HHS Public Access

Author manuscript

Aust N Z J Psychiatry. Author manuscript; available in PMC 2017 December 15.

Published in final edited form as:

Aust N Z J Psychiatry. 2017 January ; 51(1): 23–31. doi:10.1177/0004867416652736.

Inflammatory cytokines in major depressive disorder: A case–control study

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Abstract

Introduction—There is mixed evidence in the literature on the role of inflammation in major depressive disorder. Contradictory findings are attributed to lack of rigorous characterization of study subjects, to the presence of concomitant medical illnesses, to the small sample sizes, and to the limited number of cytokines tested.

Methods—Subjects aged 18–70 years, diagnosed with major depressive disorder and presenting with chronic course of illness, as well as matched controls ($n = 236$), were evaluated by trained raters and provided blood for cytokine measurements. Cytokine levels in EDTA plasma were measured with the MILLIPLEX Multi-Analyte Profiling Human Cytokine/Chemokine Assay employing Luminex technology. The Wilcoxon rank-sum test was used to compare cytokine levels between major depressive disorder subjects and healthy volunteers, before (interleukin [IL]-1 β, IL-6, and tumor necrosis factor-α) and after Bonferroni correction for multiple comparisons (IL-1α, IL-2, IL-3, IL-4, IL-5, IL-7, IL-8, IL-10, IL-12(p40), IL-12(p70), IL-13, IL-15, IFN-γ-inducible protein 10, Eotaxin, interferon-γ, monotype chemoattractant protein-1, macrophage inflammatory protein-1α, granulocyte-macrophage colony-stimulating factor and vascular endothelial growth factor).

Results—There were no significant differences in cytokine levels between major depressive disorder subjects and controls, both prior to and after correction for multiple analyses (significance set at $p \leq 0.05$ and $p \leq 0.002$, respectively).

Conclusion—Our well-characterized examination of cytokine plasma levels did not support the association of major depressive disorder with systemic inflammation. The heterogeneity of major

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Cassano reports grants from NIMH—National Institute of Mental Health, from null, during the conduct of the study; and personal fees from Janssen Pharmaceutical, from null, non-financial support from Photomedex Inc., outside the submitted work.

depressive disorder, as well as a potential sampling bias selecting for non-inflammatory depression, might have determined our findings discordant with the literature.

Keywords

Major depressive disorder; inflammation; cytokines; interleukin-1β; interleukin-6; tumor necrosis factor-α

Introduction

Chronic and recurrent major depressive disorder (MDD) are highly comorbid with other chronic medical illness, including inflammatory diseases (Cassano and Fava, 2002; Kiecolt-Glaser et al., 2015), suggesting that inflammation might contribute to the development or persistence of MDD. However, it is unclear whether MDD may be associated with inflammatory abnormalities in the absence of significant medical illness. Several studies have suggested that proinflammatory cytokines—a family of proteins that mediate immune responses to injury, infection and other organismal stress—are elevated in both serum and cerebral spinal fluids in patients with MDD (Dahl et al., 2014; Dowlati et al., 2010; Dunjic-Kostic et al., 2013; Miller et al., 2009; Noto et al., 2015; Oliveira Miranda et al., 2014; Rivera-Rivera et al., 2014; Rudolf et al., 2014; Schmidt et al., 2014; Simon et al., 2008; Young et al., 2014). A recently published study suggests that, for a subset of individuals with MDD, the inflammation plays a key role in the pathogenesis of MDD, and both inflammation and MDD seem to continuously fuel each other (Kiecolt-Glaser et al., 2015). However, contradictory findings have also been reported showing no differences in serum proinflammatory cytokines between individuals with MDD and healthy subjects (Cilan et al., 2012; Marques-Deak et al., 2007). These mixed results, and lack of definitive conclusions in the literature on the role of inflammation in MDD, may stem from the lack of rigorous characterization of study subjects, the presence of concomitant medical illnesses or medications, sample variability and small sizes, and the limited number of cytokines tested. Data to date suggest that inflammatory responses may be relevant for only a subset of depressed patients (Kiecolt-Glaser et al., 2015). In this study, in order to address these limitations, we tested a wide array of cytokines and chemokines in a large, well-characterized sample of subjects with MDD (free of psychiatric medications and significant medical illness) and age- and gender-matched healthy controls. Although a broad array of cytokines were assessed in the sample, this paper focuses on the peripheral levels of interleukin-1β (IL-1β) and IL-6 and tumor necrosis factor-α (TNF-α), given the stronger evidence of their elevation in MDD (Azar and Mercer, 2013; Dahl et al., 2014; Dowlati et al., 2010; Dunjic-Kostic et al., 2013; Miller et al., 2009; Noto et al., 2015; Oliveira Miranda et al., 2014; Rudolf et al., 2014; Schmidt et al., 2014; Thomas et al., 2005).

