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Biological Sex Differences in Depression: A Systematic Review

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Abstract

Depression is the leading cause of disability worldwide, and its prevalence is 2 times higher in women than in men. There is, however, a lack of data on sex-specific pathophysiology of this disorder. The purpose of this systematic review is to identify the biological sex differences found in major depressive disorder (MDD) in studies published in the last 10 years. We conducted a literature search using the Medline, PsycInfo, PubMed, and Web of Science databases, selecting English-language studies that included physiological measures compared by sex in addition to MDD. We identified 20 relevant studies, which consisted primarily of mixed methodology and samples. The reported physiological measures comprised a variety of serum biomarkers, gene mRNA expression, and brain activity. Findings suggest different biological patterns in those with MDD depending on sex. Specifically, women presented higher levels of inflammatory, neurotrophic, and serotonergic markers and a stronger correlation between levels of some inflammatory and neurotrophic factors and the severity of symptoms. This review provides information about possible different biological patterns for women and men with depressive disorder and may have important implications for treatment. Future research should include homogeneous samples; make comparisons based on sex, control sex hormone fluctuations and pharmacological treatment; and use consistent criteria for evaluating psychobiological changes in MDD.

Keywords

biological factors, sex differences, depression

Depression is one of the most common and recurrent psychiatric disorders and leads to impairments in interpersonal, social, and occupational functioning (Sadock & Kaplan, 2007). Major depressive disorder (MDD) is characterized by feelings of sadness, hopelessness, helplessness, anhedonia, and sleep and appetite alterations as well as insomnia and fatigue. Women tend to remember and report depressive symptoms more often than men, and these symptoms are frequently accompanied by anxiety. In addition, women report greater illness severity and functional impairment (Riecher-Rössler, 2010). According to some studies, women with depression tend to report increased appetite and weight gain, hypochondriasis, rumination, and somatic concerns (Marcus et al., 2005). Alternatively, depressed men tend to report more weight loss and are more likely to struggle with substance use disorder (Marcus et al., 2008). Additionally, the prevalence of MDD is 2 times higher in women than in men (Bekker & van Mens-Verhulst, 2007). A number of factors may underlie this disparity. Notably, women are more exposed to social and material disadvantages during their life course than men (Blofield & Martínez Franzoni, 2015). But the fact that research consistently finds this difference in MDD incidence across cultures and in community-based epidemiological studies (Seedat et al., 2009) suggests that there could be biological differences apart from race, culture, diet, education, and numerous other social and economic factors that place women at increased risk (Albert, 2015).

Among the biological variables that underlie the sex differences found in depressive disorders, sex hormones, for instance, may play an important role in the etiology of depressive disorders. Although contradictory data exist (Rohr, 2002; Seidman, Spatz, Rizzo, & Roose, 2001), researchers have reported findings regarding the role of adrenal androgen levels in depression. Males with hypogonadism, a gonadal disorder that results in decreased testosterone levels, exhibit a significantly higher prevalence of MDD compared with those who have normal physiological levels of androgens (Shores et al.,

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2004; Zarrouf, Artz, Griffith, Sirbu, & Kommor, 2009), and testosterone replacement therapy greatly improves mood and mitigates depressive symptoms in these men (Kanayama, Amiaz, Seidman, & Pope, 2007; Zarrouf et al., 2009). Similarly, men treated with androgen-depleting drugs for prostate cancer have an increased risk of developing MDD (DiBlasio et al., 2008). Generally, the majority of studies support the case that testosterone yields beneficial effects on mood in men (McHenry, Carrier, Hull, & Kabbaj, 2014). In women, testosterone concentrations are lower in depressive patients when compared to healthy controls (Giltay et al., 2012; Kumsar et al., 2014). Also, fluctuations in estrogen levels are believed to be involved in the pathogenesis of depression in women. Studies have revealed that women are more likely to experience mood disturbances and depression during times of hormonal flux such as puberty, perimenstrual, postpartum, and perimenopausal periods (Ahokas, Kaukoranta, Wahlbeck, & Aito, 2001; Parker & Brotchie, 2004; Solomon & Herman, 2009). In contrast, during menopause, when hormonal flux stabilizes, the incidence of depression in women appears to be similar to that in men (Bebbington et al., 1998). Supporting this notion, hormone replacement therapy during the perimenopausal period can be effective in preventing postmenopausal depression in women (Gordon & Girdler, 2014). However, not all researchers have had similar results (Albertazzi, Natale, Barbolini, Teglio, & Di Micco, 2000; Hsiao, Liu, & Hsiao, 2004; Kessler, 2003). Although it seems that estrogen and testosterone could have a protective effect, they could be only two of many biological factors potentially responsible for the differences between sexes in depression.

