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Interleukin-8 and lower severity of depression in females, but not males, with treatment-resistant depression

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Abstract

Introduction: In cross-sectional studies of depressed patients, relationships between depression and levels of IL-8 are inconsistent, and have not been examined in relation to sex. Given identified sex differences in longitudinal data, it is important to evaluate sex-specific cross-sectional relationships between IL-8 and depressive symptoms, which may explain some inconsistency in the extant literature. It is further unknown whether IL-8 levels may relate to specific symptom profiles among depressed patients, with or without regard to sex.

Methods: Among 108 patients with treatment resistant depression (50 females), we evaluated cross-sectional relationships between IL-8 and depression severity, as measured by the Hamilton Depression Rating Scale [HAM-D] Score, and examined sex-specific relationships, as well as relationships with depressive symptom profiles. Other inflammatory markers (IL-6, IL-10, TNF-α, CRP) were also explored in relation to HAM-D.

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Author statement

JLK: conceptualized the current study; drafted and revised the paper; conducted the statistical analysis; interpreted the statistical analysis; approved the final version of the paper. RO: edited the paper for critical intellectual content; helped guide and interpret the statistical analysis; approved the final version of the paper. GH: edited the paper for critical intellectual content; helped guide and interpret the statistical analysis; approved the final version of the paper. SJT: edited the paper for critical intellectual content; approved the final version of the paper. BW: assisted in statistical analysis; approved the final version of the paper. ECB: supervised completion of immune assays; edited the paper for critical intellectual content; approved the final version of the paper. JOB: helped interpret the statistical analysis; edited the paper for critical intellectual content; approved the final version of the paper. EC: collected data; study management; revised the paper; approved the final version of the paper. RE: conceptualized the parent study; designed the parent study; edited the paper for critical intellectual content; approved the final version of the paper. KLN: conceptualized the parent study; designed the parent study; edited the paper for critical intellectual content; helped interpret the statistical analysis; provided research supervision; approved the final version of the paper. MRI: helped conceptualize the current study; helped guide and interpret the statistical analysis; revised the paper; edited the paper for critical intellectual content; provided research supervision; approved the final version of the paper.

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Results: Higher IL-8 was associated with lower total HAM-D score (standardized β = −0.19, p = 0.049). Sex-specific effects were identified (IL-8 × sex interaction: p = 0.03), in which higher IL-8 related to lower HAM-D score in females (standardized β = −0.41, p = 0.004, effect size (sr^2) = 0.17), but not males (standardized β = 0.02, p = 0.91). Among a subset of 94 patients (41 females) who had individual HAM-D items available, we evaluated relationships between IL-8 and HAM-D factor subscores. Across sexes, higher IL-8 was associated with lower anxiety/hypochondriasis subscores (standardized β = −0.31, p = 0.002; sex interaction: p = 0.99). Sex differences were identified for relationships between IL-8 and two other HAM-D factor subscores.

Conclusions: IL-8 may be related to anxiety symptoms across sexes, but may have a sex-specific relationship with other depressive symptoms. Further evaluation of sex-specific relationships between IL-8, depression symptom profiles, treatment response, and potential neurobiological correlates, may inform mechanisms of depression pathophysiology and aid in development of precision medicine strategies.

Keywords

Depression; Anxiety; Inflammation; Interleukin-8; Sex differences

1. Introduction

Depressed patients demonstrate higher mean levels of inflammation compared to controls (Haapakoski et al., 2015). Higher inflammation, as indexed by C-reactive protein (CRP), has been associated with greater depression severity among depressed patients (Kohler-Forsberg et al., 2017), as well as in large population-based studies (Case and Stewart, 2014; Song et al., 2015).These findings imply that inflammation is an important neurobiological contributor to depression symptomatology. In line with this, higher levels of specific inflammatory markers have been associated with particular symptom profiles among depressed patients, namely interleukin(IL)-6 with sleep disturbance (Wang et al., 2019), and CRP with psychomotor slowing (Goldsmith et al., 2016) and anhedonia (Felger et al., 2016, 2018; Goldsmith et al., 2016). In a large population-based study, CRP was also associated with appetite changes, sleep disturbance, and fatigue (Jokela et al., 2016). However, despite growing consensus of the critical pathogenic role of inflammation in depression, investigation of sex-specific relationships between inflammatory markers and depressive symptoms has remained limited (Felger et al., 2018; Kohler-Forsberg et al., 2017; Rainville and Hodes, 2019). Given females suffer from depression at twice the rate of males (Bromet et al., 2011) and demonstrate greater neural and affective responses to inflammatory challenge (Moieni et al., 2015, 2019; Udina et al., 2012), investigation of sex-specific differences demands urgent attention. This work will directly inform individualized medicine strategies and improve treatment approaches for depression. Moreover, efforts to identify links between biological and behavioral phenotypes may prove useful in informing underlying disease mechanisms and potential novel treatment targets.