Materials and methods

Participants

Participants aged 18–70 years with a primary diagnosis of MDD and gender- and age-matched one-to-one controls were recruited through advertisements and referrals at the Center for Anxiety and Traumatic Stress Disorder and the Depression Clinical and Research

Program at the Massachusetts General Hospital (MGH), as part of a larger study on stress and aging (National Institute of Mental Health [NIMH] R01MH077700-05). Methods have been described elsewhere (Simon et al., 2015). Participants were assessed for psychiatric disorders in person by trained, experienced doctoral-level (MD or PhD) clinicians, using the *Structured Clinical Interview for DSM-IV* (SCID; First et al., 2002), who also completed interviewer-rated measures. Participants completed self-report measures and phlebotomy. Of those who were considered ineligible for the MDD group (n = 210), only 30% did not meet criteria for MDD in their lifetime, and most subjects were excluded for not being depressed long enough, for not being currently in a depressive episode or for the latter not qualifying as the primary diagnosis, as well as for having a body mass index (BMI) greater than 35. Participants provided written informed consent and were compensated AUD75 for study participation. All study procedures were approved by the Institutional Review Board of the MGH.

Study entry criteria for the MDD group included current chronic unipolar MDD, with a lifetime MDD duration of at least 5 years (defined as time since initial onset of MDD, with current MDD required). Previous remissions were allowed, as long as the participants were in a current major depressive episode at the time of screen and phlebotomy. Lifetime schizophrenia or any psychosis, mental retardation, organic medical disorders and bipolar disorder were exclusionary, as well as current eating disorders, and alcohol or substance-use disorders. Lifetime alcohol and substance-use disorders were allowed, however not in the 12 months prior to the study. Control participants were free of any lifetime *Diagnostic and Statistical Manual of Mental Disorders*, Fourth edition (DSM-IV) Axis I psychiatric disorder, except for past addictions similarly to the case subjects. To reduce potential additional confounders, we also excluded subjects with current cancer, chronic inflammatory disorders, epilepsy, diabetes, current unstable cardiovascular illness, surgery within the prior 4 weeks, obesity (defined as BMI > 35) and current pregnancy. Use of any psychiatric medication in the 2 weeks (4 weeks for fluoxetine) prior to screen or of anti-inflammatory medications in the 3 days prior to blood draw was exclusionary (prior use of psychiatric medications was allowed). In case of an acute infection, systematically assessed by a trained clinician using the *Cumulative Illness Rating Scale* (CIRS), or of antibiotic use, participants returned for phlebotomy 1 week after symptom resolution or completion of any antibiotics (Simon et al., 2015).

Measures

The SCID (First et al., 2002) was used to assess psychiatric disorders, including the number and total cumulative length of major depressive episodes. The 10-item clinician-administered *Montgomery–Åsberg Depression Rating Scale* (MADRS) (Montgomery and Asberg, 1979)—total scores ranging from 0 to 60—was used to assess MDD symptom severity.

