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Neutrophil to lymphocyte ratio and antidepressant treatment response in patients with major depressive disorder: effect of sex and hippocampal volume.

Marco Paolini[a,b], Yasmin Harrington[a,b], Laura Raffaelli[b], Sara Poletti[a,b], Raffaella Zanardi[c] , Cristina Colombo[b,c], Francesco Benedetti[a,b]

[a]Vita-Salute San Raffaele University, Milano, Italy

[b]Psychiatry & Clinical Psychobiology, Division of Neuroscience, Scientific Institute IRCCS Ospedale San Raffaele, Milano, Italy.

[c]Mood Disorders Unit, Scientific Institute IRCCS Ospedale San Raffaele, Milano, Italy.

Corresponding Author:

Yasmin Harrington, San Raffaele Turro, Via Stamira D'Ancona 20, 20127 Milan, Italy.

Email: y.harrington@studenti.unisr.it

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Abstract

Several factors may affect response to treatment in Major Depressive Disorder (MDD) including immune/inflammatory alterations and regional brain volumes, particularly in hippocampal regions which have shown to be influenced by inflammatory status. Neutrophil-to-lymphocyte ratio (NLR) is an inflammatory marker found to be elevated in depressed women in large population studies. Here we investigate the effect of NLR on treatment response in MDD patients, and the role of sex and hippocampal volume on influencing this relationship. A sample of 124 MDD depressed inpatients (F=80) underwent MRI acquisition, admission NLR was calculated by dividing absolute neutrophil by absolute lymphocyte counts and depression severity was assessed at admission and discharge via the Hamilton Depression Rating Scale (HDRS). As a measure of treatment response, delta HDRS was calculated. We found a significant moderation effect of sex on the relationship between NLR and Delta HDRS: a negative relation was found in females and a positive one in males. NLR was found to negatively affect hippocampal volumes in females. Both left and right hippocampal volume positively associated with Delta HDRS. Finally, left hippocampal volume mediated the effect of NLR on Delta HDRS in females. Sex moderated the relation between inflammation and treatment response in line with previous reports linking inflammation to hampered antidepressant effect in females. Further, this effect is partially mediated by hippocampal volume, suggesting that antidepressant response may be hampered by the detrimental effect of inflammation on the brain.

Keywords: Neutrophil-to-lymphocyte ratio, major depression, inflammation, hippocampus, antidepressant response, sex difference.

1. Introduction:

Depression is one of the most prevalent psychiatric disorders and a major cause of disability worldwide (Malhi and Mann, 2018), and yet its pathophysiology is still poorly understood (Otte et al., 2016). Current consensus is that even after multiple lines of treatment, one third of patients do not achieve full symptomatic remission, and even fewer meet criteria for both symptomatic and functional remission (Sforzini et al., 2022). In recent years, much focus has been put on the role of immune/inflammatory alterations in major depression pathophysiology (Miller and Raison, 2016). Depressed patients have an increased expression of pro-inflammatory cytokines and their receptors in peripheral blood and CSF compared to controls (Miller, 2009; Sørensen, 2022); the administration of pro-inflammatory cytokines has been shown to induce depression-like symptoms in cancer patients (Capuron et al., 2002), while anti-inflammatory drugs exert antidepressant activity, sustaining a role for immune-inflammatory mechanisms as potential novel treatment targets (Benedetti et al., 2022).

Furthermore, the inflammatory status of the patient has been shown to affect treatment efficacy, with a consistent literature associating baseline levels of inflammatory biomarkers with poor response to antidepressants both in controlled trials and in real-world settings (Benedetti et al., 2021; Branchi et al., 2021). In addition, the type of treatment prescribed may also play a role, with serotonergic agents exhibiting lower efficacy than treatments acting also on noradrenergic, dopaminergic, or glutamatergic neurotransmission in patients with elevated inflammatory markers (Arteaga-Henríquez et al., 2019). However, the search for reliable inflammatory biomarkers to predict antidepressant response is in its infancy, and we are still far from translation into clinical practice. Hence, there is the necessity for continuous research on pathogenic mechanisms and new predictors to address the need of tailored treatments in a personalized medicine framework (Arteaga-Henríquez et al., 2019; Benedetti and Vai, 2023).