Interleukin(IL)-8, an inflammatory cytokine and chemokine, is one of the major mediators of the inflammatory response, yet research on links between IL-8 and depression is limited. In contrast to the association between inflammatory markers such as CRP and IL-6 and greater severity of depressive symptoms (Jokela et al., 2016; Kohler-Forsberg et al., 2017;

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Wang et al., 2019), higher IL-8 levels (in the periphery or in cerebrospinal fluid) are reported to be associated with lower depression and anxiety symptom severity among depressed patients or patients who attempted suicide (Janelidze et al., 2015; Zou et al., 2018), or who are at suicide risk (Keaton et al., 2019). Nevertheless, there are conflicting findings regarding whether mean levels of IL-8 are greater, lower, or the same, in depressed patients versus controls, with meta-analyses finding no difference overall (Haapakoski et al., 2015), although it is not known whether sex differences might contribute to study heterogeneity. Interestingly, in small studies evaluating treatment response to electroconvulsive therapy (n = 40) and ketamine (n = 46), increasing levels of IL-8 over a course of treatment were associated with improvement in depression in females, but not males (Kruse et al., 2020, 2021). Hence, it is possible that sex-specific effects may moderate biomarker relationships, such that higher levels of the pro-inflammatory cytokine IL-8 may be associated with lower severity of depressive symptoms in females, but not males. Knowledge of the presence or absence of such cross-sectional differences on the basis of sex is essential to inform future research design in this field. Further, evaluation of symptomatic profiles associated with IL-8, with or without regard to sex, is essential to move forward both clinical and research understanding of the potential role of IL-8 in depressive symptom pathophysiology, for further inquiry and treatment development.

The small sample sizes of previously published longitudinal work on IL-8 and treatment response precluded the cross-sectional evaluation of relationships between IL-8 and depressive symptom profiles or sex-specific differences in the cross-sectional relationship between IL-8 and depression score. Here, by combining non-overlapping samples of treatment resistant depressed patients enrolled in studies of either ketamine or ECT, at baseline time points, including patients for whom only a baseline time point was available, we have increased the power to evaluate such relationships.

In this study, we investigated whether IL-8 levels were cross-sectionally related to depression severity, as measured by the 17-item Hamilton Depression Scale Score (HAM-D), in 108 patients (50 females) with treatment-resistant depression, and specifically evaluated whether there were sex differences in this relationship. Further, in order to investigate whether IL-8 levels might relate to specific depression symptom profiles, we also explored relationships with six previously published HAM-D factors (Goldberger et al., 2011). Given prior evidence that other markers of inflammation are associated with depression, we also explored the relationship between IL-6, TNF-α, IL-10, CRP and depressive symptom severity. Our primary hypothesis was that in this cross-sectional sample, higher IL-8 would relate to lower HAM-D scores in females, but not males, given previous findings that increasing IL-8 over a course of depression treatment with ECT (Kruse et al., 2020) or ketamine (Kruse et al., 2021) was associated with depression improvement among females but not males.

2. Patients and methods

2.1. Participants

Subjects were patients with treatment-resistant depression (N = 108, 50 females) who enrolled in neuroimaging studies at the University of California, Los Angeles (UCLA)

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Resnick Neuropsychiatric Hospital, and who had HAM-D scores and IL-8 levels available for analysis. Some patients went on to receive electroconvulsive therapy or ketamine infusion, for treatment of their depression. For patients enrolled in the ketamine study, stable regimens of psychotropic medications were continued. For patients enrolled in the ECT study, antidepressants and benzodiazepines were tapered and discontinued in collaboration with the patient's treating psychiatrist, at variable rates, depending upon the medications, the tolerability of the taper, and in an effort to consolidate often unwieldy drug regimens and to improve tolerance to ECT. This study evaluates cross-sectional relationships between IL-8 and depression severity at the baseline time point, before any treatments were given. Some participants were previously included in imaging analyses (Joshi et al., 2016; Kubicki et al., 2019; Leaver et al., 2016a, 2016b, 2018, 2019; Lyden et al., 2014; Oltedal et al., 2018; Pirnia et al., 2016; Vasavada et al., 2017; Wade et al., 2016, 2017), or treatment response studies (Kruse et al., 2018, 2020, 2021). All procedures were approved by the UCLA Institutional Review Board. Written informed consent was obtained from all participants. Data were collected between December 2011 and March 2018.