It may be that males and females exhibit different patterns of transmitting, regulating, and processing biomolecules. For instance, some authors found sex differences in dopaminergic, noradrenergic, and serotoninergic systems (Ngun, Ghahramani, Sánchez, Bocklandt, & Vilain, 2011), which are all involved in numerous mental disorders (Booij, Van der Does, & Riedel, 2003; Ruhé, Mason, & Schene, 2007). On the other hand, affective disorders are commonly associated with dysregulation of the hypothalamus–pituitary–adrenal (HPA) axis (Fernández-Guasti, Fiedler, Herrera, & Handa, 2012), and some authors have affirmed that sex differences in the incidence of MDD correlate with sex differences in HPA axis function (Zagni, Simoni, & Colombo, 2016). Taking these data into account, it appears likely that the higher prevalence of depression in women is multicausal and not due to hormonal differences only; the underlying mechanisms, however, remain unclear. A better understanding of sex-dependent neurobiological factors is critical to advance the development of gender-specific health care, providing a more personalized and integrative praxis regarding clinical signs, prevention, therapy, and caregiving. Thus, the aim of the present study was to carry out a systematic review of the literature to identify biological sex differences in depressive patients, as well as differences with their gender-matched controls, that are not due to the action of gonadal hormones.

Method

We conducted an extensive systematic search of the literature on depression from January 2007 to July 2017 that included sex differences and biological outcomes in the PubMed, PsycInfo, Medline, and Web of Science databases. We used the preferred reporting items for reviews and meta-analyses flow sheet and checklist to ensure complete reporting of the evidence-based minimum reporting items (Liberati et al., 2009). Our search terms comprised the following key word combinations: *depression* OR *depressive* OR *depressed* AND *sex differences*. Articles we selected for review met the following criteria: (1) published in English, (2) included biological measures, and (3) analyzed sex differences. We excluded studies that (1) used animal models, (2) included subjects under 18 or over 75 years of age, (3) focused on any physical illness or psychopathology other than depression, (4) focused on psychological or pharmacological interventions, or (5) included genetic variations.

We identified 5,042 articles in our initial database search (Figure 1). We imported all of these into Mendeley reference manager to identify and remove duplicates (175 articles). Of the remaining 4,867 articles, we excluded 4,722 that were clearly not relevant based on a review of titles and abstracts. Two of us completed a more thorough screening of the remaining 145 articles to ensure that they met the inclusion criteria, with two additional authors participating to resolve any uncertainty regarding eligibility, which resulted in the exclusion of 102 additional articles. Finally, we assessed the full text of the remaining 43 potentially relevant articles for eligibility, excluding those that evaluated psychological or pharmacological interventions ($n = 1$), did not analyze sex differences in biological variables ($n = 7$), were focused on any illness other than depression ($n = 12$), or did not include subjects in our selected age range ($n = 3$). Finally, we reviewed each of the 20 full-text articles that met the study criteria. All of these studies were observational and cross-sectional. Data that we extracted from the eligible articles included study design, year of publication, biological variables analysis, subject characteristics, and key findings from the investigation.

