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Inflammation and Depression Treatment Response to Electroconvulsive Therapy: Sex-Specific Role of Interleukin-8

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Abstract

Females suffer from depression at twice the rate of males and have differential neural and emotional responses to inflammation. However, sex-specific evaluation of relationships between inflammation and response to depression treatments are lacking. Some data suggest that interleukin(IL)-8 predicts treatment response to antidepressants and shows a sex-dependent relationship with depressive symptom severity. This study examines whether IL-8 predicts treatment response to electroconvulsive therapy (ECT), and whether there are sex specific effects. In 40 depressed patients (22 female), plasma levels of IL-8, as well as other markers of inflammation including IL-6, IL-10, tumor necrosis factor (TNF)-α, and C-reactive protein (CRP) were obtained prior to administration of ECT and after completion of the index treatment series. Depression treatment response was defined as ≥50% reduction in Hamilton Depression Rating Scale (HAM-D) Score. Baseline levels of IL-8 differed by responder status, depending on sex (group x sex interaction: $\beta = -0.571$, $p=0.04$), with female responders having lower levels of IL-8 at baseline as compared to female non-responders [$t(20)=2.37$, $p=0.03$]. Further, IL-8 levels from baseline to end of treatment differed by responder status, depending on sex (group x sex x time interaction: [$F(1,36)=9.48$, $p= 0.004$]), and change in IL-8 from baseline to end of treatment was negatively correlated with percentage change in HAM-D score in females ($\beta= -0.458$, $p=0.03$), but not in males ($\beta= 0.315$, $p=0.20$). Other inflammatory markers did not differ in relation to responder status and sex. Further evaluation of sex differences in the relationship between IL-8, depression, and treatment response, across disparate treatment modalities, may inform mechanisms of response and aid in development of personalized medicine strategies.

Keywords

inflammation; major depressive disorder; electroconvulsive therapy; biomarker; sex differences

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INTRODUCTION

Inflammation is a risk factor for depression[1,2], can cause depressive symptoms[3–5], is elevated in association with depression diagnosis[6], and is associated with poorer treatment response to most antidepressant strategies[7–11]. Given that depression is the leading cause of disability worldwide[12] and is related to inflammation, there is a pressing need to understand mechanisms underlying these associations, which can inform the development of more personalized treatment approaches.

Females suffer from depression at twice the rate of males[13] and demonstrate differential behavioral and neural responses to inflammation[14,15]. For example, markers of inflammation in females, but not males, are associated with anhedonia[16], as well as observed mood, cognitive symptoms, interest-activity, and suicidality[17]. Moreover, in response to inflammatory challenge, females show greater affective sensitivity with greater increases in symptoms of depression and anhedonia as compared to males[15,18], and this sex difference is also observed with regard to the neural effects of inflammation[14]. While there are substantial scientific data demonstrating differences in immune and other biological profiles between depressed males and females[19,20], relatively little research has examined sex specific differences in the association between inflammation and depression treatment response. However, a recent study highlights the importance of ongoing work in this area, identifying elevated baseline C-reactive protein (CRP) as predictive of worse antidepressant treatment outcomes in females only[21].

Inflammation is a broadly-defined term and there is a need for nuance in both the assessment of inflammation and the analysis and interpretation of results, with attention to the role of sex and consideration of various markers of inflammation. Meta-analyses have demonstrated associations between depression diagnosis and higher concentrations of IL-6, tumor necrosis factor (TNF)-α, and C-reactive protein (CRP)[6,22]; circulating concentrations of these markers have thus been of particular interest, and we have found that in contrast to most studies of antidepressant treatments, higher baseline IL-6 was predictive of decreases in depressive symptom severity following electroconvulsive therapy (ECT)[23], although treatment response was not evaluated despite the salience of treatment response in informing clinical management of depressed patients. Of additional interest relative to these usual associated markers, ECT has been found to acutely increase CRP and IL-6 without clear implications for clinical outcome[23,24], while decrease in IL-6 and tumor necrosis factor (TNF) from baseline to the end of an ECT treatment course have been associated with clinical improvement[25–28].

However, recent studies have also implicated depression related differences in IL-8, a chemokine and proinflammatory cytokine somewhat less frequently studied in depression. In a large recent meta-analysis, lower baseline levels of IL-8 were reported to predict a more favorable antidepressant treatment response[29], and our prior work suggested that lower baseline IL-8 might also predict greater reduction in depression severity following ECT, but only in females - finding a potentially meaningful effect size (0.17) in support of such a relationship, although the sample did not have adequate statistical power to test this effect[23].