Inclusion criteria were current major depressive episode, and failure to respond to at least two prior antidepressant medications in the current episode. Recurrent major depressive disorder was diagnosed using a structured clinical interview and Diagnostic and Statistical Manual of Mental Disorders criteria. Exclusion criteria were as follows: history of alcohol or substance abuse within the past 6 months and/or dependence within the past 12 months, intellectual disability, primary psychotic disorder, metal implants (i.e. pacemakers, defibrillators, aneurysm clips, etc), neurologic illness, and serious medical illness. Specifically, patients were asked at screening if they had type 1 diabetes, were insulin dependent, or had "any other serious medical illness." If "yes" to any of those questions, the potential participant was excluded at screening. Conditions not identified by the patient at screening as "serious" but identified during the subsequent consultation were excluded as "unstable medical conditions" if requiring active management as indicated by ongoing medication or applicable treatment adjustments to achieve control of the condition in question. For example, patients were excluded if baseline blood pressure was >140/90 and not normalized with intervention if indicated. Chronic inflammatory disorders requiring ongoing treatment with immune modulating agents were considered serious medical conditions and excluded. Laboratory studies were reviewed, including liver function tests and basic metabolic panel, and patients were excluded if laboratory tests suggested organ dysfunction.

2.2. Clinical assessment of depressive symptom severity

The 17-item Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960) was collected. For subjects who had individual HAM-D items available for analysis, a previously published HAM-D factor analysis of >1400 depressed outpatients (Goldberger et al., 2011) was utilized to calculate six HAM-D factor subscores, by adding the scores from the individual HAM-D items included in each factor. The six factors identified in the referenced HAM-D factor analysis included: factor 1. "insomnia symptoms" (HAM-D items 4 [early insomnia], 5 [middle insomnia], and 6 [late insomnia]); factor 2. "severity" (HAM-D items 2 [feelings of guilt], 3 [suicide], and 17 [insight]); factor 3. "core symptoms" (HAM-D items 1

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[depressed mood], 7 [work and activities], and 8 [retardation]); factor 4. “anxiety/ hypochondriasis” (HAM-D items 10 [psychic anxiety], 11 [somatic anxiety], and 15 [hypochondriasis]; factor 5. “gastrointestinal symptoms/loss of weight” (HAM-D items 12 [gastrointestinal symptoms] and 16 [loss of weight]); and factor 6. “miscellaneous items” (HAM-D items 9 [agitation], 13 [general somatic symptoms], and 14 [genital symptoms]) (Goldberger et al., 2011).

2.3. Assessment of inflammation

Non-fasting whole blood samples were collected in the morning, in EDTA tubes, chilled on wet ice, and then centrifuged at 1500 rpm (500xG) at 4 °C. Plasma was harvested into multiple aliquots, and then stored in a −80 °C freezer until assay.

Plasma concentrations of IL-1β, IL-6, IL-8, and TNF-α, and the anti-inflammatory cytokine IL-10, were measured utilizing a Bio-Plex 200 (Luminex) instrument and a high-sensitivity multiplex immunoassay (Performance High Sensitivity Human Cytokine, R& D Systems, Minneapolis, MN). Data acquisition and analyses were performed with Bio-Plex software v4.1, and a 5-parameter logistic curve fit. As previously described, this multiplex assay has excellent intra-assay (<8% coefficient of variation [CV]) and inter-assay (11–16% CV) reproducibility (Epstein et al., 2013). Multiplex assays were performed on samples diluted 2-fold according to the manufacturer’s protocol. Mean intra-assay CV was <9%, inter-assay CV was ≤15%. Plasma concentrations of CRP were determined utilizing the Human CRP Quantikine ELISA (R&D Systems) according to the manufacturer’s protocol with the following modifications: samples were diluted 500-fold, and the standard curve was extended to 0.4 ng/mL to obtain a lower limit of detection of 0.2 mg/L, taking sample dilution into account. Assays were performed in duplicate. The mean of the duplicate sample was used in all analyses.

