenon (RP) is a vasospastic response of peripheral arteries to cold, exercise or psychosocial stress likely involving alpha-adrenoceptors (AdR). Increases in autoantibodies activating alpha-AdR and/or increases in vascular alpha-AdR expression are potential underlying mechanisms.

Methods: We assessed autoantibodies targeting alpha1- or alpha2-AdR by ELISA in serum of healthy individuals with primary RP (pRP), patients with secondary RP (sRP) due to the autoimmune disease systemic sclerosis, and healthy controls without RP (HC). To delineate systemic changes in receptor expression, we subsequently measured mRNA- and protein levels of alpha-AdR subtypes in neutrophils (NEU) and peripheral blood mononuclear cells (PBMC) in a subset of pRP and additional HC.

Results: Autoantibodies against alpha2-AdR (but not those against alpha1-AdR) were higher in pRP than in sRP or HC. In further analyses we therefore focused on alpha2-AdR expression in immune cells. All three receptor subtypes (alpha2A-, B-, and C-AdR) were detectable on an mRNA- and protein level in NEU and in PMBC. Expression of mRNA (but not of protein) of these receptors were reduced in pRP compared to HC in both NEU and PMBC.

Conclusion: Our findings provide evidence for a particular role of alpha2-AdR in pRP, confirming previous reports that these receptors are key in reflex sympathetic vasoconstriction. Enhanced autoantibodies targeting alpha2-AdR and reduced mRNA but not protein expression of all three alpha2-AdR subtypes in pRP compared to HC could indicate that autoantibodies enhance alpha2-AdR signaling by stabilizing receptor protein levels and that this process in turn reduces receptor de novo synthesis.

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Investigating the immunoregulatory potential of Mycobacterium vaccae (ATCC 15483) and closely related rapid-growing Mycobacteria species

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Background: An increasing number of studies indicate that stress-induced non-resolving chronic inflammation is involved in the development of stress-related pathologies, including posttraumatic stress disorder (PTSD). Thus, immunoregulatory approaches that counterbalance overshooting immune responses should be protective in this context. In support of this hypothesis, we previously showed that repeated subcutaneous (s.c.) administrations of a heat-killed preparation of Mycobacterium vaccae (National Collection of Type Cultures (NCTC) 11659), an abundant soil saprophyte with immunoregulatory properties, is able to ameliorate the negative effects of chronic psychosocial stress induced by the chronic subordinate colony housing (CSC) paradigm, a model of PTSD in adult male mice.

Methods: In the current study, we assess the immunoregulatory potential of heat-killed preparations of M. vaccae NCTC 11659 and closely related rapid-growing mycobacteria (RGM) species, namely M. vaccae (American Type Culture Collection (ATCC) 15483T), M. smegmatis ATCC 19420T and M. fortuitum ATCC 6841T in an in vitro lipopolysaccharide (LPS)-stimulated mouse macrophage cell line (J774A1).

Results: Our results show that, although a 24h pre-incubation with each tested RGM affected basal and inhibited LPS-induced cell viability, M. vaccae ATCC 15483T was the most potent one. Subsequent in vivo experiments confirmed the immunoregulatory and stress-protective effects of M. vaccae ATCC 15483T when repeatedly administered via the non-invasive intragastric (i.g.) route prior to CSC exposure.

Conclusion: Together our data broadens the framework of using immunoregulatory RGMs for prevention and/or treatment of stress-related psychiatric disorders like PTSD.

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Pain research in a petri dish? Neuro-glial primary cell cultures of the rat dorsal root ganglia to study effects of inflammation on nociceptive signaling in vitro and ex vivo

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Background: Pain is a highly modifiable sensation and altered under various pathophysiological and psychological conditions. Hyperexcitability of nociceptors is one of many important cellular mechanisms underlying hyperalgesia, and frequently studied applying cultured cells of dorsal root ganglia (DRG). However, it remains a matter of debate, in how far primary cultures can mimic conditions of in vivo inflammation. The aim of the present study was to compare inflammatory processes in DRG under in vitro and ex vivo conditions.

Methods: Primary cell cultures of DRG were applied to study effects of in vitro stimulation with lipopolysaccharide (LPS), and intraperitoneal injection of LPS (ex vivo) on neuronal responsiveness (Ca2+-imaging), production of inflammatory mediators (RT-qPCR, bioassays), and activation of inflammatory transcription factors (immunocytochemistry).

Results: In vitro stimulation with LPS resulted in enhanced capsaicin-evoked Ca2+-responses in neurons accompanied by an increased production of pro-inflammatory cytokines (TNFα, IL-6) by DRG macrophages. We further observed an enhanced LPS-induced nuclear translocation of inflammatory transcription factors in neurons (STAT3, NF-IL6) and macrophages (NF-IL6). Intraperitoneal LPS-injection in rats resulted in significantly enhanced plasma concentrations of TNFα and IL-6, as well as increased expression of pro-inflammatory mediators in L4-L6 DRG. Cultured DRG neurons from rats that had been treated with LPS

showed enhanced capsaicin-evoked Ca2+-responses compared to controls, even 24 hours post injection.

Conclusion: We conclude, that DRG primary cultures represent an artificial, but valuable tool to study cellular mechanisms of nociceptor sensitization under inflammatory conditions in vitro and ex vivo. Therefore, they are useful to complement in vivo studies and reduce the number of experimental animals.