The CIRS (Fortin et al., 2005; Miller et al., 1992) has been well-established to accurately assess overall burden of illness with specific assessment of multiple medical comorbidities and severity to generate 13 specific medical category ratings, each rated with anchors from 0 (*no problem*) to 4 (*extremely severe*) and yielding a cumulative severity rating (total range:

0–52). The CIRS was administered by formally trained study investigators with ongoing training and review of each assessment by the study principal investigator (PI), to assess allowed medical comorbidity as a potential covariate. The *Traumatic Events Questionnaire* (TEQ; Vrana and Lauterbach, 1994) was adopted to assess cumulative exposure to a range of 11 categories of childhood and adult traumatic life events in a self-rated format, with a cumulative score double weighted for multiple exposures. The short form of the *Early Trauma Inventory Self-Report* (ETISR SF; Bremner et al., 2007) was used to assess exposure to trauma before age 18, including general trauma (11 items), physical abuse (5 items), emotional abuse (5 items) and sexual abuse (6 items). Those who reported a significant loss with the *Loss History Form* (ad hoc screening tool) also completed the *Inventory of Complicated Grief* (ICG), a 19-item scale assessing grief symptoms severity (Prigerson et al., 1995) with each item rated from 0 = *not at all* to 4 = *severe* and a total score ranging from 0 to 76. The *Perceived Stress Scale* (PSS), a 10-item self-report measure, was used to assess perceptions of stress during the previous month (Cohen et al., 1983).

Additionally, BMI, exercise frequency (days per week of strenuous exercise of at least 20-minute duration), high blood pressure (≥ 150/90) and smoking history (lifetime pack-years) were also assessed as potential confounders of cytokine levels.

Collection of blood samples and cytokine measures

Participants underwent venipuncture at rest during daytime hours. For the cytokine assays, whole blood was collected into EDTA tubes and centrifuged at 3000 r/min for 15 minutes at 4°C; plasma was then obtained. We quantitatively determined the steady state level of the circulating inflammatory (both pro- and anti-inflammatory) cytokines from plasma, including the three primary cytokines of interest: IL-1β, IL-6 and TNF-α, but also simultaneously for exploratory analyses: IL-1α, IL-2, IL-3, IL-4, IL-5, IL-7, IL-8, IL-10, IL-12(p40), IL-12(p70), IL-13, IL-15, IFN-γ-inducible protein 10 (IP-10), Eotaxin, interferon-γ (IFN-γ), monotype chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1α (MIP-1α), granulocyte-macrophage colony-stimulating factor (GM-CSF) and vascular endothelial growth factor (VEGF) using the MILLIPLEX Multi-Analyte Profiling (MAP) Human Cytokine/Chemokine Kit for 96-well assay (Millipore) run on a Luminex platform. For quality assurance, each sample was run twice, and the mean derived for each sample was used as the index value. Additionally, two kit-supplied quality controls were run on each plate in duplicate and confirmed to fall within the expected range.

Statistical methods

To test whether proinflammatory cytokines were elevated in individuals with MDD compared to controls, we used the Wilcoxon rank-sum test for each of the 22 tested cytokines—since cytokine data were not normally distributed. Samples with undetectable values were assigned a median value between zero and the assay sensitivity threshold for that particular measure. The impact of the imputed value was minimized by the use of a categorical statistical test which compares the distribution in ranks of the dependent variables, the cytokine levels. The Luminex bead technology of the MILLIPLEX assay allowed simultaneous detection of all 22 plasma cytokines in the same reaction. Subjects with MDD and their respective matched controls were run on the same plate. Cross-plate

controls were run to measure inter-plate variability. The two study-groups were compared for baseline variables, comprising demographic characteristics and clinical features. A Fisher's exact test and a two-way Student's *t*-test were applied to compare baseline variables, for dichotomous and continuous variables, respectively. A Wilcoxon rank-sum test was instead applied when nominal variables had values distributed in more than two categories. Whenever a significant difference was found between groups ($p \leq 0.05$), the selected variable was tested for its association with the primary cytokine level (IL-1β, IL-6 and TNF-α) by means of linear regression analysis ($p \leq 0.05$). If this latter association was also significant, then the predictor variable was considered a potential confounder. Of note, clinical variables deemed intrinsically related to the construct or to the genesis of depression (e.g. history of trauma, grief symptoms and perceived stress) were not included as potential confounders. None of the baseline variables tested met the criteria for confounder (education, lifetime alcohol and drug use disorder, BMI, physical activity, smoking, high blood pressure and current medical illness). Finally, we compared MDD and controls for the number of subjects with detectable levels of each measured cytokine (Fisher's exact test). Analyses were conducted using STATA 12.1 (StataCorp LP, College Station, TX). Significance level was set at 0.05 (two-sided) for the three primary cytokines tested (IL-1β, IL-6 and TNF-α) and for all comparisons on groups characteristics; for the other cytokines tested in exploratory fashion, a Bonferroni correction was adopted with significance set for a *p*-value less than 0.002 (0.05 divided by 22).