Results of the assays were evaluated and showed that 33% of samples for IL-1β had concentrations below the limit of detection of the multiplex assay (0.1–0.4 pg/mL, depending on the specific assay plate); hence IL-1β was not included in statistical analyses. For the small proportion (6%) of samples with IL-6 concentrations below the lower limit of detection (0.1 pg/mL), a value equal to one-half the lower limit (0.05 pg/mL) was assigned. For the small proportion (3%) of samples with IL-10 concentrations below the lower limit of detection (0.1 pg/mL), a value equal to one-half the lower limit (0.05 pg/mL) was assigned. TNF-α and IL-8 were detectable in 100% of samples. For the small proportion (10%) of samples with CRP concentrations below the limit of detection (0.2 mg/L), a value equal to one-half the lower limit (0.1 mg/L) was assigned. For samples with CRP concentrations above the upper limit of the standard curve (>25 mg/L, 1%), the estimated extrapolated CRP concentration was utilized.

Quality control measures were implemented and demonstrated <10% variability between assay batches.

2.4. Statistical analyses

All statistical analyses were conducted using the IBM SPSS (Version 26, IBM Corp, Armonk, New York). As cytokine and CRP data were not normally distributed, we

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performed a base-10 logarithmic transformation on the data prior to statistical analyses. One participant was excluded from IL-8 analyses as an outlier for having a log transformed IL-8 level greater than 4 standard deviations from the mean. Two participants were excluded from TNF-α analyses at outliers, for having a log transformed TNF-α level greater than 4 standard deviations from the mean. Sensitivity analyses including outliers were also completed.

Sample Size Determination: Based upon our previous work showing sex differences in the relationship between IL8 and HAM-D scores (Kruse et al., 2020, 2021), we assumed sex slope differences of at least 0.10. Targeting 90% power (alpha = .05), required n = 42 each of males and females; sample size goals were set for n = 50 given the exploration of other cytokine values.

Linear regression analyses were used to evaluate the relationship between the inflammatory markers (IL-8, IL-6, TNF-α, IL-10, and CRP) and HAM-D total, and to evaluate the interaction between sex and inflammatory marker on HAM-D scores. If inflammatory marker(s) demonstrated a significant relationships with HAM-D total, that inflammatory marker was further evaluated in relation to HAM-D factor subscores. Sensitivity analyses adjusted for age and body mass index (BMI). Several other covariates are also likely to be relevant in this context, including menstrual status, concomitant medications and tobacco smoking. However, this sample reported minimal use of other medications or tobacco, and information on menstrual status was not obtained. Further, the sample size and the inclusion of interaction terms and HAM-D factor subscores limited our ability to incorporate multiple additional covariates into the regression models. T-tests were used to evaluate mean differences between males and females for inflammatory markers, HAM-D total, and HAM-D factor subscores.

Significance was evaluated at an alpha level of $\alpha = 0.05$, two-tailed. Our primary analysis was evaluation of the relationship between IL-8 level and HAM-D, including the effect of sex on the relationship. Remaining analyses were considered exploratory; thus, no correction for multiple comparisons was completed.

3. Results

Table 1 summarizes patient demographic information, inflammatory marker levels, and HAM-D total scores and factor subscores. Forty-six percent of the 108 participants were females (n = 50). No statistically significant differences in demographic variables (i.e., age), inflammatory markers, or clinical severity variables were identified between females and males, except for HAM-D total and HAM-D anxiety/hypochondriasis, both of which were higher in females.

3.1. Inflammatory markers and depression severity

Higher IL-8 was associated with lower HAM-D score (standardized $\beta = -0.19$, $p = 0.049$), while other markers of inflammation, including IL-6, IL-10, TNF-α, and CRP did not demonstrate significant relationships with HAM-D total score (Table 2). Because age and BMI have been found to be related to markers of inflammation, sensitivity analyses adjusted

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for these two covariates, yielding similar results for IL-8 (standardized β = −0.26, p = 0.009). Sensitivity analysis including the single outlier for IL-8 also did not change results (standardized β = −0.20, p = 0.04; with age and BMI: standardized β = −0.27, p = 0.007).

