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The Virome Regulates the Effects of Chronic Stress in Mice

N. Ritz, L.A. Draper, T.F.S. Bastiaanssen, C.J.R. Turkington, V.L. Peterson, M. van de Wouw, K. Vlckova, C. Fulling, K.E. Guzzetta, A. Burokas, et al.

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Conclusions: Although pregnancy is in itself a period of great vulnerability for women's mental health, our results show that COVID-19, with its direct and indirect impact, has inflamed the expression of psychiatric symptoms in this peculiar population. However, consequences of such a combination of threatening events are still unknown; an accurate follow-up of these women may be useful to provide adequate care and to improve the management of this challenging pandemic.

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GUT MICROBIOTA REGULATES DIURNAL OSCILLATIONS IN STRESS RESPONSIVENESS

G. Tofani^{1,2}, S.J. Leigh², C.E. Gheorghe^{2,3}, T.F.S. Bastiaanssen^{1,2}, G. Clarke^{2,3}, J.F. Cryan^{1,2}, ¹ University College Cork, Anatomy & Neuroscience, Cork, Ireland; ² University College Cork, APC Microbiome Ireland, Cork, Ireland; ³ University College Cork, Psychiatry & Neurobehavioral Sciences, Cork, Ireland

Many neuropsychiatric disorders are intricately linked to stress, and patients with these conditions often display alterations in their gut microbiota profile and in circadian regulation of hormonal and behavioral timekeeping processes. In this work we explore how the gut microbiota modulate diurnal oscillations in neuroendocrinal systems resulting in different stress responsiveness across the day, to shed light into how these gut microbes could be playing a role in neuropsychiatric disorders. Glucocorticoid hormones are key to regulating the organism's response to the environment and display a robust rhythm with a distinct peak around the sleep-wake transition, which is one of the entraining cues from the brain to peripheral tissues. Stress-induced glucocorticoid secretion will act on the same tissues leading to changes in state to cope with any stressors. Although the relationship between gut microbiota and stress is well established, it is still largely unknown how the circadian component of glucocorticoid secretion plays a role in such modulation. In this study we aimed to explore the influence of the gut microbiota in the rhythmicity of the brain transcriptome and metabolome, the HPA-axis, and the downstream effects on the stress response and behavior. This study used germ-free and microbial depleted animals as models of microbial disruption. We first used RNA-sequencing of the master clock in the brain – the suprachiasmatic nucleus – as well as hippocampus, and amygdala to dissect the influence of the gut microbiota in the brain's diurnal gene expression oscillations. Rhythmicity analysis was performed using an in-house developed R package. Our analysis revealed that gut microbes are key to maintain normal gene expression across the day in these regions and that the disrupted genes are associated with pathways related to circadian rhythm and the stress response. Next, we used a multi-omics approach, combining RNA-sequencing and metabolomics of the amygdala and hippocampus for a joint pathway analysis, which indicated that glutamate metabolism is disrupted in animals with differential microbial status. Glutamate is the most abundant excitatory neurotransmitter and plays a key role in maintaining appropriate stress responsiveness. Then, to interrogate how the gut microbiota could be modulating these pathways related to the stress response in the brain, we assessed the daily oscillations of glucocorticoids in the microbially-disrupted animals and showed that corticosterone rhythmicity is disrupted by microbial status (Rhythmicity analysis, One-way ANOVA with Kruskal-Wallis post hoc test). Gene expression profiling throughout the day was performed by quantitative RT-PCR on the paraventricular nucleus of the hypothalamus, pituitary and adrenal glands and revealed alterations in clock gene expression and in genes that compose pathways important to appropriate HPA-axis function (Rhythmicity analysis, Unpaired t-test). Lastly, we demonstrated that these baseline alterations in microbially-depleted animals led to a disruption of the stress response and stress sensitive behavior in a time-of-day dependent manner (Two-way ANOVA with Kruskal-Wallis post hoc test). In summary these findings reveal that gut microbiota may be a crucial factor in maintaining appropriate stress responsiveness across the day, helping to elucidate mechanisms of microbial modulation of brain function and behavior.

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THE VIROME REGULATES THE EFFECTS OF CHRONIC STRESS IN MICE

N. Ritz¹, L.A. Draper², T.F.S. Bastiaanssen¹, C.J.R. Turkington², V.L. Peterson¹, M. Van de Wouw¹, K. Vlckova¹, C. Fulling¹, K.E. Guzzetta¹, A. Burokas¹, H. Harris², M. Dalmasso², F. Crispie³, P.D. Cotter³, A.N. Shkoporov², G.M. Moloney¹, T.G. Dinan⁴, C. Hill², J.F. Cryan¹, ¹ University College Cork, APC Microbiome Ireland- Dept. of Anatomy & Neuroscience, Cork, Ireland; ² University College Cork, APC Microbiome Ireland- School of Microbiology, Cork, Ireland; ³ University College Cork- Teagasc Food Research Centre, APC Microbiome Ireland- Dept. of Food Biosciences, Fermoy, Ireland; ⁴ University College Cork, APC Microbiome Ireland- Dept. Psychiatry and Neurobehavioural Science, Cork, Ireland