Severity of depression may be related to IL-8 levels, as a handful of studies has examined the relationship between either peripheral or cerebrospinal fluid levels of IL-8 and depression and found that levels of IL-8 negatively correlate with depression and anxiety scores among depressed patients, 68% of whom were female;[30] and patients who had attempted suicide[31]. Patients who had attempted suicide had lower IL-8 concentrations compared to controls[32]; levels of IL-8 are negatively correlated with suicide risk among females with mood and anxiety disorders[33]. Additionally, a particular allele for IL-8 (IL-8–251T), that is associated with lower circulating IL-8 levels, was significantly more common in female patients who had attempted suicide, and also associated with greater anxiety[31].

To address knowledge gaps in the relationship between IL-8 and depression treatment response, this study evaluated whether IL-8 predicts treatment response to ECT, and whether there are sex specific differences. Whereas our prior report tested correlations between baseline levels of immune markers and severity of depressive symptoms after electroconvulsive therapy (ECT), the sample size was not adequate to examine treatment response[23], or to consider sex differences. Here, with an increase in sample size, we focus on baseline to post-treatment inflammatory marker change stratified by both responder status and sex, and investigate the potential for sex and responder status to jointly associate with levels of inflammatory markers, with a primary focus on IL-8. In 40 depressed patients, including 22 females, who were administered a course of ECT, we hypothesized that lower IL-8 at baseline and subsequent increase in IL-8 across ECT treatment would relate to more favorable treatment outcome, and that these effects would be more robust in females as compared to males. Additionally, given prior interest in other markers of inflammation in relation to depression treatment response to ECT, as described above, we also explored relationships between several other inflammatory markers including CRP, IL-6, IL-10, TNF-α, and ECT treatment outcome.

PATIENTS AND METHODS

Participants

Subjects were depressed patients (N=40; 22 females, 18 males) who were scheduled to undergo ECT treatment at the University of California, Los Angeles (UCLA) Resnick Neuropsychiatric Hospital; this study reports on a subsample of those reported on previously for imaging analyses[34–45], including those who completed a course of ECT and for whom inflammatory marker data were available. Twenty-nine of the 40 current patients were included in a previous study of baseline inflammatory markers[23]. 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 February 2017.

Inclusion criteria were current major depressive episode, and failure to respond to at least two prior antidepressant medications in the index episode. DSM-IV-TR diagnosis of major depressive episode was confirmed by a board-certified psychiatrist and by using the Mini-International Neuropsychiatric Interview (M.I.N.I.)[46]. Exclusion criteria were history of alcohol or substance abuse within the past 6 months and/or dependence within the past 12 months, primary psychotic disorder, dementia, serious medical illness, onset of first episode of depression after age 50, and prior ECT and/or other neuromodulation treatment such as

vagal nerve stimulation or repetitive transcranial magnetic stimulation within 6 months of the current ECT index treatment series. Prior to receiving ECT, patients were tapered off of antidepressants and benzodiazepines (48 – 72 hours). Medication taper was done 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.

Procedures

Participants completed an index series of ECT treatments (an average of 11.8 total ECT treatments per index series, with a standard deviation of 3.4 treatments) with formal clinical assessments and blood sampling pre- and post-treatment. The time points were: baseline (prior to, but within 24 hours of the first ECT treatment); and post-treatment (within a week of completing the ECT index treatment series, approximately 4–6 weeks after baseline). Clinical assessment of depressive symptom severity and blood sampling for inflammatory markers were obtained at both time points.

ECT Treatment

Adhering to the seizure threshold (ST) titration method of ECT treatment administration, after obtaining the ST, ECT treatments were administered at 5–6x ST for right unilateral (RUL) d'Elia lead placement, using an ultra-brief pulse-width (0.3msec), and at 1.5x ST for bilateral placement, using a brief pulse-width (0.5msec). As current evidence suggests that right unilateral ultrabrief ECT following the seizure threshold titration method results in good efficacy but improved tolerability, patients start with this approach. A change to bilateral electrode placement was dependent on periodic clinical assessment and extent of improvement, and made on a case-by-case basis and in collaboration with the patient. Out of the 40 patients, 26 received exclusively unilateral lead placements (24 right unilateral, 2 with both right unilateral and left unilateral sessions), and 14 received at least one bilateral lead placement. Non-responders were more likely to progress to bilateral lead placement ($p=0.01$). See Table 1 for ECT treatment information and response rates. For the index series, ECT (5000Q MECTA Corp.) was administered three times a week, for a mean (SD) of 11.8 (3.4) sessions per subject, using a standard protocol for anesthesia (methohexital at 1mg/kg dosage) and relaxation (succinylcholine at 1mg/kg dosage). Duration of the index course of treatment was decided collaboratively by the ECT psychiatrist, patient, and patient family, with various variables considered, including degree of improvement/benefit, tolerability, and patient preference. ECT treatments were continued even after clinical improvement was noticed in responders, to ensure stability of improvement and aim for clinical remission.