Results

We included 20 studies in the final review (Table 1). The sample sizes of the studies ranged from 20 to 1,547 participants, and the ages ranged from 18 to 74 years. Researchers reported participant ethnicity in 11 of the studies, with Caucasian being predominant. Samples comprised medication-free subjects in eight of the studies and subjects undergoing stable antidepressant treatment in two studies, while authors of the remaining 10 studies did not specify pharmacological treatment. Age- and sex-matched controls were included in 15 studies, three did not specify whether control subjects were matched on sex and age, and the remaining two studies did not include healthy controls. The vast majority of the studies ($n = 18$) excluded subjects with medical conditions that could confound the target variables.

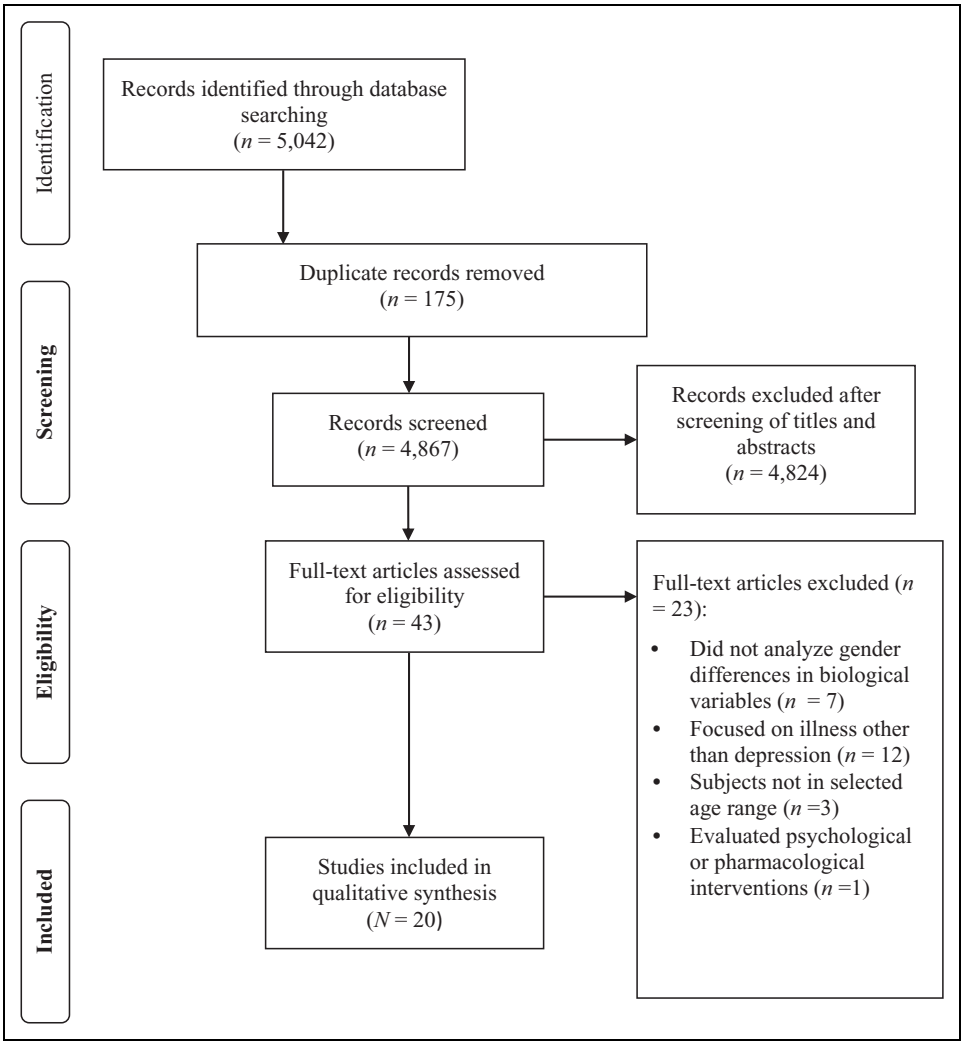

Figure 1. Preferred reporting items for reviews and meta-analyses flowchart of study selection.