Introduction: Although the microbiota-gut-brain axis has been shown to play an important role in stress response and serve as a target for stress amelioration, the focus to date has been almost entirely on the bacteriome [1]. The gut virome constitutes a major portion of the microbiome, with bacteriophages (or phages) having the potential to remodel bacteriome structure and function. Faecal filtrates, primarily composed of phages, have been shown to be a potent microbiota-based therapy, capable of improving microbiota restoration and mammalian host health during *Clostridioides difficile* infection [2], antibiotic-induced microbiota perturbation [3], and type 2 diabetes [4].

Rationale: As chronic stress changes the gut bacteriome, we hypothesized that it would also affect virome composition. To determine if these changes were causally related to stress-associated behavioural or physiological outcomes, we conducted a faecal virome transplant (FVT) collected from mice before stress and autochthonously transferred it to mice undergoing chronic social defeat stress.

Results: Chronic stress led to behavioural, immune, and bacteriome alterations in mice that were associated with changes at the level of the virome. FVT therapy led to improvements in stress-coping-related behaviours tested in the social interaction test and elevated plus maze, and restored circulating corticosterone levels during the forced swim test. At the immune level, FVT also restored stress-induced changes in peripheral Ly6Chi monocytes and neutrophils in addition to attenuating plasma IP-10 and splenocytes culture productions of TNF- α , IL-12/IL-23p40, and IL-6 inflammatory cytokines. FVT increased the levels of fifteen bacterial species that were depleted by stress and reduced five species that were increased in stressed animals. On assessment of gene expression levels in two stress-sensitive brain areas, the hippocampus and amygdala, we found that genes affected by stress and restored by FVT were evenly distributed in the hippocampus, but in the amygdala, there was a significant restoration of positively regulated genes. The top enriched Gene Ontology (GO) terms from genes affected by stress and restored by FVT were selected to specifically target functions directly involved with stress, social behaviour, the virome, and the microbiota-gut-brain axis. These GO terms consist of genes associated with fear response, immune system processes, neurotransmitter level modulation, postsynaptic neurotransmitter receptor functionality, stress response, social behaviour, and viral processes. Behavioural and immune data were analysed by orthogonal contrast, followed by Tukey's post hoc, and Benjamini-Hochberg's adjusted false discovery rate. Restoration of microbial taxa and differential transcriptomic gene expression were assessed using orthogonal contrasts in a generalized linear mixed-effects model. Conclusion These findings provide the first evidence that the gut virome is altered by stress and that naïve viromes are capable of altering stress responsivity. The bacterial population and immune modulation are affected by FVT and capable of eliciting broad effects on the host. Stress-coping behaviour and amygdalar gene expression are both buffered by FVT therapy during stress and represent key target cognate stress-sensitive systems. These data provide evidence that the virome is a viable treatment option to restore the microbiota-gut-brain axis during stress and is a potential treatment strategy for stress-related psychopathologies.

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FUNCTIONAL CONNECTIVITY PREDICTS VISUAL FIELD RECOVERY AFTER VISUAL PERCEPTUAL LEARNING IN CHRONIC STROKE

E. Namgung¹, Y.H. Kim², E.J. Lee³, Y. Sasaki⁴, T. Watanabe⁴, D.W. Kang³.
¹Asan Medical Center, Asan Institute for Life Sciences, Seoul, Korea- Rep; ²Nunaps, Inc., Seoul, Korea- Rep; ³Asan Medical Center, Department of Neurology, Seoul, Korea- Rep; ⁴Brown University, Department of Cognitive-Linguistic and Psychological Sciences, Providence, United States

Background: Visual field defect (VFD), which is common after a posterior circulation stroke, significantly reduces overall quality of life of those affected, yet its rehabilitation strategies are still being developed [1]. Visual perceptual learning (VPL), defined as the training-dependent sustained improvement in visual-perception performance, is gaining attention as a promising treatment for VFD in stroke patients [2]. Identifying predictive brain biomarkers for VPL-induced VFD recovery could help develop more personalized and targeted VPL protocols. Herein, we aimed to assess whether baseline resting-state functional connectivity (RSFC) within the visual cortices predicts VPL-induced recovery from VFD in chronic ischemic stroke.

Methods: Patients with VFD due to chronic ischemic stroke in the visual cortex were divided into two groups: training (n = 31) and no-training (n = 15). The training group received 24 VPL training sessions over 2 months, while the no-training group did not. VPL is a dual discrimination task of orientation and letters. At baseline and two months later, resting-state functional magnetic resonance imaging and Humphrey visual field tests were used to assess the RSFC in the ipsilesional, interhemispheric, and contralesional visual cortices, as well as mean total deviation (MTD) score in the affected hemi-field. The associations between the visual RSFC and MTD score were investigated at baseline and 2 months later, as well as for changes over the 2 months. The K++ means clustering was used to categorize the subgroups within the training and no-training groups based on the baseline interhemispheric visual RSFC. The visual RSFC and MTD score of the subgroups were compared at baseline and for changes over the 2 months.