Results

Participants and symptoms characteristics

Participants' characteristics by group are reported in Table 1 ($n = 236$); all MDD participants were age- and gender-matched one-to-one to a control participant. As seen in Table 1, compared to controls, participants with MDD had significantly less education, exercised less frequently, smoked more and had greater medical comorbidity (CIRS total score), but less hypertension (as assessed by one measure); they also had a greater incidence of lifetime alcohol and/or drug abuse or dependence, greater grief severity (ICG total score), trauma exposure (TEQ weighted score and ETISR number answered '*yes*') and perceived stress (PSS total score).

Mean time since MDD onset to study entry was 22.1 years (standard deviation [SD] = 14.2). Cumulative duration of mood episodes was on average 13.4 (SD = 13.5) years. Almost half (41%, $n = 46$) of participants with MDD reported past antidepressant use of 6 months or more, 48% met criteria for a current anxiety disorder (including social anxiety disorder, panic, agoraphobia, generalized anxiety disorder, posttraumatic stress disorder [PTSD] and obsessive–compulsive disorder [OCD]) and 53% for a lifetime anxiety disorder.

Cytokine levels by diagnosis

The levels of the three primary cytokines, IL-1β, IL-6 and TNF-α, as well as the other 19 cytokines tested, did not significantly differ for individuals with MDD compared to controls (see Table 2 for means and significance at $p \leq 0.05$ and $p \leq 0.002$, respectively).

Additionally, the number of detectable cytokines did not significantly differ for individuals with MDD compared to controls (see Table 2).

Discussion

Given the large body of literature supporting the hypothesis that depression is associated with high levels of inflammation, we sought to examine whether MDD is associated with abnormal cytokine levels, regardless of medical comorbidity (Dahl et al., 2014; Dowlati et al., 2010; Dunjic-Kostic et al., 2013; Miller et al., 2009; Noto et al., 2015; Oliveira Miranda et al., 2014; Rivera-Rivera et al., 2014; Rudolf et al., 2014; Schmidt et al., 2014; Simon et al., 2008; Young et al., 2014). In our large sample (n = 236) of patients with MDD and healthy controls, there existed no significant associations between depression and plasma cytokine levels (in the 3 primary ones and in the 19 remainders tested with Bonferroni correction). Interestingly, control participants had higher mean values for most of the cytokines compared to the index group, which is in contrast to the findings of a prior study from our group, using the same cytokine assays and similar selection criteria for healthy controls but using PTSD and panic disorder diagnoses to characterize the index group (Hoge et al., 2009). Our overall findings contrast with the majority of the studies published on this subject, with a few exceptions (Cilan et al., 2012; Marques-Deak et al., 2007). We therefore offer three potential and compatible explanation of the discrepancy between our findings and the existing literature.

Neuro-inflammation and heterogeneity of depression

When referring to MDD, as defined by the DSM-IV or DSM-5 (*Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition) criteria (the former was used in this study), diagnosis is based on the endorsement of a cluster of symptoms (five out of nine) for adequate length of time. We used well-validated structured interviews and rating scales, experienced clinical raters and rigorous enrollment criteria, requiring at least 5 years since the onset of the first major depressive episode and a current episode, both determined by the SCID. Our intent was to assure that MDD was a primary diagnosis of sufficient severity and length to potentially impact cytokine levels. Nevertheless, it is well understood that the very same diagnosis of MDD comprises a wide range of possible syndromes (permutations of the nine diagnostic symptoms; Fried and Nesse, 2014). Besides the heterogeneity of the clinical phenotypes of MDD, there is also a growing understanding that even similar clinical presentations might stem from different pathophysiological processes; this is true for a range of other medical conditions with downstream overlapping phenomena as well (Moylan et al., 2013).