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Longitudinal and intergenerational effects of childhood maltreatment on leukocyte telomere length of mother-newborn dyads

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Background: Childhood maltreatment (CM) has been associated with shorter leukocyte telomere length (LTL) in adulthood. There are conflicting findings on whether a maternal history of CM affects the LTL of the next generation. Pregnancy might also impact LTL since it goes along with temporary alterations in the immunometabolism. This study aimed at investigating the effects of a maternal history of CM on LTL in mothers over one year after childbirth, and in their newborns.

Methods: Leukocytes were isolated from cord blood from newborns (N= 134), and whole blood in mothers (N= 216) directly after (t0), 3 months after (t1), and 1 year after (t2) childbirth. LTL was measured by quantitative polymerase chain reaction. Childhood Trauma Questionnaire was used to create groups of mothers with and without CM. Robust linear mixed effects were calculated.

Results: Maternal LTL was shorter at t0 compared to t1 and t2. A Time-CM interaction showed that maternal LTL at t0 was shorter than at t2 only in mothers without CM but not in mothers with CM. Maternal age and maternal LTL positively predicted newborn LTL, whereas a maternal history of CM, specifically sexual abuse, predicted shorter newborn LTL as a trend, independent of the newborns' sex.

Conclusion: The effect of pregnancy on maternal LTL attrition seem to be recovered a year after childbirth only in mothers without CM. CM does not lead to a pronounced LTL attrition right after childbirth. The effect of maternal CM on newborn LTL might depend on the way CM is measured.

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How to induce chronic psychosocial stress and reliably measure social deficits in female mice

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Background: Although women compared to men are generally more susceptible to chronic stress-related psychiatric disorders, including social anxiety disorders (SADs), the majority of pre-clinical studies assessing the effects of stress still focuses on male sex. This is in large parts due to a dearth of established preclinical paradigms reliably inducing a state of chronic psychosocial stress in adult female rodents. Furthermore, behavioral tests that reliably detect stress-induced social deficits in adult female rodents are rare.

Methods: In the present study we compared the effects of Social Isolation (SI) and the Social Instability Paradigm (SIP), two models used by various groups to induce chronic psychosocial female mice, on typical stress-sensitive parameters, like plasma corticosterone

concentrations, adrenal and thymus weights. Moreover, we assessed if the social preference/avoidance test (SPAT), a behavioral test based on a rodents' natural preference of a social over a non-social stimulus, is also adequate to assess possible stress-induced social deficits in female mice.

Results: Our data indicate that while SIP promotes thymus atrophy in female C57BL/6N mice, SI had no effects at all. Furthermore, female C57BL/6N mice only preferred a social over a non-social stimulus in the SPAT, which is a prerequisite for reliable detection of stress-induced social deficits, when the social stimulus is of female sex.

Conclusion: Together, our results support the SIP to be a more powerful stressor than SI in adult female mice and the SPAT to represent a powerful tool to assess stress-induced social deficits in female mice, at least when the stimulus is of female sex.

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Systemic and local adipokines in rheumatoid arthritis and osteoarthritis mouse models

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Background: Adipokines exert effects on energy homeostasis, immune responses and pathogenic pathways in autoimmune diseases. The effect of high-fat-diet(HFD)-induced low-level inflammation on systemic and local adipokine expression in arthritis development is not fully understood and was evaluated in this study.

Methods: RA was induced in DBA/1Rj-mice (CIA, collagen-induced arthritis), OA in C57Bl/6-mice (DMM, destabilization of the medial meniscus) fed with HFD/ND (normal diet) prior to arthritis induction. After 4/6/8(CIA) or 4/5.5/7(DMM) weeks clinical/histological scorings were performed. Diet-induced changes were analyzed by weight, fatty liver score, quantification of crown-like structures (CLS, adipose tissue) and systemic CRP, adiponectin, visfatin and leptin. Local adipokine expression was evaluated by immunohistochemistry.

Results: Histological joint destruction, increased fatty liver score and bodyweight confirm a successful arthritis-induction in both models and HFD-induced obesity. CIA-induction significantly increased CRP. Histological CIA-scoring showed no difference in CIA-severity under HFD or ND. DMM- and especially CIA-induction decreased systemic leptin under ND. CIA-induction reduced local leptin expression under HFD after 5.5 and 7 weeks but not in DMM/HFD. Locally, leptin was increased in damaged areas in DMM/CIA and synovitis areas in CIA but unaltered by HFD. Local adiponectin and visfatin was reduced in CIA/HFD after 5.5 and 7 weeks but not systemically.

Conclusion: High numbers of CLS in CIA with ND and the strong reduction of leptin in CIA/HFD show that CIA-onset and severity are mainly obesity-independent while DMM is influenced by obesity similar to observations in human OA. Systemic and local adipokine distribution over time did not match in both models.

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Regulation of Natural Killer cell functions by catecholamines

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Background: Natural Killer (NK) cells are involved in the control of viral infection and tumors. They interact with catecholamines of the sympathetic nervous system. Importantly, the crosstalk between the nervous and immune system can influence the outcome of cancer therapies. Aim of this project is to understand how the engagement of catecholamine receptors influences NK cell reactivity and how chronic and acute stress alter NK cell responses.

Methods: Primary human NK cells were isolated and stimulated with catecholamines (epinephrine, dopamine or synthetic agonists/antagonists). Seahorse metabolic profiling, xCelligence analysis, FACS based receptor expression analyses and Ligand complex-based adhesion assay, IncuCyte® S3 live NK cell killing analysis, IFNg ELISA, cAMP ELISA and Western blots for NK cell signaling analysis.