Clinical assessment of depressive symptom severity

The 17-item Hamilton Depression Rating Scale (HAM-D)[47] was collected at baseline and following completion of the ECT index treatment series. Response was defined as ≥50% reduction in HAM-D score from baseline to post-treatment. Percent change in HAM-D score from baseline to end-of-treatment was used as the continuous outcome measure.

Assessment of inflammation

At baseline and following completion of the ECT index treatment series, blood samples were obtained. Because of diurnal variations in circulating cytokine levels that confound interpretation, whole blood samples were collected in the morning between 8 a.m. and 11 a.m. in EDTA tubes, chilled on wet ice, and then centrifuged at 4°C. Plasma was harvested into multiple aliquots, and then stored in a −80°C freezer until assay.

Plasma concentrations of pro-inflammatory cytokines 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,[48] this multiplex assay has excellent intra-assay (<8% coefficient of variation [CV]) and inter-assay (11–16% CV) reproducibility. Multiplex assays were performed on samples diluted 2-fold according to the manufacturer's protocol. 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/mL, taking sample dilution into account. Mean intra-assay CV was <9%, inter-assay CV was ≤15%. All biomarker assays were performed in duplicate, with all samples from a single individual tested in the same batch, and on the same assay plate. The mean of the duplicate sample was used in all analyses. Multiplex assays for cytokines were performed in 3 batches with different kit lots (batch 1: n=15 subjects; batch 2: n=14 subjects; batch 3: n=11 subjects). There were 15 overlapping samples between batches 1 and 2, and there were 20 overlapping samples between batches 1 and 3. The cytokine values of these overlapping samples were therefore used to calculate adjustment multipliers to remove the modest variability (<10%) observed across the batches (analyses using the unadjusted values generated identical effects). All time points for a particular subject were completed in the same batch, on the same plate. CRP assays were completed in a single batch.

Results of the assays were evaluated and showed that 36% 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 (5%) 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 (2.5%) 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 (6%) 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. No sample had a CRP concentration above the upper limit of the standard curve (>25 mg/L).

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

performed a base-10 logarithmic transformation on the data prior to statistical analyses. Linear regression models were used to evaluate the joint effects of group (i.e., responder, non-responder) and sex (i.e., females, males), on baseline concentrations of inflammatory markers. Follow-up analyses of significant results included independent t-tests for baseline concentrations of inflammatory markers in responders versus non-responders, stratified by sex.

Mixed linear effects models were used to evaluate the joint effects of group (i.e., responder, non-responder), sex (i.e. females, males) and time (i.e., baseline, post-treatment) on the inflammatory markers. Sensitivity analyses including the covariates age and BMI were completed for significant findings.

For those inflammatory markers in which there was evidence of a three-way interaction between group, sex, and time, linear regression analyses examined the relationship between change in the inflammatory marker (post-treatment minus baseline) and percentage change in HAM-D scores: [(post-treatment minus baseline)/baseline] x 100.

Given that we previously reported[23] the effect of baseline inflammatory markers on depression outcome following ECT in an overlapping sample (n=29) of the 40 patients evaluated in the current report, linear regression analyses evaluating effect of baseline inflammatory markers on depression outcome following ECT were repeated for the full sample evaluated in the current study (n=40) and are provided as supplementary results. Supplementary results additionally include a correlation matrix of baseline concentrations of inflammatory markers.

Significance was evaluated at an alpha level of α=0.05, two-tailed.

RESULTS

Table 1 summarizes patient demographic and treatment information. Fifty-five percent of participants were females (n=22). Fifty percent (n=20) of participants were depression treatment responders to ECT. No significant differences in demographic variables or clinical severity variables were identified between females and males, nor between responders and non-responders.

Baseline Interleukin-8 and Depression Treatment Response

Linear regression models were used to evaluate the joint effects of group (i.e., responder, non-responder) and sex (i.e., females, males) on baseline level of IL-8 (Table 2), and found a significant interaction between responder status and sex on baseline IL-8 concentration (standardized β coefficient = −0.571, p=0.04), with similar results after covarying age and BMI (standardized β coefficient = −0.582, p=0.04). Among females, responders had lower levels of IL-8 at baseline as compared to non-responders [t(20)=2.37, p=0.03]. Among males, baseline levels of IL-8 did not differ between responders and non-responders [t(16)=0.70, p=0.50] (Figure 1). There were no main effects of sex (standardized β coefficient = 0.32, p=0.17) or responder status (standardized β coefficient = 0.14, p=0.56) on

baseline IL-8 concentration. None of the other inflammatory markers at baseline showed a responder status by sex interaction (Table 2).