Our rigorous selection criteria, excluding patients with medical comorbidity, obesity and problem substance use, might have yielded a skewed sample of individuals with a '*non-inflammatory*' type of depression, in contrast to a more heterogeneous sample with MDD; Raison and Miller (2011) suggested that about a third of depressed patients have markedly elevated inflammatory markers. Similarly, in the National Health and Nutrition Examination Survey study, only 29% of depressed subjects presented markedly elevated C-reactive protein (Rethorst et al., 2014). While our MDD subjects presented with a chronic course of

depression without significant medical comorbidity, obesity, or substance use, they still presented some typical behavioral changes in exercise, consumption habits and diet. Additionally, we included patients not on antidepressants, thereby eliminating some individuals with particularly severe depression. Interestingly, although the results were not significant, control participants had higher mean values for most of the cytokines compared to the MDD group, which is in contrast to the findings of a prior study from our group, using the same cytokine assays and similar selection criteria for healthy controls but using PTSD and panic disorder diagnoses to characterize the index group (Hoge et al., 2009). However, if the study was powered enough to detect the differences between controls and MDD, it would point to controls having higher cytokines suggesting that this study did not capture an inflammatory type of MDD. Overall, our carefully selected sample might have produced a sampling error and missed MDD associated with primary neuro-inflammation—inflammatory response from microglial activation (Najjar et al., 2013; Reus et al., 2015).

Neuro-inflammation and plasma cytokine levels

For this study, only peripheral cytokine levels were assessed. As there is poor correlation between plasma and cerebrospinal fluid (CSF) cytokine levels, we cannot exclude the possibility of inflammation of the brain—microglial activation—among the subjects enrolled in this study (Bromander et al., 2012; Dellalibera-Joviliano et al., 2003; Hopkins et al., 2012).

Confounding by medical comorbidity

A third plausible interpretation of our findings considers that MDD can be induced or exacerbated by comorbid inflammatory processes and that elevated serum cytokines could mediate this phenomenon (Dantzer et al., 2008); this interpretation does not imply a primary neuro-inflammatory process. It has been demonstrated that brain activity such as the activation of subgenual anterior cingulate cortex and its connectivity with other brain regions can be, respectively, induced and decreased by peripheral inflammatory processes and by IL-6 elevation (Harrison et al., 2009). Based on this theory, prior studies that did not adequately control for medical comorbidity might have been enriched with MDD secondary to concomitant inflammatory processes. It is well-known that the prevalence of MDD is higher in medically ill patients as opposed to the general population (Cassano and Fava, 2002). In prior studies, the association between elevated plasma cytokines and MDD might just be a reflection of the impact of peripheral cytokines on depression: when elevated, they are likely to trigger or worsen depression. It is also possible that some associations found in prior studies between MDD and elevated plasma cytokines were just coincidental. It is plausible that, in some studies, the association of elevated anti-inflammatory cytokines with MDD occurred in the absence of primary neuro-inflammation and of a mediating effect of the same cytokines toward depression. Our study's strength is in addressing and avoiding some of these confounding factors. In fact, we recruited a carefully selected sample, based on well-characterized lifetime comorbidities, environmental stressors and unhealthy lifestyles. Our results question whether residual confounding—by factors known to be associated with both depression and cytokine levels—might have affected the findings in some of the studies on the same topic.

Study limitations

Study limitations include the cross-sectional nature of this study with depression history dependent on structured clinician interviews only, the lack of data on other potential factors such as subtype of depressive episode (e.g. atypical versus melancholic depression) and the high number of undetectable cytokines in both groups due to possible measurement error. Many factors contribute to the variability in cytokine measurement, such as stability of each cytokine during the blood/plasma processing time, freeze–thaw cycles and storage. These factors influence both cytokines' detectability and measurement and ultimately produce high variability in cytokines' levels between studies (De Jager et al., 2009). Within our study, variability in cytokine levels was accounted for by testing simultaneously cases and controls. Furthermore, our rigorous entry criteria developed to limit confounding variables, such as the exclusion of some medical conditions, may have selected an unrepresentative cohort of patients with MDD and may have diminished the ecological validity of our comparison. The exclusion of individuals with concomitant medical conditions may have contributed to a selection bias of a non-inflammatory type of depression. As well, enrolled patients were required to be free of antidepressants at study entry to examine MDD without the influence of antidepressants, which themselves (i.e. selective serotonin reuptake inhibitors [SSRIs]) may have anti-inflammatory effects (Hannestad et al., 2011). This may have limited severity and chronicity of the sample; of note, less than half of the sample reported lifetime antidepressant use for over 6 months (40%). Finally, our study was not powered to detect smaller between groups differences that have been reported in prior research (Dowlati et al., 2010); however, because most of the cytokine levels in the controls were more elevated than individuals with MDD, it is unlikely that our relative lack of statistical power prevented us from detecting a small effect of MDD on increased inflammatory cytokines.

