Disclosure statement:
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Neutrophil/lymphocyte ratio is increased in elderly patients with first episode depression, but not in recurrent depression

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Human immune system is a complex structure that defends the organism against diseases, although immune disorders may sometimes lead to autoimmunity, inflammatory illnesses or even cancer. Inflammation is the process of the immune system being stimulated as the reaction to infection. Recently, many researchers have been focused on the association between depression and inflammation, considering the co-occurrence of these two conditions [1]. One of the inflammatory parameters is the neutrophil-lymphocyte ratio (NLR). It is widely available, easy to measure and, unlike many others, inexpensive. The NLR is a ratio between absolute neutrophil count to absolute lymphocyte count.
We performed a retrospective, cross-sectional study with the aim of to determine the NLR in elderly patients with unipolar depression compared with non-depressed. NLR was measured in 684 Caucasian subjects (depressed: n = 465, non-depressed: n = 219), aged ≥60. There were two subgroups within depressed patients: first episode depression (n = 138, 29.6%) and recurrent depression (n = 328, 70.3%). We found that NLR was significantly lower in depression ((1.78±1.31, median: 1.45) compared with healthy control 1.95±0.73 (median: 1.85 z = 5.85, p <0.001). It was significantly higher in first episode depression (2.11±1.76, median: 1.68) compared with recurrent depression (1.64±1.04, median: 1.35 z = 3.65, p <0.001). There was a positive correlation with exacerbation of symptoms. Since the severity of depression was higher among patients with first episode, we have compared NLR between two sub-types of depression of the same severity. We found that for severe depression (but not for mild or moderate), first episode patients had higher NLR compared with patients with recurrent depression (2.32±1.72 median: 1.88 vs. 1.75±1.06 median: 1.42, respectively; z = 3.10, p = 0.002). We found non-specific effect of treatment with antidepressants or antipsychotics on lower NLR after analyzing three sub-groups of patients: those taking no medications on the study entry (n = 63), patients taking only one antidepressant (and no benzodiazepines, antipsychotics or mood stabilizers; n = 174) and patients taking only one antipsychotic (n = 86). First, we have found that unmedicated depressed patients had higher NLR compared to controls (2.10±2.13 vs. 2.01±0.75, z = 2.85, p = 0.004). We have also confirmed that in the unmedicated patients NLR was highest in the first episode depression groups and lowest in the recurrent depression (p <0.001).
In conclusion our findings may have important clinical consequences. Severity of symptoms are positively correlated with NLR, which indicates increased proinflammatory state in this sub-type of depression. This observation may indicate that with increasing severity of depression, the risk of cardiovascular events is also rising, which leads to higher mortality [2, 3]. Finally, we have found that treatment with antidepressants and antipsychotics may reduce NLR value, showing a beneficial effect of these medications in terms of cardiovascular risk. In elderly patients with depression even a small reduction of such risk may translate into better prognosis and improve quality of life. The difference between first episode and recurrent depression in terms of inflammatory biomarkers requires further studies.

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The effect of transcutaneous vagus nerve stimulation on interleukin 6 and c-reactive protein during stress in depression