Results: Acute epinephrine exposure leads to an 8-fold increase of the cAMP level in the cytoplasm, affects NK cell signaling and reduces NK cell activation. Our data show that epinephrine interrupts up to 70% of the protein interaction between LFA-1 and ICAM-1 and leads to a 26% reduced killing capability. Additionally, epinephrine inhibits mitochondrial respiration and prolongs glycolysis of CD16-activated NK cells. In contrast, dopamine does not alter the metabolic profile, but inhibits IFNg production by 15% in NK cells. Interestingly, chronic exposure to beta-2 adrenergic receptor (beta2AR) agonists does not interfere with beta2AR expression, but completely abolishes the inhibitory effects of acute epinephrine stimulation on NK cell functions.

Conclusion: These different responses may explain some effects of acute and chronic stress on the immune system.

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Altered brain structure in chronic visceral pain: specific differences in gray matter volume and associations with visceral symptoms and chronic stress

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Background: Patients with chronic-inflammatory or functional bowel disorders experience recurring abdominal pain in concert with other gastrointestinal symptoms, such as altered bowel habits, which are often exacerbated by stress. Despite growing interest in the gut-brain axis and its underlying neural mechanisms in health and disease, abnormal brain morphology and possible associations with visceral symptom severity and chronic stress remain unclear.

Methods: We accomplished parallelized whole-brain voxel-based morphometry analyses in two patient cohorts with chronic visceral pain, i.e., ulcerative colitis in remission and irritable bowel syndrome, and healthy individuals. In addition to analyzing changes in gray matter volume (GMV) in each patient cohort versus matched healthy controls using analysis of covariance, multiple regression analyses were conducted to assess correlations between GMV and symptom severity and chronic stress, respectively.

Results: Results revealed reduced GMV in frontal cortex and anterior insula in ulcerative colitis compared to healthy controls, supporting alterations in the central autonomic and salience networks. Conversely, in irritable bowel syndrome distinctly different, more

widespread differences from healthy controls were observed, comprising both decreased and increased GMV within the sensorimotor, central executive and default mode networks. While associations between visceral symptoms and GMV within frontal regions were altered in both patient groups, correlations with chronic stress were only found for irritable bowel syndrome, encompassing numerous brain regions and networks.

Conclusion: Together, these findings complement and expand existing brain imaging evidence in chronic visceral pain, supporting distinct alterations in brain morphology in patients with chronic-inflammatory and functional bowel disorders despite considerable overlap in symptoms and comorbidities.

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Effects of acute inflammation on the acquisition and extinction of conditioned visceral pain-related fear in healthy humans

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Background: Impaired extinction of pain-related fear memories can lead to persistent or resurging fear of pain, contributing to the development of chronic pain conditions. The mechanisms underlying maladaptive pain-related learning remain incompletely understood. Given that inflammation can interfere with learning and memory processes, we conducted two fMRI studies in healthy humans to assess the impact of acute inflammation on the acquisition and extinction of conditioned pain-related fear.

Methods: Healthy volunteers (N=95) underwent a differential fear conditioning paradigm with visceral pain as clinically-relevant unconditioned stimulus (US) and an equally aversive tone as non-noxious US. Participants were randomized to receive an injection of lipopolysaccharide (LPS) or placebo before either acquisition (study 1) or extinction training (study 2). Behavioral and neural responses to visual conditioned stimuli predicting either visceral pain (CS+VISC) or aversive tone (CS+AUD), or to a safety cue (CS−) were assessed.

Results: Fear learning engaged modality-specific brain regions of the central salience and memory networks, with enhanced fear learning to the CS+VISC compared to the CS+AUD. Despite pronounced LPS-induced effects on inflammatory markers and negative affect, we did not find evidence that inflammation resulted in altered fear learning and extinction at the behavioral level. However, in study 1, we found significantly greater neural activation in amygdala, hippocampus and caudate-putamen in response to the CS+VISC during extinction training in LPS-treated participants.

Conclusion: Inflammation during fear acquisition promotes the establishment of a more robust neural signature of the memory trace for visceral-pain predictive cues, which may constitute a primer for maladaptive fear extinction.

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Stress is not always stress: a comparison of cortisol and Brain Derived Neurotrophic Factor (BDNF) in hair after natural disaster stress and academic stress

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Background: Animal experiments demonstrate particularly negative stress effects for high intensity and complex stress paradigms. Translation is challenging as biological sampling options in humans are limited.

Methods: Natural disaster stress and academic stress were compared in 72 healthy Mexican Veterinary Medicine students exposed to the September 19th 2017 earthquake (S19) and in 72 unexposed students (MSUS) at semester beginning (T1 - minimal academic stress) and during exams (T2 - high academic stress) using hair to measure both the hypothalamus pituitary adrenal stress axis marker cortisol and the neuroendocrine plasticity marker brain derived neurotrophic factor (BDNF).

Results: Hair-cortisol was dramatically higher in S19 than MSUS at T1. Inversely, the level of hair-BDNF was lower in S19 than MSUS. S19 compared to MSUS at T1 also scored lower in Profiles of Mood States (POMS) `friendliness´ and higher in `fatigue-inertia´, Perceived Stress Scale (PSS), and State and Trait Anxiety Index (STAI). No significant changes were observed in S19 from T1 to T2 and hair-cortisol and PSS were still higher, while hair-BDNF was lower in S19 then MSUS at T2. By contrast, hair-BDNF, POMS `fatigue-inertia´, and STAI increased while `friendliness´ dropped in MSUS from T1 to T2 so that MSUS had equally high POMS and STAI compared to S19 at T2.