Conclusion

In conclusion, after rigorously selecting chronically depressed patients without significant medical comorbidity and with mild to moderate severity of depression, we found no significant association between plasma cytokines and presence of MDD; our results are in contrast with the extant literature. Our rigorous criteria aimed at preventing confounding by medical comorbidity (peripheral inflammation) and by concurrent treatments might also have led to the selection bias of a '*non-inflammatory*' type of MDD, ultimately preventing us from testing the association of MDD with neuro-inflammation.

Strict inclusion and exclusion criteria in rigorous human studies, including clinical trials, might select fora particular, underlying biological phenotype, while the clinical phenotype of MDD is deceptively representative of the average depressed patient.

Acknowledgments

Dr Bui reports grants from Osher Center for Integrative Medicine, outside the submitted work.

Dr Mischoulon reports other from Bowman Family Foundation, FisherWallace, Nordic Naturals, Methylation Sciences, Inc. (MSI), and PharmoRx Therapeutics, other from Massachusetts General Hospital (MGH) Psychiatry Academy; other from Lippincott Williams & Wilkins, outside the submitted work.

Dr Fava reports grants from Research Support: AstraZeneca; Avanir Pharmaceuticals; Cerecor; Eli Lilly and Company; EnVivo Pharmaceuticals, Inc.; Euthymics Bioscience, Inc.; Forest Pharmaceuticals, Inc.; FORUM Pharmaceuticals; Janssen R&D, LLC; Johnson & Johnson Pharmaceutical Research & Development; Lundbeck Inc.; MSI; National Center for Complementary and Alternative Medicine (NCCAM); National Coordinating Center for Integrative Medicine (NiiCM); National Institute of Drug Abuse (NIDA); NIMH; Neuralstem, Inc.; Novartis AG; PamLab, LLC; Pfizer Inc.; PharmoRx Therapeutics; Photothera; Reckitt Benckiser; Roche Pharmaceuticals; RCT Logic, LLC (formerly Clinical Trials Solutions, LLC); Stanley Medical Research Institute (SMRI); Takeda; Tal Medical; other from Advisory Board/Consultant: Acadia; Alkermes, Inc.; AstraZeneca; Avanir Pharmaceuticals; AXSOME Therapeutics; Biogen; Bristol-Myers Squibb; Cerecor; Dinippon Sumitomo Pharma Co. Inc.; Eli Lilly and Company; Euthymics Bioscience, Inc.; Forest Pharmaceuticals, Inc.; FORUM Pharmaceuticals; GenOmind, LLC; GlaxoSmithKline; Intracellular; Janssen Pharmaceutical; Johnson & Johnson Pharmaceutical Research & Development, LLC; Lundbeck Inc.; Merck & Co., Inc.; MSI; Naurex, Inc.; Nestle Health Sciences; Neuralstem, Inc.; Novartis AG; Nutrition 21; Osmotica; Otsuka Pharmaceuticals; Pamlab, LLC; Pfizer Inc.; PharmoRx Therapeutics; Pharmaceutical Product Development, LLC (PPD); Puretech Ventures; PsychoGenics; RCT Logic, LLC (formerly Clinical Trials Solutions, LLC); Ridge Diagnostics, Inc.; Roche; Sanofi-Aventis US LLC; Servier Laboratories; Sunovion Pharmaceuticals; Taisho Pharmaceutical; Takeda Pharmaceutical Company Limited; Tal Medical, Inc.; VistaGen personal fees from Speaking/Publishing: American Society of Clinical Psychopharmacology; Belvoir Media Group; Continuing Medical Education Institute/Physicians Postgraduate Press, Inc.; MGH Psychiatry Academy from Royalty/patent, other income: Patents for Sequential Parallel Comparison Design (SPCD), licensed by MGH to PPD; and patent application for a combination of Ketamine plus Scopolamine in Major Depressive Disorder (MDD), licensed by MGH to Biohaven. Copyright for the MGH Cognitive and Physical Functioning Questionnaire (CPFQ), Sexual Functioning Inventory (SFI), Antidepressant Treatment Response Questionnaire (ATRQ), Discontinuation-Emergent Signs and Symptoms (DESS), Symptoms of Depression Questionnaire (SDQ), and State vs Trait; Assessability; Face Validity; Ecological Validity; Rule of the Three P's (SAFER); Lippincott, Williams & Wilkins; Wolkers Kluwer; World Scientific Publishing Co. Pte Ltd other from Stock/Other Financial Options: Equity Holdings: Compellis; PsyBrain, Inc., outside the submitted work.