Differences in Interleukin-8 in Relation to Depression Treatment Response

Mixed linear effects models showed that levels of IL-8 changed differentially from baseline to post-treatment in relation to responder status and sex, with a statistically significant interaction between group (responder status) x sex x time [$F(1,36)=9.48$, $p=0.004$], which remained significant after covarying age and BMI [$F(1,35.94)=9.45$, $p=0.004$]. (Table 2, Figure 2). None of the other inflammatory markers changed differentially in relation to responder status and sex.

To further examine the associations between treatment differences in IL-8 and depression response to ECT, percentage difference in HAM-D score was calculated from baseline to post-treatment. Linear regression analyses showed that change in IL-8 (post-treatment minus baseline) was negatively related to percentage change in HAM-D score (post-treatment minus baseline) in females ($\beta= -0.458$, $p=0.03$). No such relationship between treatment differences in IL-8 and HAM-D was found in males ($\beta= 0.315$, $p=0.20$) (Figure 2).

See Table 2 for pre- and post-treatment IL-8 concentrations stratified by responder status and sex.

DISCUSSION

Here we report that lower IL-8 concentration at baseline, and subsequent increase in IL-8 over the course of ECT treatment, are each associated with depression improvement among females, but not males. Our previous work identified higher baseline IL-6 as a potential predictor of depression improvement following ECT[23], without regard to sex. Here, exploratory analyses of IL-6, IL-10, TNF-α, and CRP, did not identify sex-specific relationships with ECT treatment outcome.

Similar to our IL-8 findings in females treated with ECT, a recent meta-analysis found that responders to antidepressant medication had lower baseline concentrations of IL-8[29], though this was without evaluation according to sex. In contrast to our findings, the meta-analysis did not identify increasing IL-8 as a correlate of treatment response to antidepressants. The meta-analysis, however, could not evaluate the potential role of sex in these relationships. While relationships between inflammation and depression that are driven primarily by one sex may sometimes be strong enough to drive significance in the overall sample, we suspect that meaningful relationships between inflammatory markers and depression may go undetected when investigators control for sex instead of exploring relationships with sex.

Though we are unaware of any previous sex-specific evaluation of relationships between IL-8 and treatment response, IL-8 was previously found to be negatively correlated with depression and anxiety scores among depressed patients[30] and patients who attempted suicide[31]. Additionally, patients who attempted suicide had lower IL-8 concentrations compared to controls[32], and IL-8 concentration was negatively associated with suicide risk among females with mood and anxiety disorders (males were not included in the study)[33].

Thus, at least among females with depression, our findings are consistent with literature suggesting that “more” IL-8 may be better; relationships between IL-8 and symptom severity among psychiatric populations to date have largely been inverse. In other words, lower IL-8 concentrations are associated with greater symptom burden among depressed patients. In our study, female responders to ECT started with lower baseline IL-8, and increasing IL-8 was associated with decreasing HAM-D scores in females only. These findings, together with extant literature, suggest the possibility that low IL-8 in depressed females may be associated with both greater symptom severity and also greater propensity to respond to treatment interventions, at least ECT, as IL-8 concentrations increase from that low baseline.

At first glance, the suggestion that lower concentrations of IL-8 may associate with greater symptom severity seems contrary to the general notion that proinflammatory markers are “bad” for mental health, given established associations between higher concentrations of inflammatory markers and depression. However, the literature indicates a need for nuance rather than black-and-white thinking as it relates to the spectrum of inflammation. In a study of a TNF-α inhibitor for depression, for example, patients with low inflammation fared worse when treated with the TNF-α inhibitor compared to placebo, suggesting that further lowering inflammation might be harmful in patients without elevated baseline levels[49]. Indeed, cytokines at physiological levels are necessary for various processes related to neuroplasticity and neurogenesis[50]. Specifically with regard to ECT, a linked neuroimmune and neurotrophic mechanism of ECT response has been postulated[51], given that ECT induces rapid changes in inflammatory markers[23,52], while also leading to volumetric increases in the hippocampus and other regions[38,45,53,54]. This, paired with pre-clinical evidence that an inflammatory challenge leads to hippocampal neurogenesis and reversal of depressive-like behaviors in stressed animals[55], suggests that the acute inflammatory effects and corresponding neurotrophic effects of ECT may be part of the therapeutic mechanism.