The majority of investigators screened participants for depressive disorder based on *Statistical Manual of Mental Disorders*, Fourth Edition, criteria (Berent, Zboralski, Orzechowska, & Galecki, 2014; Birur, Amrock, Shelton, & Li, 2017; Boldrini, Underwood, Mann, & Arango, 2008; Cannon et al., 2009; Chopra et al., 2009; De Azevedo Cardoso et al., 2014; Frey, Skelin, Sakai, Nishikawa, & Diksic, 2010; Gray, Hyde, Deep-Soboslay, Kleinman, & Sodhi, 2015; Hayley et al., 2015; Hinkelmann et al., 2012; Kaufman et al., 2015; Ruhé, Booij, Reitsma, & Schene, 2009; Seney, Tripp, McCune, Lewis, & Sibille, 2015; Szewczyk et al., 2009; Tripp et al., 2012; Yang, Xie, Hu, Mao, & Su, 2008). Other investigators screened participants using the Hamilton Depression Rating Scale (HDRS; Kreinin et al., 2015). Häfner, Emeny, et al. (2011) and Häfner, Zierer, et al. (2011) applied the DEpression and EXhaustion subscale, while Köhler-Forsberg et al. (2017) used the Schedules for Clinical Assessment in Neuropsychiatry interview to establish the diagnosis.

We addressed the significant sex differences in 16 biological parameters and findings of depressive symptoms each study examined (Table 1). Some of the studies focused on serotonin-related indicators (Boldrini et al., 2008; Frey et al., 2010; Kaufman et al., 2015; Ruhé et al., 2009; Szewczyk et al., 2009), dopamine receptors (Cannon et al., 2009), glutamate receptors (Gray et al., 2015), tyrosine (Berent et al., 2014), gamma-aminobutyric acid (GABA)-related genes (Seney et al., 2015; Tripp et al., 2012), and leptin (Birur et al., 2017; Häfner, Zierer, et al., 2011). Chopra et al. (2009) and Hinkelmann et al. (2012) measured cortisol levels, while other authors focused on inflammatory markers (Birur et al., 2017; Häfner, Emeny, et al., 2011; Köhler-Forsberg et al., 2017). A number of researchers also analyzed brain-derived neurotrophic factor (BDNF; De Azevedo Cardoso et al., 2014; Hayley et al., 2015; Kreinin et al., 2015; Seney et al., 2015; Tripp et al., 2012). Finally, one study measured S100 calcium-binding protein (S100B) levels (Yang et al., 2008). Despite the great heterogeneity among study samples and a wide variability in the methods of evaluating depressive symptoms, the studies all included healthy controls and had reasonably consistent results and recommendations. Below, we outline the critical

Table 1. Summary of the Characteristics of Studies Examining Biological Sex Differences in Major Depressive Disorder.