Conclusion: Exams exert anxiety and mood disturbances that can be well coped with and increase neuronal plasticity markers detectable in hair, while earthquakes represent a severe real-life stress with a dramatic impact on mood and neuroendocrine indicators of health deterioration.

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The role of estrous cycle induced cytokine expression on neuroinflammation in NF-kB p50 knock out mice and its impact on learning and behavior

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Background: The innate immune response plays an essential role for the migration of leucocytes into the vaginal tissue during the estrous cycle of mice. This proinflammatory process does not only affect the female reproductive tract but also has systemic effects on the cerebral cortex which need further investigation. Numerous studies proved that because of the hormonal changes across the different estrous phases (proestrous, estrous, metestrous, diestrous), especially for the female steroids 17-ß-estradiol and progesterone, Th1 and Th2 cytokines are modulated according to the peak or lack of estradiol.

Methods: We hypothesized that the inflammatory response during the proestrous and estrous phase has an influence on cognition of the mice, particularly on learning processes and anxiety-like behavior. Furthermore, the effect of ageing was modulated by using a NF-kB p50 knock out strain. NF-kB induces cellular apoptosis and is suppressed by estrogen. Accordingly, the presence of female steroids could inhibit the expression of inflammatory mediators. The estrous phase was non-invasively determined by vaginal lavage performed every day for a total of two weeks to make sure that the estrous cycle was synchronized between the mice. Additionally, the vaginal smear was cytologically characterized by the typology of presented cells. The cognition will be tested by an estrous adjusted test protocol in the IntelliCage for a duration of 5 days and following tests in the black-and-white-box paradigm. We want to show how these changes in the cytokines and cognitive performance can be linked to neuroinflammation and can provide more knowledge of gender specific neurodegenerative diseases.

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A role for n3 fatty acids in the modulation of LPS-induced fever or hypothermia: combined lipidomics in a multimodal pathway analysis of brain lipid mediators

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Background: During systemic inflammation, circulating mediators are detected by circumventricular organs like the vascular organ lamina terminalis (OVLT), a critical brain structure for fever induction. We aimed to investigate the role of n3 fatty acids (FA) on brain inflammation, immune-to-brain communication and fever during lipopolysaccharide-induced (LPS) systemic inflammation in wild type and fat1 mice, which produce n3 FAs endogenously.

Methods: Multimodal analyses, combining telemetric recording of body core temperature with expression of inflammatory marker proteins and enzymes involved in lipid metabolism, targeted LC-MS/MS, untargeted lipidomics and MALDI-MSI revealed new spatiotemporal insights into dynamics and roles of hypothalamic/OVLT lipid mediators for brain inflammation and immune-to-brain communication.

Results: A high LPS-dose induced short lasting fever in wild type (WT) mice, which was absent in fat1 mice followed by hypothermia in both genotypes. This response was accompanied by significantly lower signs of inflammation like circulating IL-6 levels or hypothalamic expression of components of the signal transducer and activator of transcription-3 and nuclear factor-kB signaling of fat-1 mice after LPS-stimulation compared to WT counterparts. Out of 1000 lipids included, a remarkable increase of the potentially anti-inflammatory endocannabinoids monoacylglycerol MG(20:4) and MG(22:6) in fat-1 vs. WT mice 24 h after LPS treatment illustrated changes of endocannabinoid signaling due to n3-FAs enrichment. Novel inflammatory lipid targets were revealed (e.g. acylcarnitines [CAR(16:0)]), which can modulate inflammation but remain to be further investigated as to their role in brain inflammation and sickness responses.

Conclusion: Overall, n3-FAs enrichment promoted resolution of inflammation by pro-resolving, anti-inflammatory mechanisms involving hypothalamic resolvin D1 dampening fever post-LPS-stimulation.

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Adrenaline, noradrenaline, and cortisol alter immune cell numbers and promote innate immune functionality of domestic pigs in an intravenous infusion model

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Background: Although the domestic pig plays an increasing role as a model organism for human physiology, knowledge about the porcine immune system under the influence of stress hormones is fragmentary. Particularly, the effects of catecholamines on porcine leukocytes have rarely been studied. Therefore, this study examined the effects of adrenaline,

noradrenaline, and cortisol treatment on number and functionality of porcine blood immune cells.

Methods: Castrated male pigs (n=34) were equipped with indwelling vein catheters and treated with either adrenaline, noradrenaline, cortisol (resembling physiological stress concentrations), or saline via intravenous infusion for 48h. Blood samples were collected at -24h, -22h, 0h, 2h, 24h, 48h and 120h. Leukocyte numbers and T cell subsets were determined by flow cytometry. Mitogen-induced lymphocyte proliferation was examined by measuring 3H-thymidine incorporation and phagocytic activity of neutrophils and monocytes was assessed by measuring fluorescent particle ingestion.

Results: Pigs receiving cortisol showed lower blood T and B cell numbers accompanied by inhibited lymphocyte proliferation but increased monocyte phagocytosis after 24h and 48h of infusion. Noradrenaline caused decreased lymphocyte proliferation after 2h of treatment and both catecholamines promoted phagocyte activity. Also, several blood T cell subsets were decreased after 2h.