IL-8, in addition to its role as a pro-inflammatory cytokine, may have neuroprotective and neurotrophic properties, modulating calcium release[56] and neurotransmitter release[57], defending against Fas-mediated death of astrocytes[58], and prolonging neuronal survival[59]. It is conceivable that when IL-8 levels are too low, homeostatic neurophysiological processes may be disrupted. It is unclear how ECT may lead to sex-specific increases in IL-8 in association with treatment response, though the acute inflammatory response initiated by ECT[23,24] could plausibly activate central nervous system production of IL-8 by astrocytes and microglia[60,61]. However, we do not have central measures of IL-8 in the current study, nor is it clear that peripheral measures of IL-8 reflect central measures, though both have been found to negatively correlate with symptoms. With regard to sex differences, estradiol has been found to increase secretion of IL-8 by immature dendritic cells in culture[62]; thus, there may be a relationship between sex hormones and IL-8. However, across studies in both humans and rodents, physiological and psychological stressors that induce inflammation result in sex-specific neural and behavioral effects[14,18,63], but the underlying mechanisms leading to such differences require further study. The effect of sex on the relationship between IL-8, symptom severity, and depression treatment response, among depressed patients, including potential neural correlates, warrants investigation in future studies.

We did not find evidence of significant sex-specific relationships between ECT treatment outcome and IL-6, IL-10, TNF-α, and CRP levels. While higher inflammation at baseline (as indexed by IL-6[23] and CRP[64]) may predict better treatment response to ECT, we did not find any difference in such relationships on the basis of sex. However, inflammatory markers have indeed been found to be differentially related to depression symptoms according to sex. For example, anhedonia[16], observed mood, cognitive symptoms, interest-activity, and suicidality[17] were positively associated with levels of CRP in females but not males. The current study did not evaluate symptom profiles, but focused on treatment response. We are unaware of previous studies evaluating sex-specific relationships between inflammation and treatment outcome that would either support or refute our negative results.

There are several study limitations. Antidepressants and benzodiazepines were tapered and discontinued within 48–72 hours of ECT initiation, and it is unknown whether this taper may impact inflammatory markers. Additionally, as a naturalistic treatment study evaluating biomarkers of response to ECT, there was no randomized arm with which to compare inflammatory or depressive changes. Additionally, replication of results in independent samples with larger samples would be helpful in both determining the stability of the current findings as well as investigating effects that were not statistically significant in the current sample but still fairly large. Another limitation is that we are unable at this time to independently manipulate IL-8 levels to directly test this effect, which might be a strategy of future pre-clinical work. Further, we did not assay for sex hormones, we do not have central measures of inflammation, and we do not have measurements of some markers of inflammation that are also of interest in depression work, such as interferon gamma or IL-17, all of which would be a strength of future work in this area.

This report provides novel evidence that baseline IL-8 and treatment-related IL-8 change may be uniquely related to depression improvement in females, but not males, treated with ECT. Together with previous work demonstrating that higher baseline IL-6 may predict better ECT treatment outcome, this sex-specific finding for IL-8 represents progress toward identifying a panel of inflammatory markers that associate with subsequent treatment response to ECT. Females suffer from major depression at twice the rate as males; the current study suggests that IL-8 may be of particular importance in the future study of depression among females. Further evaluation of sex differences in the relationship between IL-8, depressive symptoms, and depression treatment response is warranted, in larger cohorts of patients, and across disparate treatment modalities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The authors declare no conflict of interest.

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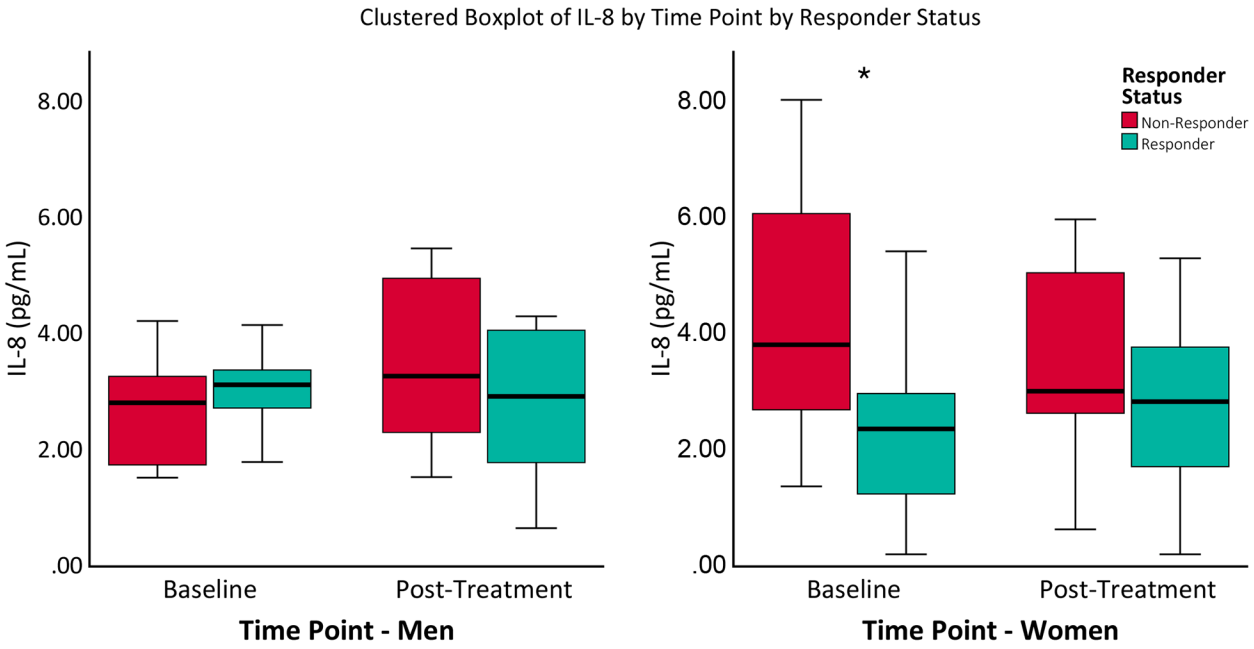