3.2. Interleukin-8 and HAM-D factor subscores

We further examined whether IL-8 was associated with unique symptom profiles, by calculating six factor subscores derived from a published factor analysis of HAM-D items among >1400 depressed outpatients (Goldberger et al., 2011). Factor subscores were calculated for the subset of patients (n = 94; 87%) who had individual HAM-D items available for analysis. Higher IL-8 was associated with lower HAM-D Anxiety/Hypochondriasis scores (which included HAM-D items 10 [psychic anxiety], 11 [somatic anxiety], and 15 [hypochondriasis]), across both sexes (standardized β = −0.31, p = 0.002). No other significant relationships emerged between IL-8 and the remaining HAM-D factors (all p's > 0.1).

3.3. Sex differences

Sex was found to moderate the relationship between IL-8 level and total HAM-D score (p = 0.03), with females demonstrating higher IL-8 in relation to lower HAM-D score (standardized β = −0.41, p = 0.004, effect size (sr^2) = 0.17), but with no such relationship identified in males (standardized β = 0.02, p = 0.91, effect size (sr^2) < 0.01) (Fig. 1). When these analyses were adjusted for age and BMI, findings did not substantially change (females: standardized β = −0.43, p = 0.004, effect size (sr^2) = 0.17; males: standardized β = −0.06, p = 0.66, effect size (sr^2) < 0.01). When analyses included the single IL-8 outlier, findings did not markedly change, but the p value for the interaction term moved to trend level (from 0.03 to 0.07). There was no significant effect of sex on the relationship between HAM-D total score and any other inflammatory marker (i.e. IL-6, IL-10, TNF-α, or CRP; Table 2).

For the relationship between IL-8 level and Anxiety/Hypochondriasis, no sex difference was identified (*p* value for interaction term = 0.99). However, a significant sex interaction moderating the relationship between IL-8 and factor subscore was identified for two other factors: HAM-D Core Symptoms (sex interaction: p = 0.02), which included HAM-D items 1 [depressed mood], 7 [work and activities], and 8 [retardation], and HAM-D Miscellaneous Symptoms (sex interaction: p = 0.006), which included HAM-D items 9 [agitation], 13 [general somatic symptoms], and 14 [genital symptoms]. For both of these factors, higher IL-8 trended or was significantly associated with lower factor scores among females (Core Symptoms: standardized β = −0.24, p = 0.13, effect size (sr^2) = 0.06; Miscellaneous Symptoms: standardized β = −0.33, p = 0.04, effect size (sr^2) = 0.11), and higher factor scores among males (Core Symptoms: standardized β = 0.25, p = 0.07, effect size (sr^2) = 0.06; Miscellaneous Symptoms: standardized β = 0.25, p = 0.07, effect size (sr^2) = 0.06). When these analyses were adjusted for age and BMI, findings did not substantially change, though were modestly strengthened among both sexes, with p values moving from trend level to significant for both factor subscales among males (Core Symptoms: standardized β = 0.29, p = 0.04, effect size (sr^2) = 0.08; Miscellaneous Symptoms: standardized β = 0.29, p = 0.05, effect size (sr^2) = 0.08), and the remaining weak trend level finding among females

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modestly strengthened from p value of 0.13 to 0.07 (Core Symptoms: standardized β = −0.30, p = 0.07, effect size (sr^2) = 0.09; Miscellaneous Symptoms: standardized β = −0.35, p = 0.04, effect size (sr^2) = 0.12).

Given that females had statistically higher mean scores for the HAM-D Anxiety/Hypochondriasis factor subscore (Table 1), and given the highly significant relationship identified between IL-8 level and this factor, we completed a sensitivity analysis to evaluate whether sex continued to moderate the relationship between IL-8 level and total HAM-D score, when the Anxiety/Hypochondriasis factor score was subtracted from the HAM-D total score. After subtracting the Anxiety/Hypochondriasis score from HAM-D total, the sex interaction remained significant (p = 0.01); higher IL-8 continued to relate to lower HAM-D score among females (standardized β = −0.38, p = 0.02, effect size (sr^2) = 0.14), but not males (standardized β = 0.18, p = 0.21, effect size (sr^2) = 0.03). When these analyses were adjusted for age and BMI, findings did not substantially change (Females: standardized β = −0.36, p = 0.03, effect size (sr^2) = 0.12); Males: standardized β = 0.20, p = 0.17, effect size (sr^2) = 0.04).