Conclusion: Overall, we found differential effects of the main mammalian stress hormones, indicating an adaption rather than a simple immunosuppression, as shown in the shift towards innate immune functionality. This study fills a gap in basic research about the porcine immune system and finds many similarities to humans. This also strengthens the role of the domestic pig as a model in psychoneuroimmunology.

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The cholinergic system takes center stage in the skin´s response to stress: Chrna7 at the switch between pro- and anti-inflammatory responses in allergic inflammation

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Background: Stress as elicited by perceived threats enhances allergic inflammation. This involves sensory neuropeptides and neurotrophins. The role of the cholinergic system (CS) in this context is unknown.

Methods: We employed an established mouse model for allergic dermatitis (AID) and noise induced stress (NiS) to assess CS markers, inflammation and the effect of neurotrophin depletion.

Results: Quantitative rtPCR revealed multiple changes in CS markers such as increased VChAT, ChAT, ACh, Ch, BChE, AChE, Chrna7, Chrna9, Chrm3 and Chrm5 mRNA levels and decreased CrAT, OCT3, and SLURP2 in AID+NiS skin, but no change of SLURP1, LYNX1, Chrnb2, Chrnb4 and ChrnE mRNA levels. With respect to inflammation markers, NiS downregulated HDAC5, HIF1α, Src, HMGB1, IL1β, IL1R1, IGFBP5, TNFα and TNFR1 and induced a shift of the IL10/TNFα ratio towards IL10 in AID skin. These changes were associated with an NiS worsened AID as evidenced by enhanced epidermal thickening and increased neurogenic inflammation assessed by histomorphometry and cell activation assays. Anti-NGF blocked most of the observed NiS effects and in addition lead to a steep increase in SLURP1.

Conclusion: The cholinergic stress-axis enhances TH-2 driven allergic inflammation, which can be reversed by NGF.

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Stress reactions and test performance in a Zoom session with and without the camera running

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Background: The pandemic brought a sudden switch in working culture with many office workers having to shift their work to a home office setting. It is currently unclear, if the specific setting relates to stress. We therefore asked whether a performance test carried out per Zoom leads to physiological and psychological stress reactions, and if these reactions are moderated by switching the PC camera On vs Off.

Methods: N=107 students completed a verbal fluency test and were assigned to the conditions camera on vs off. Cortisol, salivary alpha-amylase (sAA) and reported stress (RS) were recorded one minute before and three times after the test.

Results: There was an increase in cortisol levels ($t(106) = 3.06$, $p = .003$), in RS ($z = 7.2$, $p < .001$), and in sAA ($t(107) = 1.96$, $p = .54$). The camera conditions didn't affect responses in cortisol levels ($t(105) = .91$, $p = .37$), RS ($t(106) = .56$, $p = .57$), but in an unexpected direction in sAA (($t(106) = 1.94$, $p = .06$). Test performance was higher in the camera off condition ($t(106) = 2.24$; $p = .027$).

Conclusion: These results show that an performance test online conducted triggered stress reactions. The running camera was not associated with higher stress responses, however with weaker performance. The perception of one's own person on the screen may call for attention resources that are needed for the verbal fluency test. The higher sAA response when the camera was off should be replicated in further studies.

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From chronic stress to systemic inflammation to cortical thickness: pathways in healthy, mid-aged adults?

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Background: Growing evidence supports a neurobiological link between systemic inflammation and loss of structural brain integrity. Similarly, physiological correlates of long-term stress, such as elevated levels of glucocorticoids, have been associated with structural degradation in the hippocampus and the human neocortex. Although systemic inflammation is associated with greater exposure to glucocorticoids, little is known about how these two processes interact in affecting brain structure.

Methods: The present study examined the interplay between systemic inflammation and long-term glucocorticoid exposure in their effect on cortical thickness and hippocampal volume by means of structural equation models (SEMs; N = 169, mean age = 39.4, 64.5% female). Systemic glucocorticoid exposure was measured via hair cortisol and cortisone concentrations. Systemic inflammation was indicated by blood serum levels of interleukin-6, high-sensitive C-reactive protein and the systemic inflammation index (SII). As measure of cortical atrophy, we used cortical thickness, which is more anatomically specific than volumetric measures and more sensitive to degenerative changes.

Results: Although SEMs can account for complex interactions, our results contrast previous findings: no significant connections were found between physiological stress, systemic inflammation and cortical thickness.

Conclusion: One reason for the diverging results could be our comparably young and healthy sample. This finding supports increasing evidence that neurophysiological associations found in at-risk populations do not generalise to healthy, middle-aged samples. Nonetheless,

investigating neurodegenerative processes on a systemic level remains a promising approach. The present investigation may serve as a baseline for future work on interactions between stress physiology, inflammation and brain structure in pathological or ageing populations.

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Sex-specific effects of early life adversity in combination or not with chronic psychosocial stress during adulthood on physiological parameters in C57BL/6N mice

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Background: Early life adversity (ELA) and chronic psychosocial stress during adulthood represent independent risk factors for many somatic and affective disorders associated with an activated immune status and chronic low-grade inflammation.

Methods: Here, we investigate in C57BL/6N male and female mice whether early life adversity (ELA) increases stress vulnerability later in life. ELA was induced by maternal separation (MS; 3h per day, postnatal day (PND) 1-14; controls: noMS group), chronic psychosocial stress during adulthood in males by the chronic subordinate colony housing (CSC; controls: single housed controls, SHC) and in females by the social instability paradigm (SIP; controls: group housed controls, GHC).