Figure 1. Interleukin-8 at Baseline and Post-Treatment, in Responders versus Non-Responders, Stratified by Sex

Figure 1. At baseline there was a significant group (i.e. responder, non-resonder) by sex interaction for IL-8 concentration; female responders had lower baseline IL-8 than female non-responders [t(20)=2.37, p=0.03]. Baseline IL-8 did not differ between male responders vs. non-responders [t(16)=0.70, p=0.50]. Mixed linear effects models showed that levels of IL-8 changed differentially from baseline to post-treatment in relation to responder status and sex, with a three way interaction of group (responder status) x sex x time [F(1,36)=9.48, p=0.004], which remained significant adjusting for age and BMI [F(1,35.94)=9.45, p=0.004].

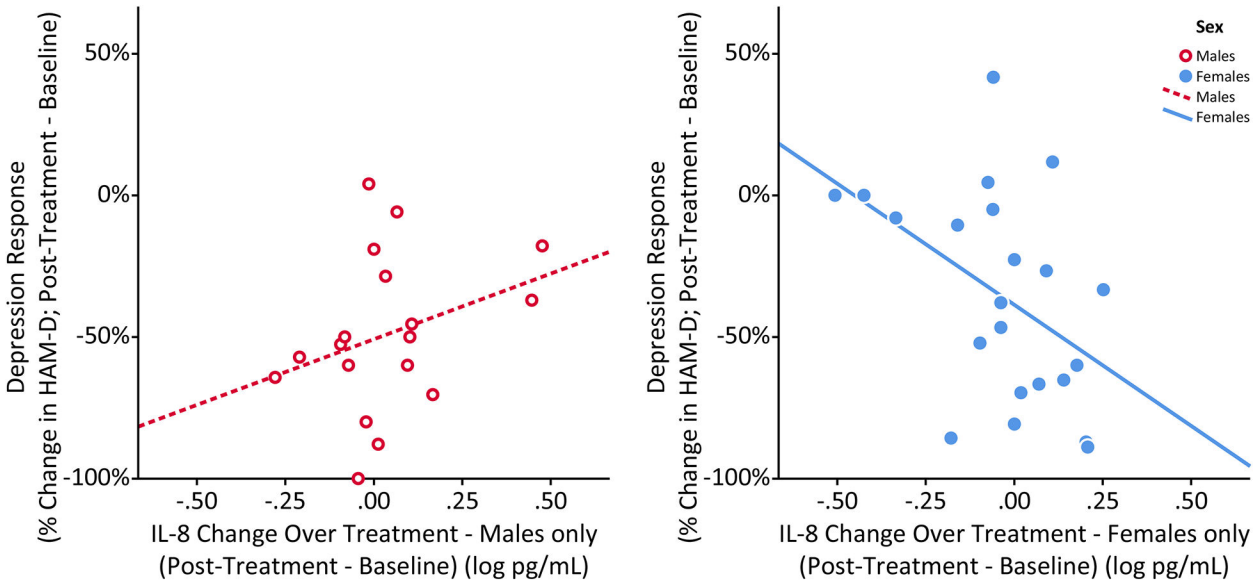

Figure 2. Interleukin-8 Change from Baseline to Post-Treatment Associates with HAM-D Percentage Change in Females, but Not in Males.

Figure 2. Linear regression analyses showed that the difference in IL-8 (post-treatment minus baseline) was negatively related to percentage difference in HAM-D score in females ($\beta = -0.458$, $p=0.03$), in which increases in IL-8 over treatment were associated with decrease in HAM-D scores. No such relationship between treatment differences in IL-8 and HAM-D was found in males ($\beta = 0.315$, $p=0.20$).