Results: Baseline interhemispheric visual RSFCs at baseline and 2-month were positively associated with the MTD scores at baseline and 2-month, respectively. Higher interhemispheric visual RSFC at baseline had the strongest relationship with greater MTD score after 2-month training. Only the subgroup with higher baseline interhemispheric visual RSFC showed greater VFD improvement by VPL training: The interactions between the interhemispheric visual RSFC at baseline and VPL led to improvement in MTD scores and largely influenced the degree of VFD recovery. VPL-induced changes in the interhemispheric visual RSFC and MTD score were positively associated after adjusting age, sex, and stroke lesion volume. The no-training group did not show any of the above-mentioned findings.

Conclusions: The present study highlights critical insights regarding the neural plasticity, neurobehavioral associations, and predictive brain biomarker of VPL-induced VFD recovery in chronic ischemic stroke. Importantly, higher baseline interhemispheric RSFC in the visual cortex could potentially predict greater VPL-induced VFD recovery in patients with chronic stroke patients. Our study finding, which suggests baseline interhemispheric RSFC in the visual cortex as a promising brain biomarker for predicting VPL-induced VFD recovery, may facilitate development of tailored VPL protocols.

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EARLY PREDICTORS IN LEARNING-BASED LANGUAGE DISABILITIES: A SYSTEMATIC REVIEW AND META-ANALYSIS

M. Alabbad¹, T. Abualait². ¹Saudi Ministry of Health, Medical Rehabilitation and Long-Term Care Department, Eastern Province, Saudi Arabia; ²Imam Abdulrahman Bin Faisal University, Physical Therapy Department, Dammam, Saudi Arabia

Introduction: Language-based learning disabilities LBLDs is a common cause of academic incompetence as difficulties in language and literacy skills hinder comprehension and communication capabilities. Behavioral, neurocognitive, neurophysiological and neuroimaging measures would be useful in elucidating the underlying process of LBLDs which would be crucial for identifying early predictors of such disorders. The focus of this work was on three main specific language-based learning developmental disorders including dyslexia, dyscalculia, and dysgraphia.

Aim: We aimed to conduct a comprehensive review of LBLDs studies that investigated the major early neurophysiological, neuroimaging, and neurocognitive predictors of LBLDs in children, and to determine the robustness of each predictor and evaluate the effect size of different predictors.

Methods: The PubMed, Scopus and Web of Science WoS were searched for literature related to (neurocognitive, neurophysiological, and neuroimaging) measurements used to identify early predictors of LBLDs from January 2000 to November 2021. PRISMA guidelines were applied. Meta-analysis was performed using Jamovi version 2.2 and the CRAN module, and effect size was carried out using a random-effects meta-analysis model. Primary analyses were performed for each of the three types of LBLDs predictors, and subgroup analyses by separate outcomes.

Results: We included 86 studies with 12,245 subjects on neuroimaging (N = 45), neurophysiological (N = 29), and neurocognitive predictors (N = 12). When all neuroimaging (Functional Magnetic Resonance Imaging fMRI, Magnetic Resonance Imaging MRI, Magnetoencephalography MEG, Magnetic source imaging MSI, and functional near-infrared spectroscopy fNIRS), neurophysiological (mismatch negativity MMN, late discriminative negativity LDN, and event-related potential ERP), and neurocognitive (language skills, phonological awareness, naming, knowledge, reading fluency, and visual memory) predictors were combined separately in analysis, the overall effect size was found to be 0.396, 0.305 and 0.458 indicating all neurological predictors included in present study had medium to strong predicting power for LBLDs. overall, during neurophysiological analysis, we discovered that reduced-amplitude LDN and difficulties with late-stage auditory processing among children at risk for dyslexia had the highest effect size 0.987. Furthermore, many studies using neuroimaging measures discovered a decrease in activity in the superior temporal gyrus STG during various reading tasks in children with dyslexia and dyscalculia, with the largest effect size of 0.498. Finally, most studies discovered that developmental (dyslexia, dyscalculia, and dysgraphia) were significantly associated with decreased phonological awareness, naming speed, deletion tasks, digit span subtests, verbal word memory, and deficits in phonological and non-phonological tasks using neuropsychological and cognitive assessments, with an overall effect size of 0.458.

Conclusions: Early predictors of LBLDs would be useful as targets for specific prevention and intervention programs to be implemented at very young ages, which could have a significant clinical impact. There is a scarcity of research on developmental dysgraphia and dyscalculia, which highlights the importance of conducting research experiments on such disorders given their high prevalence and significant impact on learning abilities. A novel finding of neuroimaging predictors combined with neurocognitive and neuropsychological batteries may have implications for future research.

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