Results: In line with own previous data, CSC vs. SHC males showed thymus involution, adrenal enlargement and a reduced in vitro adrenal corticosterone (CORT) response to adrenocorticotropic hormone (ACTH) stimulation in the noMS group, while these effects were absent in respective MS males. Plasma CORT was neither affected by MS nor CS, with the latter being again in line with own previous data. SIP vs. GHC females showed thymus atrophy in the noMS group. Adrenal explants of MS, but not noMS females were responsive to in vitro ACTH stimulation, with SIP MS females preventing this sensitization.

Conclusion: Together, our findings indicate that ELA ameliorates rather than aggravates the vulnerability to chronic psychosocial stressors during adulthood, arguing rather in favor of the “match-mismatched hypothesis” then of the concept of “additive effects of repeated life stressors”.

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Effects of anti-inflammatory drug treatment on psychological and bodily sickness symptoms during experimental endotoxemia: A randomized controlled study in healthy volunteers

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Background: Systemic inflammation contributes to the etiology and pathophysiology of affective conditions at least in a subset of patients. First clinical evidence suggests a beneficial role of anti-inflammatory treatment in inflammation-associated depression. Herein, we combined human experimental endotoxemia as an established model to induce acute systemic inflammation with the administration of ibuprofen as a non-selective cyclooxygenase inhibitor. This design allowed to test if anti-inflammatory drug treatment ameliorates inflammation-induced dysthymia, anxiety, and bodily sickness symptoms.

Methods: We herein analyzed data from an ongoing randomized double-blind study. N=52 healthy volunteers received either ibuprofen (600mg, per os) or placebo 45 minutes before administration of 0.8ng/kg lipopolysaccharide (LPS). Plasma cytokines and cortisol as well as dysthymia, state anxiety, and bodily sickness symptoms using standardized questionnaires were repeatedly assessed before and up to six hours post LPS-injection.

Results: LPS application led to significant increases in dysthymia, state anxiety, and bodily sickness symptoms (all $p<.001$, time effects). Increases in dysthymia and state anxiety as well as in bodily sickness symptom scores were significantly less pronounced in ibuprofen-treated volunteers (all $p<.01$, interaction effects). Analysis of inflammatory parameters is currently in progress.

Conclusion: Our data showed that an anti-inflammatory treatment with ibuprofen ameliorates inflammation-induced psychological and bodily sickness symptoms. Together, our findings support increasing evidence of a therapeutic potential of anti-inflammatory treatments in the context of inflammation-associated affective conditions. Further research is needed to elucidate underlying mechanisms and the generalizability to chronic inflammation.

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Dopamine affects bone formation in arthritis patients

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Background: Bone remodeling dysfunction contributes to inflammatory diseases including rheumatoid arthritis (RA). Current therapies target osteoclasts to reduce bone degradation, but treatments would be required to promote bone protection by acting directly on osteoblasts. Recently, dopamine was found in inflamed joints in RA and dopamine receptor (DR) expression was observed in synovial tissue. Thus, we aimed to determine the implication of dopamine in the bone formation process in RA.

Methods: Presence of dopamine receptors in bone tissue of RA or osteoarthritis (OA) patients was examined by immunohistochemistry. DR in isolated osteoblasts was analyzed by flow cytometry. Influence of dopamine on human osteoblasts was tested in vitro, supplementing the medium with specific DR-agonists. Cytokine release in supernatants was measured by ELISA. Mineralization was evaluated by Alizarin red staining.

Results: All DR were observed in bone tissue as well as in isolated human osteoblasts. Isolated osteoblasts expressed tyrosine hydroxylase, the rate limiting enzyme for dopamine production, and contained dopamine. The activation of D2-like DR significantly increased bone mineralization in RA osteoblasts. Macrophage-migration-inhibitory-factor (MIF) was increased after D2-like DR stimulation in RA osteoblasts but no significant differences were observed for IL-6 and IL-8.

Conclusion: DR were found in the bone remodeling area and dopamine can be produced by osteoblasts, thus suggesting a local autocrine/paracrine pathway of dopamine in the bone. D2-like DRs are responsible for bone mineralization in osteoblasts from RA patients without a

substantial increase of proinflammatory cytokines, thus suggesting the targeting of D2-like DR as a promising therapeutic strategy to counteract bone resorption in arthritis.

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Impact of fatigue on rheumatic diseases

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Fatigue is a common, disabling, and difficult-to-manage problem in rheumatic diseases. The concept of fatigue is difficult to define. No clear and widely accepted definition of fatigue is available. The symptoms of fatigue are defined as an overwhelming, debilitating, and sustained sense of exhaustion that decreases the ability to function and carry out daily activities. Prevalence estimates of fatigue within musculoskeletal diseases vary considerably (35 % - 82 %). Data about the role of fatigue for the patient's quality of life, diagnostic tools in fatigue detection, factors contributing fatigue like disease activity and psychological factors, some experimental studies to verify the biological background of fatigue will be presented. Management of fatigue including pharmacological and non-pharmacological treatment is also part of this talk.