4. Discussion

Among patients with treatment resistant depression, we have found that higher IL-8 levels were related to lower depression severity among females, but not males. Our results extend prior conflicting findings and indicate that the relationship between IL-8 and severity of depressive symptoms is sex specific (Isung et al., 2012; Zou et al., 2018), a biologic vulnerability that was not considered in the prior research. Interestingly, one prior study found that higher IL-8 was associated with lower suicide risk, and this study sample was limited only to females (Keaton et al., 2019).

When relationships between IL-8 level and HAM-D factor scores were examined, higher IL-8 level was significantly related to lower Anxiety/Hypochondriasis factor scores across both sexes. This is consistent with published cross-sectional work identifying negative relationships between IL-8 and anxiety among depressed and suicidal patients (Janelidze et al., 2015; Zou et al., 2018). These findings suggest that IL-8 may link strongly with anxiety symptoms across sexes, but that other symptoms of depression may have a sex-dependent relationship with IL-8. These cross-sectional findings are essential in informing future research evaluating relationships between depression, treatment outcome, and psychoneuroimmunologic measures. This work further demonstrates the importance of evaluating sex as a biological factor impacting the relationship between inflammatory markers and depressive symptoms, and may at least in part explain inconsistency in the literature to date on relationships between IL-8 and depression, which has not typically been evaluated on the basis of sex. In the case of IL-8, the current study suggests that depressive symptoms may not only be more strongly linked to IL-8 among females, but that IL-8 may in fact inversely relate to some depressive symptom profiles among females versus males, while other symptom profiles (i.e. anxiety) relate to IL-8 across both sexes. Further interrogation of these signals in future basic and clinical work is essential in clarifying the potential pathophysiologic versus protective role of IL-8 among depressed patients and/or patients at risk of depression, depending upon sex.

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Potential neurobiological mechanisms underlying relationships (with or without regard to sex) between IL-8 level and depression or anxiety severity remain unclear. Of interest, IL-8 is secreted in culture in response to estradiol (Bengtsson et al., 2004), and thus conceivably may vary depending upon sex hormone levels, though the current study did not identify different mean levels of IL-8 between sexes. Additionally, IL-8 may have neuroprotective properties (Araujo and Cotman, 1993; Giovannelli et al., 1998; Puma et al., 2001; Saas et al., 2002), though it remains unclear whether or why potential neurobiological effects of IL-8 might vary by sex. It is conceivable that IL-8 signaling, e.g. through receptor expression or target cell populations, may be impacted by sex differences. For example, in the setting of major depression, there are sex specific differences in the genes regulating vascular endothelial growth factor (VEGF) signaling (Blokland et al.,), and IL-8 upregulates VEGF mRNA and protein levels in endothelial cells (Martin et al., 2009). Thus, there may be a sex-specific impact of IL-8 on VEGF signaling and vascular maintenance, potentially subtly impacting blood flow in the brain. Further basic research is warranted to examine how higher levels of IL-8 may contribute to decreased depressive and anxiety-like symptoms, preferentially in females. In combination with these basic animal studies, clinical neuroimaging approaches examining potential neural correlates of IL-8 across and between sexes will also provide further insight.

In the current study we did not replicate previous work linking CRP level and depression symptom severity. While the reasons for this are unclear, it might relate to our sample of treatment refractory depressed patients. Higher inflammation is related to poorer response to antidepressant treatment (Eller et al., 2008; Lanquillon et al., 2000), and a greater number of antidepressant treatment failures (Haroon et al., 2018). However, it remains unknown whether inflammatory marker levels may relate to symptom severity differently on the basis of treatment refractoriness.

There are several study limitations that warrant consideration. First, while this cross-sectional sample allows for the identification of correlations between biological factors and clinical profiles, the data do not show causation. Also, we examine a treatment resistant depressed population, which represents a subpopulation of the broader community samples of patients with depression. As noted previously, rates of inflammation are higher, on average, in this treatment refractory sub-group. Consequently, our results might not be translatable to non-treatment refractory depression. Further, the only clinical severity measure available for all participants in the current sample was the HAM-D, and the longitudinal stability of the evaluated HAM-D factor subscores is low (Goldberger et al., 2011). More detailed assessment of dimensional affective and behavioral constructs in relation to IL-8 would be a strength of future work. While stable doses of psychotropic medications were continued for patients enrolled in the ketamine trial, most psychotropic medications were tapered and discontinued in advance of ECT, for patients enrolled in the ECT study; it is unknown whether continuation versus taper of certain psychotropic medications may impact inflammatory markers. Additionally, detailed data regarding non-psychiatric medication use were not available; though serious medical conditions were excluded (including those that would require systemic corticosteroids or traditional immune modulating agents, etc), the lack of data regarding use of other medications that may impact the immune system, e.g. non-steroidal anti-inflammatory drugs, is a limitation of the current