In recent years, growing attention has been paid to the possible usefulness of neutrophil-to-lymphocyte ratio (NLR) as an inflammatory marker in MDD: originally developed as a prognostic marker in oncology, it has since been investigated as a risk and prognostic factor for cardiovascular and infectious diseases, and associated with overall mortality in population studies (Song et al., 2021). NLR is considered to be an indicator of subclinical inflammation which reflects the balance between innate and adaptive immunity (Faria et al., 2016), and it can be easily derived from a routine complete blood count. The role of NLR has been investigated in several psychiatric conditions (Brinn and Stone, 2020), and was found to be associated with bipolar disorder, schizophrenia, and suicidal behavior (Dadouli et al., 2022; Mazza et al., 2020; Sandberg et al., 2021; Velasco et al., 2020). Concerning MDD, consistent meta-analytic evidence attested higher NLR in patients compared to controls (Mazza et al., 2018; Su et al., 2022).

Several studies also reported sex differences in the relationship between NLR and depression. Recent large population studies in adult and geriatric patients found that NLR associated with depressive symptomatology only in females and not in males (Liang et al., 2020; Meng et al., 2019). Unlike other psychiatric conditions, sex differences are substantial in MDD (Salk et al., 2017): females are around two times more likely to develop depression, and albeit the underlying causes behind this unbalance are not yet fully understood, a higher susceptibility to inflammation and its mood effects has been hypothesized (Derry et al., 2015).

Conversely, very few studies have investigated the possible usefulness of NLR as a predictor of antidepressant efficacy. A study found higher baseline NLR levels to progressively normalize during 3 months of SSRI treatment, paralleling antidepressant effects (Demircan et al., 2016). Two studies associated higher NLR levels with higher response rates (Llorca-Bofí et al., 2021) or with higher improvements on the Global Assessment of Functioning scale (Vos et al., 2021) in patients suffering from psychotic depression and treated with a variety of combined antidepressant and antipsychotic treatment, as well as electroconvulsive therapy (ECT).

The association between low-grade inflammation and brain structure and function in mood disorders has also been consistently reported (Benedetti et al., 2020; Felger, 2018). In particular, inflammation affects hippocampal volumes, as the hippocampus is very sensitive to stress and immune changes (Borsini et al., 2020). Reduced hippocampal volumes are one of the most robust findings in brain imaging studies of MDD patients (Schmaal et al., 2016), and also among the few consistent brain structural predictors of poor treatment response (Enneking et al., 2020). Several inflammatory markers have been associated with hippocampal volumes in MDD, including IL-6 (Frodl et al., 2012; Kakeda et al., 2018; Marsland et al., 2008) and soluble tumor necrosis factor receptors 1 (sTNFR-1) and 2 (sTNFR-2) (Schmidt et al., 2016), but no study has investigated the possible role of NLR.

To address these issues, in the present study we assessed the effect of NLR on treatment response in a sample of patients suffering from MDD, also testing for interactions with type of treatment prescribed (purely serotonergic vs noradrenergic or dopaminergic additional action) and sex. Furthermore, we investigated the possible mediating effects of hippocampal volumes on the relationship between NLR and treatment response.

2. Experimental procedures:

2.1. Participants

Our study was performed on a sample of 130 inpatients with a diagnosis of MDD suffering from a Major Depressive Episode without psychotic features (DSM-5 criteria) admitted to the Mood Disorders ward of San Raffaele Hospital in Milan. Patients had been referred for hospital specialized clinical treatment of depression by their general practitioners or psychiatrists in charge, and were discharged as soon as their conditions allowed it. The severity of depressive symptomatology was assessed via the 21-item Hamilton Depression Rating Scale (HDRS), both at admission and discharge, by a trained psychiatrist; as per standard HDRS scoring, only the first 17 items were used to calculate each participant total score (Hamilton, 1960). Only patients with HDRS score of 14 or above, corresponding to the APA cutoff for moderate depression (Rush et al., 2009), were included in the study. To measure changes in symptom severity, a Delta HDRS score was calculated by subtracting each patient's HDRS score upon discharge from their HDRS score upon admission. Complete blood cell count was obtained upon admission; furthermore, all patients underwent 3T MRI acquisition within 2 weeks after admission.

Exclusion criteria were current diagnosis of any additional psychiatric disorder, including alcohol and/or substance dependence or abuse in the last 6 months, intellectual disability, pregnancy, major medical and neurological disorders, and medical conditions affecting the immune system (i.e., ongoing inflammatory diseases, autoimmune diseases, cancer).