Table 1.

Baseline Characteristics and Treatment Information for the Study Sample (n=40)

	Overall	Sex differences (males vs females)			Group differences (responders vs non-responders)		
		Male	Female	Sex difference[1]	Responders (n=20)	Non-Responders (n=20)	Responder difference[1]
Demographic Information							
Sex, M/F, n	18/22	45%	55%		11/9	7/13	p=0.20
Age, mean (SD), y	41.8 (13.7)	44.7 (14.5)	39.4 (12.9)	p=0.23	45.0 (12.6)	38.6 (14.4)	p=0.15
BMI, mean (SD), kg/m^2	26.0 (4.8)	27.3 (3.6)	24.9 (5.4)	p=0.10	27.5 (4.7)	24.5 (4.4)	p=0.05
Education, mean (SD), y	15.47 (2.5)	15.4 (2.4)	16.0 (2.6)	p=0.42	15.8 (2.7)	15.6 (2.4)	p=0.81
Clinical information							
Age at depression diagnosis, mean (SD), y	25.3 (12.5)	25.7 (12.1)	25.0 (13.1)	p=0.87	27.4 (13.1)	23.2 (11.8)	p=0.29
Current episode duration, mean (SD), y	2.1 (2.9)	2.5 (3.5)	1.8 (2.3)	p=0.48	2.1 (3.1)	2.2 (2.8)	p=0.86
Lifetime illness, mean (SD), y	16.4 (11.5)	18.9 (12.0)	14.4 (10.9)	p=0.21	17.5 (11.7)	15.3 (11.5)	p=0.56
Unipolar/bipolar depression, n	33/7	16/2	17/5	p=0.43	16/4	17/3	p=1.0
ECT treatment information							
Unilateral/bilateral lead placement, n	26/14	10/8	16/6	p=0.33	17/3	9/11	p=0.02
Number of index ECT treatment sessions, mean (SD)	11.8 (3.4)	12.9 (4.0)	10.9 (2.4)	p=0.06	10.8 (3.2)	12.8 (3.3)	p=0.07

[1]Differences evaluated with t-test or χ^2 test

Table 2.

Interleukin-8 Concentrations (and Exploratory Markers) in Relation to Responder Status and Sex

	Inflammatory Marker Concentration [median (Q1–Q3)]		Joint Effects of Responder Status (Group) and Sex on Inflammatory Marker Concentration		
Primary Analyses (IL-8)	**Baseline**	**Post-ECT Index**	**Model**	**Standardized β Coefficient or F value**	***p* value**
IL-8, pg/mL * (n=40)	3.0 (2.0–4.1)	3.0 (1.8–4.4)	Regression: Group x Sex[1]	β = −0.57	0.04
Non-responders (n=20)	3.3 (2.1–5.9)	3.1 (2.1–5.4)	(on *baseline* IL-8 only)		
Male (n=7)	2.8 (1.5–3.5)	3.3 (1.7–5.5)	Mixed Model (pre/post):		
Female (n=13)	3.8 (2.5–6.2)	3.0 (2.3–5.5)	Group x Sex[2]	F(1,36)=1.44	0.24
Responders (n=20)	2.8 (1.9–3.4)	2.9 (1.7–4.1)	Group x Time[2]	F(1,36)=0.14	0.71
Male (n=11)	3.1 (2.7–3.4)	2.9 (1.7–4.2)	Sex x Time[2]	F(1,36)=1.84	0.18
Female (n=9)	2.4 (1.2–3.4)	2.8 (1.6–4.1)	Group x Sex x Time[2]	F(1,36)=9.48	0.004
Exploratory Analyses (IL-6, IL-10, TNFa, CRP)					
IL-6, pg/mL * (n=40)	1.5 (1.0–2.2)	1.3 (0.9–1.9)	Regression: Group x Sex[1]	β = −0.04	0.88
Non-responders (n=20)	1.3 (0.7–2.0)	1.0 (0.7–1.6)	(on *baseline* IL-6 only)		
Male (n=7)	0.8 (0.7–1.8)	0.7 (0.7–0.9)	Mixed Model (pre/post):		
Female (n=13)	1.5 (0.6–2.5)	1.3 (0.7–2.6)	Group x Sex[2]	F(1,36)=0.01	0.91
Responders (n=20)	1.8 (1.3–2.6)	1.5 (1.2–2.0)	Group x Time[2]	F(1,36)=0.33	0.57
Male (n=11)	1.5 (1.2–1.9)	1.4 (1.1–1.7)	Sex x Time[2]	F(1,36)=1.71	0.20
Female (n=9)	2.3 (1.6–3.8)	2.0 (1.5–4.3)	Group x Sex x Time[2]	F(1,36)=0.02	0.89
IL-10, pg/mL * (n=40)	0.7 (0.4–1.0)	0.6 (0.4–1.0)	Regression: Group x Sex[1]	β = 0.36	0.20
Non-responders (n=20)	0.5 (0.3–1.2)	0.6 (0.3–1.0)	(on *baseline* IL-10 only)		
Male (n=7)	0.8 (0.3–1.5)	0.6 (0.2–1.0)	Mixed Model (pre/post):		
Female (n=13)	0.4 (0.3–1.1)	0.5 (0.3–0.9)	Group x Sex[2]	F(1,36)=1.10	0.30
Responders (n=20)	0.7 (0.5–1.0)	0.7 (0.4–1.0)	Group x Time[2]	F(1,36)=0.68	0.42
Male (n=11)	0.6 (0.4–0.8)	0.6 (0.4–1.1)	Sex x Time[2]	F(1,36)=0.03	0.86
Female (n=9)	0.9 (0.7–1.1)	1.0 (0.6–1.0)	Group x Sex x Time[2]	F(1,36)=1.11	0.30