Dr Simon reports grants from NIMH, from null, during the conduct of the study; grants from American Foundation for Suicide Prevention, grants from Department of Defense, grants from Highland Street Foundation, grants from National Institute of Health, other from MGH Psychiatry Academy, other from Pfizer Pharmaceuticals, outside the submitted work.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the National Institute of Mental Health (NIMH) (Grant Number NIMH R01MH077700-05).

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Table 1

Demographic and clinical characteristics.

	Control (*n* = 118)		MDD (*n* = 118)		*p*-value
Demographic characteristics					
Age (years), mean (SD)	42.1	13.1	42.1	13.1	0.98
Sex, *N*(%) Female	65	55%	65	55%	1
Race, *N*(%)					0.14
White	79	67%	90	76%	
Black or African American	22	19%	17	14%	
Asian	7	7%	4	3%	
Native American/Alaska Native	0	0%	2	2%	
Other	9	8%	4	3%	
Ethnicity, *N*(%)					0.7
Non-Hispanic/Latino	107	91%	107	91%	
Hispanic/Latino	10	9%	8	7%	
Education level, *N*(%)					<0.001
Graduate school	40	34%	23	20%	
College graduate	50	43%	37	32%	
College, partial	21	18%	33	29%	
High school graduate or less	6	5%	16	14%	
Clinical characteristics					
Years since MDD Onset, mean (SD)	n/a	n/a	21.6	13.8	n/a
Years of depressive episodes, mean (SD)	n/a	n/a	13.3	13.4	n/a
MADRS total score, mean (SD)	2.2	2.6	28.3	6.3	<0.001
Any anxiety disorder—current, *N*(%)	n/a	n/a	56	51%	n/a
Any anxiety disorder—lifetime, *N*(%)	n/a	n/a	63	57%	n/a
Antidepressant use >6 months, *N*(%)	n/a	n/a	43	42%	n/a
Mood stabilizer use >6 months, *N*(%)	n/a	n/a	4	3%	n/a
Benzodiazepine use >6 months, *N*(%)	n/a	n/a	12	11%	n/a
Antipsychotic use >6 months, *N*(%)	n/a	n/a	7	6%	n/a