Treatment was administered by the psychiatrist in charge of the patient upon clinical need. Patients were prescribed at least one antidepressant drug: according to our standard treatment protocols, selective serotonin reuptake inhibitors (SSRIs) were preferentially administered; drugs acting on 5-HT and norepinephrine (SNRIs) and tricyclic antidepressants were administered to patients who had not responded to SSRIs in their previous clinical history (Middleton et al., 2005). Add-on treatments for depression included Bupropion, Mirtazapine, Reboxetine, low dosage Aripiprazole or Amisulpride, Lithium, benzodiazepines, and other hypnotic drugs (sup. Table 1). Drug treatment at discharge was recorded for each patient; antidepressant dosages were converted into the equivalent dose of Imipramine (Bollini et al., 1999). Patients were also divided between those receiving purely serotonergic drugs (SSRIs) and those receiving treatments acting also on noradrenergic or dopaminergic neurotransmission.

After a complete description of the study was given to the participants, written informed consent was obtained. All the research activities were approved by the local ethical committee.

2.2. Brain Imaging

T1-weighted images were acquired on two 3.0 Tesla scanners: 64 patients underwent a 3T MRI scan in a Gyroscan Intera scanner, Philips, Netherlands employing an 8 channels SENSE head coil (T1-weighted MPRAGE sequences: TR 25.00 ms, TE 4.6 ms, field of view FOV=230 mm, matrix=256×256, in-plane resolution 0.9×0.9 mm, yielding 220 transversal slices with a thickness of 0.8 mm); 66 patients were acquired in a 3T Ingenia CX scanner, Philips, The Netherlands using a 32-channel sensitivity encoding SENSE head coil (T1-weighted MPRAGE sequence: TR 8.00 ms, TE 3.7 ms, field of view FOV = 256 mm, matrix = 256 x 256, in-plane resolution 1 x 1 mm, yielding 182 transversal slices with a thickness of 1 mm).

Images were visually inspected as part of the quality check procedure, and then processed using the Computational Anatomy Toolbox (CAT12) preprocessing pipeline (Gaser et al., 2022) for SPM12 (www.fil.ac.UK/spm/) in Matlab R2016b, which also allows for the extraction of ROIs tissue volumes. This included segmentation into grey matter, white matter, and cerebrospinal fluid, bias regularization, non-linear modulation, and normalization to MNI space using DARTEL to a 1.5 mm isotropic MNI template. Bilateral hippocampal volumes were estimated according to the Neuromorphometric Atlas and converted in percentage of total intracranial volume (TIV) with the formula: (Hippocampal Volume * 100) / TIV (O'Brien et al., 2011).

2.3. Blood Sampling and NLR calculation

All patients underwent routine venous blood sampling with a subsequent complete blood count the morning after admission to the psychiatric ward. Blood was collected after overnight fasting (9-12 hours) from the antecubital vein into EDTA anticoagulant using vacuum tubes (BD Biosciences, 368856 vacutainers). Cell blood counts were obtained using the Sistema Sysmex

Serie XN 9000 automated hematology analyzer. Data on absolute neutrophil and lymphocyte counts were extracted from medical charts. NLR was calculated by dividing absolute neutrophil count by absolute lymphocyte count for each patient. Provided that our study focused on the effects of low-grade sub-clinical inflammation, to exclude possible confounding effects of undiagnosed infective processes or other pathological conditions, only patients with neutrophil and lymphocyte counts within normal ranges (1500 to 7700 cells/μL for neutrophils, 1000 to 4800 cells/μL for lymphocytes) were included in the analysis.

2.4. Statistical Analysis

Statistical analyses were performed with IBM SPSS statistics for Windows, Version 26.0 (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp); mediation and moderation analyses were performed via SPSS "Process" Macro, version 4.0 (Hayes, 2017).

First, we tested the relationship between NLR and treatment response, by entering in a multiple regression analysis Delta HDRS as dependent variable, NLR as independent variable, and age, sex, HDRS scores upon admission, duration of hospitalization, Imipramine equivalents, and type of treatment (0 = purely serotonergic; 1 = also noradrenergic or dopaminergic) as covariates. Furthermore, to test the possible moderating effect of type of treatment and sex, two moderation analyses were performed entering NLR as the independent variable and Delta HDRS as the dependent variable. In the first model, type of treatment was entered as a moderator, and in the second, sex. Age, HDRS scores upon admission, duration of hospitalization, and Imipramine equivalents were used in both models as nuisance covariates. Sex was also entered as a covariate in the first moderation, while type of treatment was used in the second model.