Authors (Year)	Sample Size	Age (Years)	Postmortem	Criteria for MDD Diagnosis	Tissue Source and Method	Key Findings
Berent et al. (2014)	MDD: female = 20, male = 24	Total mean: 51	No	DSM-IV, HDRS, and CGIs	Source: Serum Method: EIA	FT3 levels: depressed men > depressed women
Birur et al. (2017)	MDD: female = 61, male = 42; CTL: female = 67, male = 30	Range: 19–65	No	DSM-IV	Source: plasma Method: RIA	Leptin: MDD women > control women, Adiponectin: MDD women > MDD men IL-8, IFN-γ: MDD women < control women IL-5: MDD women > control women IL-6: MDD women < control women IL-12: MDD women > MDD men IL-1β and TNF-α: negative correlation with total MADRS score in MDD men; positive correlation with total MADRS score in MDD women
Boldrini et al. (2008)	MDD: female = 4, male = 6 CTL: female = 4, male = 4	MDD/suicides mean: 44 Control mean: 45	Yes	Psychological autopsy according to DSM-IV	Source: DRN Method: quantitative receptor autoradiography	5-HT1A receptor binding: control women > control men; MDD women < MDD men
Cannon et al. (2009)	MDD: female = 11, male = 7 CTL: female = 11, male = 8	Total mean: 31	No	Psychological autopsy according to DSM-IV	Source: MC Method: PET	D1-receptor binding: MDD patients < control patients in the left MC
Chopra et al. (2009)	MDD: female = 26, male = 28	MDD mean: 43.3 Control mean: 39.4	No	DSM-IV and HDRS	Source: saliva Method: RIA	Cortisol stress responses to the TSST: (1) RANOVA—MDD female > control females, control women = control men. (2) AUC cortisol—control women < MDD women. (3) Mean peak % change in cortisol—control men > MDD men
De Azevedo Cardoso et al. (2014)	MDD: female = 25, male = 25 CTL: female = 95, male = 95	Range: 18–29	No	SCID and DSM-IV	Source: serum Method: ELISA	NGF levels: women with moderate/severe depression > mild depression; positive correlation with disease duration in women and negative correlation in men BDNF levels: negative correlation with disease duration in women
Frey et al. (2010)	MDD: female = 13, male = 12 CTL: female = 13, male = 12	MDD: female mean = 37, male mean = 43 CTL: female mean = 36, male mean = 36	No	DSM-IV and HDRS	Source: brain Method: PET and magnetic resonance	α-[11C]MTrp: MDD women > MDD men
Gray et al. (2015)	MDD F = 27 CTL F = 13 MDD M = 26 CTL M = 19	Range: 13–75	Yes	DSM-IV	Source: DLPFC Method: PCR	GluRs mRNA expression: MDD women < control women
Häfner, Emeny, et al. (2011)	MDD: female = 260, male = 314 CTL: female = 440, male = 533	Range: 35–74	No	DEEX scale	Source: serum Method: IRMA	CRP: socially isolated depressed men > rest of men; socially integrated depressed men < socially integrated not-depressed men
Häfner, Zierer, et al. (2011)	MDD: female = 216, male = 245 CTL: female = 370, male = 398	Range: 35–74	No	DEEX scale	Source: serum Method: ELISA	Leptin: socially isolated and depressed men > socially integrated and nondepressed men
Hayley et al. (2015)	MDD: female = 9, male = 10 CTL: female = 10, male = 9	Control male mean: 55 Control female mean: 55 MDD male mean: 43 MDD female mean: 48	Yes	DSM-IV	Source: FPC and HIPP Method: Western blot analysis	FPC BDNF levels: depressed men > control men; overall levels in men < in women HIPP BDNF levels: MDD men > control men; MDD women = control women
Hinkelmann et al. (2012)	MDD: female = 37, male = 15 CTL: female = 35,male = 15	Total mean: 35	No	DSM-IV and HDRS	Source: saliva Method: RIA	Basal cortisol cycle: (1) Cortisol ANCOVAs—control women = MDD women; control men <MDD men. (2) AUC—control women = MDD women; control men < MDD men
Kaufman et al. (2015)	MDD: female = 34, male = 16 CTL: female = 32, male = 25	Range: 18–65	No	DSM-IV, SCID I, HDRS, BDI, and CGIs	Source: VPFC, MPFC, DLPFC, ACN, CIN, AMY, HIPP, PHG, INS, TEM, PAR, and OCC Method: PET	5-HT1A binding: control women > control men; MDD women < MDD men; MDD women > control women; MDD men > control men
Köhler-Forsberg et al. (2017)	MDD: female = 142, male = 89	Total mean: 40.5	No	SCAN interview	Source: serum Method: IRMA	CRP: positive correlation with MADRS scores among women
Kreinin et al. (2015)	MDD: female = 34, male = 17 CTL: female = 22, male =16	Range: 25–64	No	HDRS	Source: plasma BDNF Method: ELISA	BDNF levels: positive correlation with HDRS in women but not in men