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Pain and inflammation in rheumatic diseases

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Pain is a challenge to the rheumatologists. Not only patients with active arthritis as well as patients with a good therapeutic response and remission of arthritis complain of persistent joint pain. It was proposed that a chronic pain stimulus may have stronger impact in a chronic inflammatory state, and the process towards a pain condition may be influenced by individual predisposition for development of chronic pain. In addition, the features of peripheral and central pain processing may be exacerbated by inflammation, and disturbed pain processing may be a feature contributing to widespread pain. Concept of resilience can be applied to fibromyalgia and other chronic pain situations. There are many different strategies of pain therapy such as pharmacological and non- pharmacological in patients with rheumatic diseases. Special role have right now JAK-Kinase inhibitors. The knowledge of placebo mechanisms may help to improve pain treatment in chronic pain conditions.

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Influence of real-life psychosocial stressors on immune system dynamics: a time series analysis approach

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Background: This integrative single-case study investigated the influence of emotionally meaningful daily incidents on immune system dynamics in a female patient with prior breast cancer.

Methods: The 60 year-old subject collected her entire urine for a period of 32 days in 12-hour intervals (63 consecutive urine samples) to determine interleukin-6 (IL-6) (ELISA), neopterin (cellular immune parameter) (HPLC), and creatinine (HPLC). In addition, each morning and evening, the patient filled out questionnaires regarding her emotional state and daily routine (e.g. medication, sleep, physical activity). Moreover, weekly, the patient was interviewed to identify past week's emotionally meaningful daily incidents. Time series analysis consisted of ARIMA modeling and cross-correlational analyses.

Results: Using interview and questionnaire data, a time series of emotionally stressful mother-related incidents was constructed. This stressor series was found to be temporally connected with significant ($p < .05$) changes in urinary IL-6 and neopterin concentrations. Specifically, urinary IL-6 concentrations showed anticipatory increases within 24h prior to meaningful mother-related stressors and subsequent decreases after a total of 36–48h following stressors. Urinary neopterin concentrations showed ultimate increases in response to mother-related stressors thereby mirroring findings on urinary IL-6 levels.

Conclusions: The results of this study indicate opposing roles of IL-6 and neopterin in stress-related inflammatory responses. Moreover, findings suggest that the temporal delays of stress responses under real-life conditions might exceed those typically found in laboratory experiments which may be due to the emotional processing of meaningful experiences.

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Efficacy of sertraline versus celecoxib in major depressive disorder: macrophage migration inhibitory factor for patient stratification

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Background: A mounting body of evidence supports the role of inflammatory activation for treatment resistance in a subgroup of patients with Major Depressive Disorder. Thus, individualized treatment approaches are needed. The present study investigated potential biomarkers that may indicate treatment success to standard therapy or an alternative anti-inflammatory agent.

Methods: A phase IIa randomized placebo-controlled trial was performed to assess efficacy of sertraline plus placebo (n = 23) and sertraline plus celecoxib (n = 20) in patients with Major depressive disorder. Thereby, levels of inflammatory compounds in responders/remitters and non-responders/non-remitters prior and during the treatment phase were analyzed. Levels of macrophage migration inhibitory factor, neopterin, and tumor necrosis factor alpha were determined by enzyme-linked immunosorbent assay; response and remission were measured by reduction of the Montgomery Åsberg Depression Rating Scale score.

Results: In both treatment groups a significant decline in depression symptoms but no difference between both groups was observed. Only for macrophage migration inhibitory factor a predictive pattern emerged: Baseline levels were significantly lower in sertraline plus placebo remitters than non-remitters (similar trend in responders and non-responders). Responders to celecoxib showed higher baseline levels than non-responders as a trend.

Conclusion: The results are preliminary due to the small sample sizes of patient subgroups. Nevertheless, high levels of macrophage migration inhibitory factor indicated non-remission to sertraline and potentially response to celecoxib. Thus, the present study provides valuable

evidence for this immune compound as a promising biomarker for patient stratification for treatment choice.

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The alpha7 nicotinic acetylcholine receptor – a protective factor against endothelial to mesenchymal transition (EMT) in fibrosis?

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Background: Systemic sclerosis (SSc) is a complex autoimmune disease leading to excessive production of collagen and microvascular injuries resulting in tissue fibrosis. Activated myofibroblasts, a mesenchymal cell population, play a central role in tissue remodeling. Interestingly, vascular endothelial cells can differentiate to extracellular matrix producing myofibroblast-like cells via endothelial to mesenchymal transition (EMT). Previously, we reported that pharmacological agonists of the alpha7 nicotinic acetylcholine receptor (alpha7nAChR) have a promising protective potential in human dermal fibroblasts (HDF) and experimentally induced skin fibrosis. We have identified the alpha7nAChR as an essential mediator of the molecular action of the antifibrotic effect of alpha7nAChR in HDF and skin.

Methods: Here, we aim to investigate a novel facet of the pathogenesis of fibrosis addressing to effect of alpha7nAChR on EMT in human dermal microvascular endothelial cells (HDMEC).

Results: Our first preliminary data proved the expression of the alpha7nAChR in primary HDMEC at RNA level using semi-quantitative RT-PCR. Further, the presence of this receptor could be confirmed at protein level via Western immunoblotting in HDMEC. Immunofluorescence analysis with a specific anti-alpha7nAChR antibody disclosed expression and a cell membrane associated localisation of this receptor in these cells. Finally, we demonstrated that the alpha7nAChR is functional in HDMEC by measurements of calcium influx using specific alpha7nAChR agonists and blocking experiments with alpha-bungarotoxin an alpha7nAChR antagonist.