Second, to test the effect of NLR on hippocampal volumes, the former was entered as the independent variable in a multiple regression model, with hippocampal volumes as dependent variables and age, sex, and MRI scan as nuisance covariates. The regression analysis was also performed in the two sexes separately.

Third, the effect of hippocampal volumes on treatment response was investigated in the context of a multiple regression model, with Delta HDRS as the dependent variable, hippocampal volumes as the independent variables and age, sex baseline HDRS, duration of hospitalization, MRI scan, and Imipramine equivalents as nuisance covariates. Again, the regression analysis was performed in the two sexes separately.

Finally, we tested the possible mediating effect of hippocampal volumes between NLR and treatment response, taking into account the moderating effect of sex. We therefore performed a moderated mediation analysis, investigating first the possible indirect effect of NLR on delta HDRS through hippocampal volumes in the two sexes, and then the possible moderating role of sex on the direct or indirect effect of the models and the possible presence of a moderated mediation. Again, NLR was entered as the independent variable, Delta HDRS as the dependent variable, hippocampal volumes as mediators, sex as moderator, and age, HDRS scores upon admission, duration of hospitalization, MRI scan, and Imipramine equivalents as nuisance covariates. The indirect effect was assessed through the bootstrap method (number of bootstrap samples = 5000) and 95% confidence intervals were estimated.

3. Results

3.1. Demographic and clinical characteristics

Clinical and demographic characteristics of the sample are reported in Table 1. Six patients were excluded because of neutrophil count outside the normal range, and therefore all the analyses were performed on a total of 124 patients (F=80; M=44). HDRS scores at admission and discharge were not significantly different among sex groups, but time to achieve a clinical condition allowing discharge from the hospital (duration of hospitalization) was longer in males ($p=0.027$), as well as the dose of antidepressant prescribed ($p=0.050$). Males had higher absolute volumes of TIV and of bilateral hippocampi ($p<0.001$); however, after expressing hippocampal volumes as percentage of TIV this sex difference was no longer apparent (Table 1). Left hippocampal volumes were lower than the right volumes, both in absolute value (2.837 vs 3.040, $p<0.001$) and when expressed as percentage of TIV (0.206 vs 0.220, $p<0.001$). This difference was observed also in the two sexes separately (Females: 2.728 vs 2.928, $p<0.001$; 0.206 vs 0.221, $p<0.001$; Males: 3.035 vs 3.243, $p<0.001$; 0.205 vs 0.219, $p<0.001$).

3.2. Effect of NLR on treatment response

Sex significantly influenced the effect of NLR on treatment response. We did not identify an effect of NLR on Delta HDRS in the multiple regression analysis on the whole sample, and no moderating effect of type of treatment on their relationship. On the other hand, the moderation analysis showed that the effect of NLR on Delta HDRS was significantly different according to sex ($b = 3.898$, $t = 2.965$, $p = 0.004$): a highly significant negative association between NLR and Delta HDRS was detected in females ($b=-1.492$, $t=-2.729$, $p=0.007$), while a positive one was identified in males ($b=2.406$, $t=2.049$, $p=0.043$) (Figure 1).

3.3. Effect of NLR on hippocampal volumes

Inflammatory status was found to have a detrimental effect on hippocampal volumes. NLR negatively affected left hippocampal volumes in the whole sample ($\beta=-0.239$, $t=-2.735$, $p=0.007$), with a trend towards significance in the right hippocampus ($\beta=-0.169$, $t=-1.935$, $p=0.055$). Testing the effect separately in the two sexes, no effect was observed in males on left or right hippocampal volumes, while in females, we found a significant negative effect of NLR on the left ($\beta=-0.282$, $t=-2.624$, $p=0.010$) and right ($\beta=-0.220$, $t=-2.048$, $p=0.044$) hippocampus.

3.4. Effect of hippocampal volumes on treatment response

Hippocampal volumes were found to be associated with antidepressant response. A significant positive effect on Delta HDRS was found for both left ($\beta=0.135$, $t=1.986$, $p=0.049$) and right ($\beta=0.149$, $t=2.178$, $p=0.031$) hippocampal volumes in the whole sample. Performing the analysis separately in the two sexes, no effect was found in males, while significant positive effects were found in females for bilateral hippocampi (Left: $\beta=0.208$, $t=2.600$, $p=0.011$; Right: $\beta=0.177$, $t=2.148$, $p=0.035$).