(continued)

Table 1. (continued)

Authors (Year)	Sample Size	Age (Years)	Postmortem	Criteria for MDD Diagnosis	Tissue Source and Method	Key Findings
Ruhé et al. (2009)	MDD: female = 32, male = 17 CTL: female = 22, male = 16	Range: 25–55	No	SCID, BDI, HDRS, and DSM-IV	Source: midbrain and diencephalon Method: SPECT imaging	Midbrain SERT: MDD men < control men Diencephalon SERT: MDD men < control men; MDD women > control women
Seney et al. (2015)	MDD: female = 10, male = 10 CTL: female = 10, male = 9	Total mean: 46	Yes	DSM-IV	Source: sgACC Method: PCR	SST mRNA expression: MDD women < control women
Szewczyk et al. (2009)	MDD: female = 13, male = 12 CTL: female = 13, male = 12	MDD: female mean = 56, male mean = 55 CTL: female mean = 56,male mean = 54	Yes	DSM-IV and SCID	Source: PFC Method: Western blot analysis	5-HT1A: MDD women < control women NUDR: MDD women < control women; no differences in men
Tripp et al. (2012)	MDD: female = 25, male = 26 CTL: female = 25, male = 26	Total mean: 50	Yes	Psychological autopsy according to DSM-IV	Source: ACN Method: PCR	CORT, Snap25, Vgf, SST, NPY, GAD1, GAD2, and PVALB mRNA expression: more robust reduction for MDD men than for MDD women
Yang et al. (2008)	MDD: female = 35, male = 19 CTL: female = 21, male = 14	Range: 18–58	No	DSM-IV and HDRS	Source: serum Method: ELISA	S100B levels: depressed women > depressed men; control women = control men

Note. α-[11C]MTrp = α-[11C]methyl-L-tryptophan brain trapping constant; 5-HT1A = serotonin receptor 1A; ACN = anterior cingulate cortex; AMY = amygdala; ANCOVAs = analyses of covariance; AUC = area under the curve; BDI = Beck Depression Inventory; BDNF = brain-derived neurotrophic factor; CGIs = Clinical Global Impression Scale for severity; CIN = cingulate (posterior) cortex; CORT = cortistatin; CRP = C-reactive protein; CTL = control; DEEX = DEpression and EXhaustion Scale; DLPFC = dorsolateral prefrontal cortex; DRN = dorsal raphe nucleus; DSM-IV = Statistical Manual of Mental Disorders, 4th ed.; EIA = enzyme immunoassay; ELISA = enzyme-linked immunoassay; FPC = frontopolar prefrontal cortex; FT3 = free triiodothyronine; GAD = glutamate decarboxylase; GluRs = glutamate receptors; HDRS = Hamilton Depression Rating Scale; HIPP = hippocampus; IFN = interferon; IL = interleukin; INS = insular cortex; IRMA = immunoradiometric assay; MADRS = Montgomery Asberg Depression Rating Scale; MC = middle caudate; MDD = major depressive disorder; MPFC = medial prefrontal cortex; mRNA = messenger ribonucleic acid; NGF = nerve growth factor; NPY = neuropeptide Y; NUDR = nuclear deformed epidermal autoregulatory factor; OCC = occipital cortex; PAR = parietal cortex; PCR = real-time quantitative polymerase chain reaction; PET = positron emission tomography; PFC = prefrontal cortex; PHG = parahippocampal gyrus; PVALB = parvalbumin; RANOVA = repeated-measures analysis of variance; RIA = radioimmunoassay; S100B = S100 calcium-binding protein; SCAN = Schedules for Clinical Assessment in Neuropsychiatry; SCID = Structured Clinical Interview for DSM; SERT = serotonin transporter; sgACC = subgenual anterior cingulate cortex; Snap25 = synaptosomal-associated protein 25; SPECT = single-photon emission computed tomography; SST = somatostatin; TEM = temporal cortex; TNF = tumor necrosis factor; TSST = Trier social stress test; Vgf = neurotrophic growth factor inducible; VPFC = ventral prefrontal cortex.

information on the variables we extracted from the articles and the sex differences the authors found.