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Introduction: Vagus Nerve Stimulation (VNS) is currently applied for treatment resistant uni- and bipolar depression and constitutes one of the few available neuro-stimulatory treatments. Although long-term effects do show beneficial effects of invasive VNS [1], the invasive form of VNS comes with several caveats: patients need to undergo surgery, the treatment is currently only available for treatment resistant cases and effects often become visible after a considerable treatment duration (~6 months). The more novel, transcutaneous form of VNS (tVNS) increases its appeal as a non-invasive treatment alternative and enables the systematic investigation of the underlying neurophysiological processes. Since inflammatory abnormalities have been reported in major depressive disorder (MDD) [2], patients with MDD experience high levels of stress, and VNS can reduce inflammatory activation [3] and possibly stress experience, VNS may provide a new option for treatment. We here explore the transcutaneous form of VNS for its potential to reduce inflammatory responses during stress exposure.
Aim: Explore the effect of tVNS on inflammatory marker responses during stress exposure.
Methods: Diagnosis of MDD, or absence thereof for healthy controls, was confirmed using the MINI Diagnostic Interview. Seventeen patients and 23 controls of the MODULATE trial were exposed to each tVNS and sham stimulation on two separate test days, in a counterbalanced order. Stimulation for the tVNS was performed in the cymba conchae, sham stimulation at the earlobe of the right ear. During the stimulation of approximately 1 hour, all participants performed a computerized version of the Mental Arithmetic Stress Test. Patients were fasted, and all procedures took place between 8.00 am and 12.00 am. Stimulation started after the first blood draw and continued throughout the remainder of the experiment. During the stress task, participants completed a baseline, stress and recovery phase. After 45 minutes post-stress, stimulation was discontinued and blood samples were acquired. Interleukin 6 (IL-6) and CRP levels were determined in serum in the central laboratory of the hospital, according to local procedures. Statistical analyses were performed with R version 4.2.1, using Generalized Linear Mixed Models with random intercept, condition (sham/tVNS), timepoint (pre/post-stress), group(MDD/controls) and the interaction of condition X timepoint X group, with either IL-6 or CRP as dependant variables. Post-hoc contrasts were computed. Currently, recruitment for the study is still ongoing.
Results: With the current sample size, no significant effect emerged for either IL-6 or CRP. For IL-6, there was a non-significant increase in IL-6 for the MDD group, during the post-stress timepoint (interaction estimate=3.34, t=1.84, p=0.069), and tVNS non-significantly decreased post-stress levels in the MDD group (estimate: -3.30, t=-1.28, p=0.204). No change was observed in CRP post-stress for MDD (estimate=-0.01, t=-0.22, p=0.825), and tVNS or sham did not change this relationship (estimate=0.00, t=0.06, p=0.954).
Conclusions: The preliminary results of the MODULATE study did not show any impact of tVNS on change in interleukin 6 or CRP post stress. Preliminary estimates point towards a non-significant modest blocking effect of tVNS on stress-induced increases of IL-6 levels in MDD. However the final sample size needs to be reached to draw final conclusions.

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Different relationship of neurological and non-neurological conditions with non-suicidal self-injury among youth with emotional disorders

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Introduction: Non-suicidal self-injury (NSSI) is a phenomenon of a considerable concern since it is quite prevalent in the young population (especially among youth with mental health disorders), and although it is not driven by suicidal intentions, it is found to be a predictor of suicidal risk [1]. NSSI may be related with a variety of factors, and among others, neurological and non-neurological medical disorders. However, research on this topic is still sparse. Existing findings indicate that chronic medical conditions may be a risk factor for engaging in NSSI (separately or in combination with the mental health conditions) [2]. Neurological conditions (such as epilepsy or migraine) have been relatively consistently associated with the risk of NSSI, while the data on the relationship of the non-neurological disorders (asthma, allergies, diabetes, psoriasis, etc.) with NSSI is mixed [3, 4, 5]. Due to the existing knowledge gap, the aim of our study was to investigate the predictive effects of different types of medical comorbidities in childhood and adolescence, on the presence of NSSI in the past year, among youth with emotional disorders.
Method: The study sample included 185 young patients (15–24 years old, 61.1% females) with emotional disorders (depressive disorders, anxiety disorders, adjustment disorders, or mixed disorders of conduct and emotion), treated at a day hospital. The patients were excluded from the study if they had a psychotic disorder, intellectual disability, or substance dependence disorders. The data was collected retrospectively, from the medical records, and included the following: socio-demographics (gender, age,) the data on NSSI episodes in the past year, the scores on the Global Assessment of Functioning (GAF) scale at admission, the diagnosis at discharge, the overall duration of psychiatric treatment, the data on the presence of the neurological disorders or injuries, and non-neurological disorders (such as metabolic-endocrinological, cardio-vascular, gastro-intestinal, nephrological, hematological, immunological, oncological, otorhinolaryngological, ophthalmological, orthopedic) during childhood and adolescence, as well as the data on the family history (psychiatric and medical). The data was analyzed by a logistic regression model, with the socio-demographics, neurological and non-neurological comorbidities of the patients, their family history (psychiatric and medical), their GAF scores, diagnosis (depression vs. other disorders) and the overall duration of psychiatric treatment as predictors, whereas NSSI was the outcome variable.
Results: The logistic regression model was significant (Chi-square=34.936, p=0.000), and it explained 17.2 (Cox & Snell R Square = 0.172) to 27.0% (Nagelkerke R Square=0.270) of the chance of having the NSSI episodes in the past year. The patients were more likely to have NSSI if they had a history of neurological comorbidities (OR=2.422, p=0.049), and less likely to have NSSI if they had a history of non-neurological comorbidities (OR=0.390, p=0.049).
Conclusions: The findings of this study speak in favor of the possibly different relationship of neurological (potential risk factor) and non-neurological (potential protective factor) medical comorbidities with the NSSI in young patients with emotional disorders. More research is needed in this direction, since the implications could be of considerable importance for designing prevention strategies.
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Altered salience network activation during emotional processing and anticipation in drug-naïve depressed patients