3.5. Moderated mediation analysis

Left hippocampal volume mediated the effect of inflammation on treatment response in females, but not in males (Figure 2). No indirect effect was found for right hippocampal volume.

First, stratifying the sample according to sex, the two mediation analyses identified a significant effect of NLR on left hippocampal volume, and of left hippocampal volume on delta HDRS in females (b =-0.007, t=-2.514, p=0.014; b=45.610, t=2.223, p=0.029, respectively), but not in males (Figure 2, top).

Second, a moderated-mediation analysis in the whole sample detected a significant indirect effect of NLR on Delta HDRS through left hippocampal volumes in females (b=-0.319, 95% BCa CI [-0.945, -0.017]), but not in males, meaning that left hippocampal volumes mediated the effect of inflammation on antidepressant response in females only (Figure 2, bottom right). Direct effects of NLR on HDRS scores remained significant, with a negative direction in females (b=-1.243, t=-2.004, p=0.047), and a positive trend toward statistical significance in males (b=2.628, t=1.966, p=0.052), with a significant moderating effect of sex (b=3.871, t=2.634, p=0.009) (Figure 2, bottom left). Whole sample effects were significant for the effect of NLR on hippocampus, and for the effect of hippocampus on delta HDRS, but not for sex interactions on the "a" and "b" path of the model. Therefore, the global index of moderated mediation was non-significant.

Among covariates, duration of hospitalization negatively associated with delta HDRS (b=-0.169, t=3.710, p<0.001), possibly reflecting a more difficulty to treat condition; and baseline HDRS significantly predicted decrease of scores (higher baseline, higher decrease: b=0.767, t=8.440, p<0.001). No other significant associations were found for the other covariates.

4. Discussion

This is the first study to identify a moderating effect of sex, and a mediating role of hippocampal volumes, in the adverse effects that peripheral inflammatory markers exert on antidepressant efficacy.

First, we identified a significant moderating effect of sex on the relationship between NLR and treatment response, with NLR levels negatively affecting treatment response in females and positively in males. The adverse effect of inflammatory status on treatment response we found in females is in line with what has previously been reported in both sexes (Liu et al., 2020) and in females specifically (Kruse et al., 2020) using other biomarkers. Furthermore, several large population studies reported an association between NLR levels and depressive symptoms only in females (Liang et al., 2020; Meng et al., 2019). Interestingly, a recent study on the antidepressant effects of adjunct minocycline in treatment resistant depression showed a higher dependence of clinical improvement on baseline inflammatory markers in females, despite comparable antidepressant efficacy in the sex groups (Lombardo et al., 2022); this suggests that the moderating effect of sex on the relation between inflammation and treatment response could be partially

independent from the type of drug prescribed (or at least extend beyond drugs acting solely on monoaminergic systems).

The positive effect of NLR on treatment response in males was less expected: however, literature on the effect of NLR on treatment response is sparse, with only two studies reporting better response patterns associated with higher NLR in patients with psychotic depression (Llorca-Bofí et al., 2021) (Vos et al., 2021). While we only included patients suffering from a non-psychotic depressive episode, the positive association we found in males would be in line with these studies. A possible explanation provided in both studies for the reported association between NLR and better treatment response is the use of drugs acting not only on serotoninergic, but also on noradrenergic and dopaminergic neurotransmission: MDD patients with increased levels of inflammatory markers (particularly CRP and IL-6) have been reported to exhibit worse response rates to purely serotoninergic drugs, but better to drugs also acting on other neurotransmitters (Arteaga-Henríquez et al., 2019). However, in our study we found no moderating role of the type of treatment in the relationship between NLR and treatment response.

Second, NLR associated with reductions in bilateral hippocampal volumes, with significant effects in females. Several studies have already reported a negative association between inflammatory markers and hippocampal volumes in MDD patients, healthy individuals and bipolar patients, possibly related to the effect of inflammation on hippocampal neurogenesis and synaptic plasticity (Kakeda et al., 2018; Kohman and Rhodes, 2013; Tsai et al., 2019). Adult neurogenesis in the hippocampus primarily occurs in the subgranular zone of the dentate gyrus and can be sensitive to homeostatic changes in neuroinflammation (Zhao et al., 2008). Inhibiting inflammatory responses through the administration of an anti-inflammatory drug has been shown to restore hippocampal neurogenesis after endotoxin induced inflammation in rats (Monje et al., 2003).