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study. Additionally, we did not assay for sex hormones in the current study, which would be useful in further examining identified sex differences. Further, future studies should collect data on contraception methods and menstrual status, not available in the current study. Central measures of IL-8 (e.g. from cerebrospinal fluid) would also be a strength of future research. While it is not clear that peripheral measures of IL-8 reflect central measures, both peripheral and central IL-8 have been found to correlate cross-sectionally with symptom severity (Janelidze et al., 2015; Keaton et al., 2019; Zou et al., 2018). Replication of results in an independent sample, complete with these complementary biological measures, will be important to determine the stability and broader relevance of the current findings.

Despite these limitations, this report provides novel evidence that higher IL-8 level relates to lower overall depression severity in females only, and to lower anxiety across depressed patients of both sexes. Together with previous work demonstrating sex specific effects of IL-8 on depression treatment outcome, the current findings suggest that IL-8 may be beneficial for mood and anxiety symptoms, and may play a sex-specific role in the underlying pathophysiology, manifestation, and recovery of depression symptoms. Further interrogation of potential biological and behavioral mechanisms underlying sex specific relationships with IL-8 is warranted.

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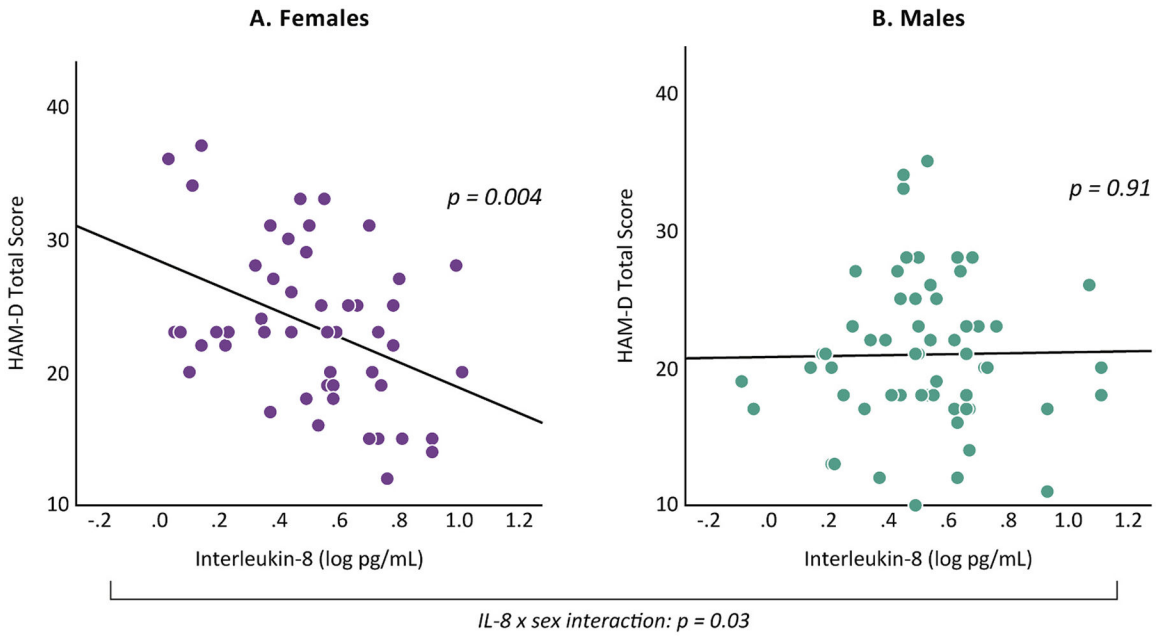

Fig. 1.

Interleukin-8 in relation to depression symptom severity in treatment-resistant patients, stratified by sex.

Log transformed plasma levels of IL-8 in relation to total HAM-D score are shown in female (panel A) and male (panel B) subjects, with *p* values shown from linear regression analyses. A significant sex interaction (p = 0.03) was identified. Females had a statistically significant relationship between IL-8 level and HAM-D score (standardized $\beta = -0.41$, p = 0.004, effect size (sr^2) = 0.17).