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Background: Major Depression Disorder (MDD) is characterized by a large-scale network dysfunction, contributing to impairments in cognitive and affective functioning. Deficits in default mode (DMN), limbic (LN), and salience (SN) networks have been widely reported [1]. Core regions of these networks have also been implied in emotional processing and anticipation [2-4]. Therefore, the aim of this study was to explore DMN, LN, and SN modulation during the processing and anticipation of emotional stimuli in MDD, and further investigate how these networks are functionally connected with the rest of the brain.
Methods: Twenty-one drug-naïve depressed patients (8 males, mean age = 37.48±12.01, mean education = 11.52±4.78 years) and 15 age, sex, and education matched controls (5 males, mean age = 31.53±13.52, mean education = 14.40±4.34 years) were included. All participants completed a psychological assessment and an fMRI session on a 1.5 T scanner. During the fMRI acquisition, participants performed the Affective Pictures Paradigm [4], in which they were instructed to passively observe positive, negative, and neutral pictures. The pictures were cued by a word indicating their emotional valence (Cued Condition) or by a meaningless letter combination (Uncued Condition). fMRI data were preprocessed with fMRIPrep (version 20.2.5) [5]. Group independent component analysis (ICA) was performed using GIFT (version 3.0c) to investigate how DMN, LN, and SN were modulated during the task. Psychophysiological interactions (PPI) analyses were performed in SPM12 to explore the functional coupling between task-dependent networks and all the other regions of the brain. Benjamini-Hochberg false discovery rate (FDR) correction was used to correct for the comparison of multiple networks (ICA analysis), and for PPI statistical significance was set at a cluster-level family-wise error (FWE) corrected p-value < .05.
Results: A significant interaction between Cue, Valence and Group was found ($F(1,34) = 6.394$, $p = .016$, p FDR-corr = .048, $\eta p2 = .158$) for the SN. For uncued pictures, patients presented higher activation in this network when observing negative vs. neutral pictures compared to positive vs. neutral pictures, whereas the opposite pattern was displayed by controls. For cued pictures, patients showed increased activation in the SN when observing positive vs. neutral pictures compared to negative vs. neutral pictures, and the controls had a similar activation pattern for both contrasts. No significant main effects nor interactions were found for the DMN and LN. Using a mask of SN as a seed in PPI analyses, patients showed increased functional connectivity between the SN and the left amygdala compared to controls, when observing negative vs. neutral pictures (MNI coordinates: x=-19, y=-4, z=-16; $t = 5.67$; cluster size = 8 voxels).
Conclusions: SN is altered during the processing and anticipation of emotional pictures in drug-naïve depressed patients. While processing emotional stimuli, patients showed increased activation of this network for negative vs. neutral pictures, suggesting a higher salience for negative stimuli in depression. However, when anticipating emotional stimuli, they invert their pattern (hyperactivating the SN for positive vs. neutral pictures), which may suggest a mood-brightening effect caused by the emotional cue.
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