Inflammation can affect neurogenesis through several pathways: activated microglia can lead to apoptosis of neuronal progenitor cells and lower neuronal stem cell proliferation in animal models (Chesnokova et al., 2016); IL-6 exposure has been shown to cause neural progenitor cells to express cyclin-dependent kinase inhibitor 1 (p21) which arrests the cell cycle leading to reduced proliferation in mice (Chesnokova et al., 2016) (Zonis et al., 2013); inflammation decreases brain derived neurotrophic factor (BDNF) expression, a key mediator in neural plasticity (Calabrese et al., 2014); furthermore, the activation of the hypothalamic-pituitary-adrenal (HPA) axis and the subsequent release of glucocorticoids also might have a detrimental effect on neurogenesis (Odaka et al., 2017). Hippocampal neurogenesis is also believed to be crucial for antidepressant drug action: preclinical studies demonstrated that impaired hippocampal neurogenesis – obtained via x-irradiation of the mouse brain - canceled the positive effects of antidepressants on depressive-like behaviors (Santarelli et al., 2003), and antidepressants are speculated to act also through the common pathway of increasing neurogenesis (Malberg et al., 2021). Accordingly, reduced hippocampal volume is among the most consistent and replicated brain correlate of poor antidepressant response (Enneking et al., 2020) and bilateral hippocampal volumes were associated to treatment response also in our sample.

Despite the widely investigated associations among inflammation, response to treatment, and hippocampal volumes, this is the first study to report that the volume of the left hippocampus mediates the relationship between NLR and treatment response in females, while failing to find

such an association in males. Sex differences in inflammatory and immune responses are well documented, and they are believed to be partially related to sex hormones (Klein and Flanagan, 2016). Besides being more prone to develop autoimmune diseases, females are also more susceptible to inflammation-induced mood and behavioral changes (Derry et al., 2015; Miller et al., 2009; Quintero et al., 2012), and a growing body of literature points toward a sex specific effect of inflammatory status on behavior and psychopathology (Derry et al., 2015; Lasselin et al., 2018; Lombardo et al., 2021). Our findings suggest that these sex differences might be associated with specific brain structures vulnerability to inflammatory insults.

The identification of the left hippocampus, and not the right one, as a mediator between inflammation and treatment response might not simply be due to chance. As already reported in numerous animal and human studies (Shinohara et al., 2008; Woolard and Heckers, 2012), and as well in our sample, left hippocampal volumes were lower than right ones. Several hypotheses have been put forward to explain hippocampal asymmetry: left and right hippocampus might differ in glutamate-induced synaptic plasticity, susceptibility to hypothalamic–pituitary–adrenal axis activation and adult neurogenesis (Hou et al., 2013). All these mechanisms could also impact the mediating role the hippocampus has on the relationship between inflammation and antidepressant response.

The direct effect of NLR on treatment response also remained significant in the mediation model, indicating that hippocampal volumes only partially mediated the relationship between inflammation and antidepressant response. This implies that the opposite effect of NLR on treatment response in females and males is at least partially independent from its effect on hippocampal volume; the inflammatory status might affect treatment response through several others mechanisms implicated in major depression pathophysiology, such as the kynurenine pathway, the inflammatory-metabolic crosstalk, and the modulation of neural plasticity (Branchi et al., 2021).

Strengths of the present study are its naturalistic design in a specialized clinical setting, and state of the art imaging and analytical methods, but we acknowledge some limitations. Reflecting the epidemiology of depression, our sample was unbalanced for sex, comprising roughly half the number of males compared to females. Patients were recruited in a single center, thus limiting the generalizability of the findings. NLR can be influenced by other factors known to be tied to inflammation such as smoking status, physical inactivity and adiposity (Howard et al., 2019), which we were unable to control in our study and which might have a higher prevalence in males compared to females (Higgins et al., 2015). Furthermore, we controlled for the effect of antidepressant treatments entering Imipramine equivalents as a nuisance covariate in all the analyses, but given the real-world nature of our study, we could not control for the wide variety of treatments prescribed.