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	Control (*n* = 118)		MDD (*n* = 118)		*p*-value
Lifetime alcohol or drug abuse/dependence, *N*(%)	9	9%	34	31%	<0.0001
History of loss (based on ICG)	71	69%	82	77%	0.17
ICG total score, mean (SD)	6.6	7.9	18.4	14.3	<0.0001
TEQ weighted score, mean (SD)	1.7	2.4	4.1	4.4	<0.0001
ETISR (no. answered yes), mean (SD)	4.7	4.4	9.4	6.0	<0.0001
PSS total score, mean (SD)	8.4	5.8	24.4	6.1	<0.0001
Medical history					
Height (in), mean (SD)	66.9	3.5	66.9	3.7	0.97
Weight (Ibs), mean (SD)	159.4	33.0	168.0	38.1	0.07
BMI, mean (SD)	24.99	4.1	26.3	4.5	0.02
Menopausal status, *N*(%)					0.16
Pre-/Peri-menopausal	36	65%	31	56%	
Post-menopausal/Hysterectomy	19	35%	24	44%	
Exercise level, *N*(%)					0.0003
Never/Less than once a month	10	9%	31	28%	
Less than once a week	18	16%	20	18%	
Few times a week	24	21%	20	18%	
Several times a week	54	47%	28	25%	
Every day	10	9%	12	11%	
Smoking status, *N*(%)					0.003
Current smoker	8	7%	25	22%	
Past smoker	25	22%	29	26%	
Never smoked	83	72%	59	52%	
Pack years smoking (in smokers), mean (SD)	1.5	5.7	1.7	6.5	0.89
Any lifetime medical illness, *N*(%)	88	83%	97	88%	0.36
Hypertension (BP ≥ 150/90), *N*(%)	22	22%	12	11%	0.04
CIRS total score, Mean (SD)	2.6	2.2	3.4	2.8	0.01

SD: standard deviation; MDD: Major Depressive Disorder; MADRS: *Montgomery–Åsberg Depression Rating Scale*; ICG: *Inventory of Complicated Grief*; TEQ: *Traumatic Events Questionnaire*; ETISR: *Early Trauma Inventory Self-Report*; PSS: Perceived Stress Scale; BMI: body mass index; BP: blood pressure; CIRS: *Cumulative Illness Rating Scale*.

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Table 2

Cytokine levels (pg/mL) by diagnosis.

	MDD		Controls			MDD	Controls	
Cytokine	**Mean**	**SD**	**Mean**	**SD**	***p*-value**	**% Detectable**	**% Detectable**	***p*-value**
Eotaxin	66.05	31.01	72.33	36.59	0.22	99%	100%	1.00
GM-CSF	10.06	28.84	28.18	101.16	0.56	38%	39%	1.00
IFN-γ	23.56	62.16	43.67	91.59	0.08	80%	85%	0.32
IL-1α	25.92	111.27	130.20	809.22	0.22	42%	46%	0.61
IL-1β	1.94	4.28	3.56	7.83	0.54	27%	24%	0.67
IL-2	1.54	5.92	4.88	20.48	0.75	31%	30%	1.00
IL-3	1.01	2.67	1.16	3.59	0.34	17%	13%	0.37
IL-4	4.93	32.42	4.85	25.85	0.72	8%	8%	1.00
IL-5	1.07	4.43	2.77	11.85	0.08	26%	15%	0.03*
IL-6	11.62	35.14	15.21	31.88	0.24	67%	61%	0.30
IL-7	6.64	18.88	9.45	29.87	0.06	41%	33%	0.19
IL-8	21.84	39.74	27.93	45.14	0.06	97%	96%	1.00
IL-10	9.27	46.03	10.51	34.32	0.23	61%	59%	0.80
IL-12(p40)	16.57	34.64	51.51	169.31	0.47	43%	43%	1.00
IL-12(p70)	8.75	21.46	30.01	145.37	0.81	52%	45%	0.31
IL-13	11.75	34.71	29.92	168.75	0.54	41%	37%	0.60
IL-15	1.88	3.35	4.12	8.44	0.20	37%	31%	0.42
IP-10	445.46	309.40	491.77	356.59	0.14	100%	100%	1.00
MCP-1	158.63	47.22	164.24	50.53	0.37	100%	100%	1.00
MIP-1α	18.52	30.13	34.57	71.43	0.03*	83%	79%	0.43
TNF-α	5.63	4.65	6.36	8.91	0.50	98%	98%	1.00
VEGF	236.46	325.23	342.22	441.46	0.03*	88%	84%	0.37

MDD: major depressive disorder; SD: standard deviation; IL: interleukin; TNF-α: tumor necrosis factor-α; IFN-γ: interferon-γ; MCP-1: monotype chemoattractant protein-1; MIP-1α: macrophage inflammatory protein-1α; GM-CSF: granulocyte-macrophage colony-stimulating factor; VEGF: vascular endothelial growth factor.

*A Bonferroni correction was adopted with significance set for a *p*-value less than 0.002.