Conclusion: This preliminary work represents the basis for intensive future investigations of endothelial cells in fibrosis to clarify the role of the alpha7nAChR in EMT and support therapeutic exploitation of alpha7nAChR receptor agonists in fibrotic skin diseases.

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Fibroblast function in vitro modulated by the melanocortin tripeptide derivatives KdPT and WOL074-029

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Background: We previously reported on the impact of the melanocortin peptide alpha-melanocyte-stimulating hormone (alpha-MSH) on fibroblast function including skin fibrosis. Truncated peptides from the C-terminal domain of alpha-MSH as well as some derivatives have persevered immunomodulating effects but do not bind to the melanocortin-1 receptor (MC-1R). Thus, they do not elicit MC-1R-mediated pigmentation as an obligatory adverse effect of MC1R agonistic peptides. Among the melanocortin tripeptide derivatives is Lys-Pro-d-Thr (KdPT) which not only suppressed interleukin-IL-1beta-mediated expression of proinflammatory cytokines but also exhibited beneficial effects in animal models of inflammatory bowel disease as well as in patients with Crohn´s disease.

Methods: Here we investigated whether KdPT and another more stable derivative, WOL074-029 are capable of suppressing fibroblast activation induced by transforming growth factor-beta1 (TGF-beta1).

Results: Both KdPT and WOL074-029 suppressed mRNA expression of collagen I, fibronectin I, connective tissue growth factor and alpha-smooth muscle actin in human dermal fibroblasts (HDF) compared with TGF-beta1 alone as shown by real-time RT-PCR analysis. These effects were dose-independent and detectable at subnanomolar levels of both peptides. In accordance, secretion of collagen I was significantly suppressed by KdPT and WOL074-029. The peptides did not interfere with smad2/3 signalling as shown by Western immunoblotting and immunofluorescence analysis. Interestingly, expression of PepT2 but not PepT1 was present in HDF raising the possibility that KdPT and WOL074-029 elicit the observed effects by these tripeptide transporters.

Conclusion: Future studies are in progress to further define the mode of action of KdPT and WOL074-029 in fibroblasts and the in vivo relevance of these findings.

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Baseline and inflammation-induced state fatigue impact motivated behavior in the context of a SARS-CoV-2 vaccination model

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Background: Fatigue is understood as multidimensional with at least physical (e.g., effort expenditure) and mental (e.g., reward learning) components that affect motivated behavior, but their interaction is not fully understood. Here, we jointly objectify both components in a validated experimental setup to better understand how they contribute to changes in behavioral motivation under physiological fatigue.

Methods: In a repeated-measures design (N = 55), we use ongoing vaccinations against SARS-CoV-2 as a model for immune-related fatigue, and employ an experimental task where reward magnitude depends on both choice and physical effort exertion. Using mixed-effects models, we analyze the effects of baseline fatigue, vaccination-induced state changes of fatigue and their interaction on five outcome measures of task performance.

Results: SARS-CoV-2 vaccination increased state fatigue. Together with baseline fatigue levels, these state fatigue increases predicted altered behavioral outcomes. Greater increases in state fatigue predicted reduced confidence while learning when to express effort, whereas baseline fatigue was associated with greater coregulation of effort and confidence. In line with vulnerability-stress models of disease, task performance was decreased in participants with high baseline level of fatigue who additionally showed greater vaccination-induced state changes of fatigue.

Conclusion: Our approach could help explain the wave-like dynamics in many fatigue-associated clinical conditions, where short-lived stressful events result in exceptional severe impairments. Moreover, the interplay of baseline and state changes suggests that an exclusive focus on either the short-lived peaks or long-lasting, habitual levels of fatigue could constrain our understanding of individual trajectories and effects on everyday life activities.

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The effect of LPS and ketoprofen on stress and immune responses, central monoamines and social behaviour in pigs

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Background: Immune activation has been suggested as a major factor influencing social interactions in pigs, with outbreaks of damaging behaviours such as tail biting as a possible result. To address this, cytokine activated signalling pathways that may be involved in inducing behavioural alterations were examined by using an LPS-model.

Methods: Fifty-two female pigs (11-12 weeks) were allocated to four treatments comprising two injections: saline–saline, saline–LPS (1.2 µg kg-1), ketoprofen (6 mg kg-1)–saline, and ketoprofen–LPS. General activity and social behaviour were observed at specific time intervals. Saliva was analysed for cortisol, adenosine deaminase and haptoglobin. Plasma was analysed for tryptophan and kynurenine. At 72 hours after the injection, the pigs were humanely killed, and the frontal cortex, hippocampus, hypothalamus, and brain stem were sampled and analysed for cytokines, tryptophan, kynurenine and monoamines.

Results: LPS activated the HPA-axis, triggered the acute phase response and elicited behavioural signs of sickness within six hours after the challenge. Ketoprofen attenuated these effects. LPS did not affect central pro-inflammatory cytokines (TNF-α, IFN-γ, IL-18), but depleted peripheral and central tryptophan. Dopamine concentrations in the hypothalamus of LPS-injected pigs were significantly lower compared to saline-injected pigs. LPS-injected pigs had significantly lower concentrations of serotonin in their hypothalamus and noradrenaline in their hippocampus than pigs that were pre-treated with ketoprofen. Changes in social interactions were detected at both individual and group level.

Conclusion: Thus, a controlled immune activation altered neurotransmitters and neuromodulators in the brain that are hypothesised to play an important role in the regulation of mood and behaviour.