Despite these limitations, this study adds several elements to the current understanding of inflammation effects on the brain and their relationship with treatment response, providing a possible mechanistic explanation of the link between peripheral inflammatory status and antidepressant efficacy. Sex and sex differences in immunological profiles will likely become increasingly relevant in future studies of treatment response and in the development of tailored approaches to antidepressant therapy. Our results could represent a first step towards a

personalized approach to treatments that we expect will have a growing impact on the psychiatric clinical practice in the coming years.

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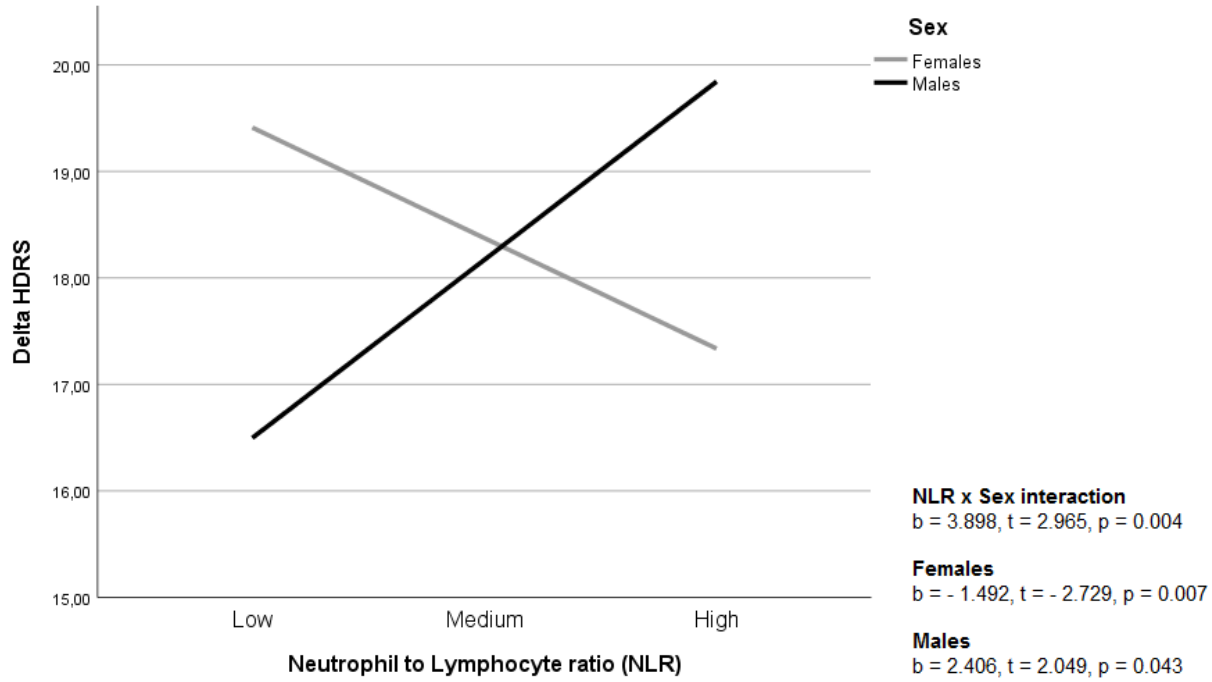

Figure 1: Relation between neutrophil to lymphocyte ratio and treatment response in the two sexes. Low = -1SD; Medium = mean; High = +1SD.