Primary Analyses (IL-8)		Inflammatory Marker Concentration [median (Q1–Q3)] Baseline	Post-ECT Index	Joint Effects of Responder Status (Group) and Sex on Inflammatory Marker Concentration Model	Standardized β Coefficient or F value	*p* value
TNF-α, pg/mL * (n=40)		6.0 (4.9–7.6)	6.3 (4.9–7.5)	Regression: Group x Sex[1]	β = 0.03	0.91
	Non-responders (n=20)	6.2 (4.8–7.6)	5.8 (4.7–6.9)	(on *baseline* TNF-α only)		
	Male (n=7)	5.3 (4.7–6.0)	5.5 (4.7–6.8)	Mixed Model (pre/post):		
	Female (n=13)	6.9 (4.7–7.9)	6.0 (4.2–7.6)	Group x Sex[2]	F(1,36)=0.95	0.34
	Responders (n=20)	6.0 (5.0–7.6)	6.8 (5.1–7.8)	Group x Time[2]	F(1,36)=1.34	0.26
	Male (n=11)	5.8 (4.4–7.5)	6.1 (4.2–7.5)	Sex x Time[2]	F(1,36)=0.04	0.85
	Female (n=9)	6.6 (5.6–8.9)	6.9 (6.1–13.7)	Group x Sex x Time[2]	F(1,36)=4.07	0.05
CRP, mg/L * (n=40)		0.8 (0.3–3.0)	1.2 (0.8–3.8)	Regression: Group x Sex[1]	β = 0.34	0.21
	Non-responders (n=20)	0.6 (0.3–3.4)	1.1 (0.6–3.8)	(on *baseline* CRP only)		
	Male (n=7)	0.4 (0.2–4.2)	1.1 (0.4–2.4)	Mixed Model (pre/post):		
	Female (n=13)	0.7 (0.3–2.8)	1.0 (0.6–5.5)	Group x Sex[2]	F(1,36)=1.27	0.27
	Responders (n=20)	1.0 (0.3–3.0)	1.8 (0.9–4.3)	Group x Time[2]	F(1,36)=0.05	0.82
	Male (n=11)	0.9 (0.2–1.9)	1.2 (0.8–2.6)	Sex x Time[2]	F(1,36)=0.18	0.67
	Female (n=9)	3.1 (0.7–10.9)	3.9 (1.5–7.0)	Group x Sex x Time[2]	F(1,36)=0.85	0.36
		HAM-D Scores [mean (SD)]				
		Baseline	**Post-ECT Index**			
HAM-D Score (n=40)		24.1 (5.9)	13.3 (7.5)			
	Non-responders (n=20)	22.7 (5.6)	19.2 (5.7)			
	Male (n=7)	25.4 (4.7)	20.3 (7.0)			
	Female (n=13)	21.2 (5.6)	18.6 (5.1)			
	Responders (n=20)	25.4 (6.0)	7.4 (3.2)			
	Male (n=11)	23.7 (6.3)	7.7 (3.6)			
	Female (n=9)	27.4 (5.2)	7.0 (2.8)			

* Values were transformed by base 10 logarithm before statistical analyses, but original scale medians and IQR are presented.

[1] Linear regression model evaluating the joint effect of responder status and sex on the baseline concentration of the inflammatory marker.

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[2]Linear mixed effects model evaluating the joint effect of responder status, sex, and time, on concentration of inflammatory markers over treatment.