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Table 1

Demographics, clinical information, and inflammatory marker concentrations for study sample with treatment-resistant depression (n = 108).

		Sex differences		
Demographic Information	**Overall**	**Female**	**Male**	***p* value**[1]
Sex, F/M, n	50/58	46%	54%	
Age, mean (SD), y	42.4 (12.7)	42.4 (12.4)	42.6 (13.1)	0.94
BMI, mean (SD), kg/m2	26.2 (5.6)	25.6 (6.5)	26.8 (4.8)	0.27
Education*, mean (SD), y	5.7 (1.4)	5.9 (1.4)	5.5 (1.4)	0.19
Clinical information				
Age at depression diagnosis, mean (SD), y	23.1 (10.1)	22.9 (9.9)	23.3 (10.4)	0.86
Current episode duration, median (IQR), y	2.0 (5.9)	1.3 (3.0)	2.0 (7.3)	0.13
Lifetime illness, mean (SD), y	20.0 (11.8)	19.2 (11.3)	20.6 (12.4)	0.54
Unipolar/bipolar depression, n	89/17	47/10	42/7	0.79
Inflammatory Marker Concentrations[2]				
IL-8, median (Q1-Q3), pg/mL	3.4 (2.3–4.7)	3.5 (2.2–5.2)	3.3 (2.4–4.6)	0.56
IL-6, median (Q1-Q3), pg/mL	1.4 (0.8–2.0)	1.5 (0.7–2.5)	1.4 (0.8–1.9)	0.87
IL-10, median (Q1-Q3), pg/mL	0.5 (0.3–0.8)	0.4 (0.3–0.9)	0.5 (0.3–0.7)	0.45
TNF-a, median (Q1-Q3), pg/mL	6.0 (4.7–7.6)	5.8 (4.5–7.2)	6.2 (4.9–8.3)	0.48
CRP, median (Q1-Q3), mg/L	0.8 (0.4–2.1)	1.0 (0.5–3.8)	0.6 (0.4–1.6)	0.22
Depression Scores; mean (SD)				
HAM-D total score (n = 108)	22.1 (5.8)	23.5 (6.0)	21.0 (5.5)	0.02
HAM-D total excluding anxiety factor (n = 94)	17.1 (4.5)	17.6 (4.6)	16.6 (4.3)	0.29
Factor Scores (n = 94, 41 females)				
HAM-D Factor 1 (Insomnia Symptoms)	2.6 (1.9)	3.0 (2.1)	2.3 (1.7)	0.06
HAM-D Factor 2 (Severity)	3.3 (1.3)	3.3 (1.4)	3.3 (1.3)	0.85
HAM-D Factor 3 (Core Symptoms)	6.8 (1.6)	6.9 (1.6)	6.7 (1.6)	0.68
HAM-D Factor 4 (Anxiety/Hypochondriasis)	4.1 (2.0)	4.7 (1.8)	3.6 (2.0)	0.007
HAM-D Factor 5 (GI Symptoms/Weight Loss)	1.0 (1.1)	1.0 (1.1)	0.9 (1.1)	0.72
HAM-D Factor 6 (Miscellaneous Symptoms)	3.4 (1.5)	3.4 (1.5)	3.4 (1.5)	0.94

*International Standard Classification of Education, UNESCO Institute for Statistics: Levels range from 0 (less than primary education) to 8 (doctoral level or equivalent); level 3 is equivalent to a high school diploma.(2012).

[1]p value shown for differences evaluated with *t*-test, Mann-Whitney *U* test, or Fisher's exact test.

[2]Inflammatory markers log transformed prior to analyses, including t-tests, but non-transformed medians and quartiles shown here.

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Table 2

Inflammatory markers in relation to Hamilton depression rating scale (HAM-D) total score.

	Overall				Females			Males		
	standardized β	**effect size (sr^2)**	***p* value**	***p* value for interaction**	**standardized β**	**effect size (sr^2)**	***p* value**	**standardized β**	**effect size (sr^2)**	***p* value**
Interleukin-8	−0.19	0.04	0.049	0.03	−0.41	0.17	0.004	0.02	<0.01	0.91
Interleukin-6	0.08	0.01	0.42	0.89						
Interleukin-10	0.13	0.02	0.18	0.55						
Tumor Necrosis Factor-α	0.01	<0.01	0.93	0.79						
C-Reactive Protein	0.04	<0.01	0.66	0.54						