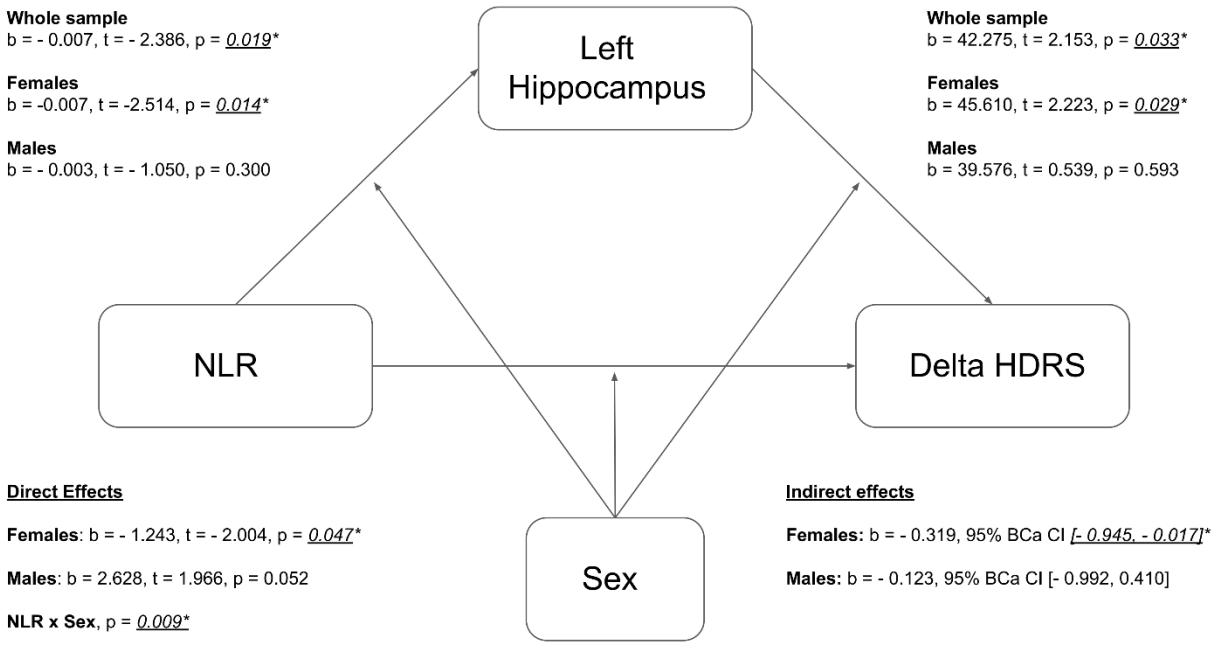

Figure 2: Results of the moderated mediation analysis. Top left: effect of neutrophil to lymphocyte ratio on left hippocampal volumes. Top right: effect of left hippocampal volumes on treatment response. Bottom left: direct effect of neutrophil to lymphocyte ratio on treatment response. Bottom right: indirect effect of neutrophil to lymphocyte ratio on treatment response through left hippocampal volumes.

	Whole Sample (n = 124)	Females (n = 80)	Males (n=44)	χ^2/t-test p
Age	49.35 ± 10.83	48.70 ± 11.30	50.54 ± 9.94	0.366
Admission HDRS	24.14 ± 5.52	24.36 ± 5.11	23.75 ± 6.23	0.556
Discharge HDRS	5.73 ± 4.98	5.47 ± 4.29	6.20 ± 6.07	0.437
Delta HDRS	18.41 ± 6.02	18.89 ± 5.37	17.54 ± 7.04	0.236
Duration of Hospitalization (days)	28.01 ± 9.76	26.57 ± 8.69	30.61 ± 11.10	**0.027**
Imipramine Equivalents	222.48 ± 88.37	210.97 ± 84.58	243.39 ± 92.20	**0.050**
Type of treatment (ser/oth)*	67/57	46/34	21/23	0.296
Neutrophil to Lymphocite ratio	1.72 ± 0.69	1.68 ± 0.50	1.80 ± 0.69	0.348
Total intracranial volume (TIV)	1383.24 ± 137.46	1328.51 ± 105.97	1482.73 ± 133.10	< **0.001**
Left Hippocampus volume	2.84 ± 0.31	2.73 ± 0.24	3.03 ± 0.32	< **0.001**
Right Hippocampus volume	3.04 ± 0.34	2.93 ± 0.29	3.24 ± 0.33	< **0.001**
L. Hippocampus as % of TIV	0.206 ± 0.017	0.206 ± 0.019	0.205 ± 0.015	0.739
R. Hippocampus as % of TIV	0.220 ± 0.0185	0.221 ± 0.020	0.219 ± 0.014	0.548

Table 1: clinical and demographic characteristics of the sample. Type of treatment: "ser" = predominantly serotonergic treatment; "oth" = also noradrenergic or dopaminergic treatments.

		Whole Sample (n = 124)	Females (n = 80)	Males (n = 44)
Prescribed antidepressants	SSRI	76 (61.29%)	52 (65.00%)	24 (54.54%)
	SNRI	40 (32.26%)	24 (30.00%)	16 (36.36%)
	TCAs	8 (6.45%)	4 (5.00%)	4 (9.10%)
Prescribed add-on treatments	Amisulpride	14	9	5
	Aripiprazole	2	2	0
	Bupropion	3	1	2
	Mirtazapine	14	4	10
	Reboxetine	2	2	0
	Lithium	7	6	1

Supplementary table 1: Details on prescribed pharmacotherapies.