Regarding the serotonin system, Szewczyk et al. (2009) found diminished protein expression of the serotonin receptor 1A (5-HT1A) somatodendritic autoreceptor in the prefrontal cortex of female subjects with MDD. Boldrini, Underwood, Mann, and Arango (2008) found that 5-HT1A receptor binding was higher in control females than control males; however, among individuals who had committed suicide, 5-HT1A binding was lower in females than in males. Kaufman et al. (2015) observed similar results in depressed patients. On the other hand, Frey, Skelin, Sakai, Nishikawa, and Diksic (2010) showed that medication-free women with MDD had higher normalized α-[11C]MTrp K*N (an index of 5-HT synthesis) than depressive men in multiple subregions of the cerebral cortex and limbic system. Ruhé, Booij, Reitsma, and Schene (2009) found that depressed males had significantly lower serotonin transporter (SERT) availability in the midbrain and diencephalon than healthy men; in contrast, depressed females had higher SERT availability in the diencephalon compared with healthy women, but there were no differences in the midbrain.

Within the dopaminergic system, Cannon et al. (2009) revealed reduced dopamine Type 1 (D1) receptor binding in the left middle caudate in depressed patients compared to controls. Despite significant differences in D1-receptor binding between the right and left hemispheres in controls, this normal asymmetry was absent in the dorsal putamen in depressed females (Cannon et al., 2009). In a postmortem study, Gray, Hyde, Deep-Soboslay, Kleinman, and Sodhi (2015) reported an association between increased dorsolateral prefrontal cortex expression of several types of glutamate receptor genes and MDD, with the most striking increases in female subjects with MDD compared to controls.

Several researchers studied neurotrophic factors such as nerve growth factor (NGF), BDNF, and the astroglial-derived neurotrophic factor S100B. De Azevedo Cardoso et al. (2014) found increased serum NGF levels in women with moderate/severe depression compared to those with mild depression. Furthermore, they observed a positive correlation between the duration of the illness and NGF levels in women, whereas the correlation was negative for men. These same authors also found a negative correlation between serum BDNF levels and the duration of the illness in female patients with MDD, whereas they observed no differences in men. Hayley et al. (2015) obtained similar results in the frontopolar prefrontal cortex in depressed (suicidal) women. However, these authors also found lower hippocampal BDNF levels in control males versus males with MDD but did not observe this difference in women. They did find lower overall BDNF levels in men compared with women. In contrast, Kreinin et al. (2015) found that there were positive correlations between serum levels of BDNF at baseline and both HDRS score and severity of illness in women but not in men. Meanwhile, Yang, Xie, Hu, Mao, and Su (2008) observed higher levels of S100B in depressed patients than in controls. They also indicated that depressed women showed higher levels of S100B protein than depressed men, whereas there were no sex differences in controls.

Furthermore, investigators have found sex differences in BDNF- and GABA-dependent genes such as cortistatin, synaptosomal-associated protein 25, neurotrophic factor growth inducible, somatostatin (SST), neuropeptide Y, glutamate decarboxylase 1, glutamate decarboxylase 2, and parvalbumin. Tripp et al. (2012) observed lower mRNA expression of these genes in the subgenual anterior cingulate cortex (sgACC) in postmortem subjects with depression, and the reduction was even more robust for depressed males when compare to depressed females. Seney, Tripp, McCune, Lewis, and Sibille (2015) observed a similar difference regarding SST expression in the sgACC, finding reduced SST expression in postmortem female subjects with MDD compared with postmortem control women but not finding the same difference in males with and without MDD. They also observed a negative correlation between depressive symptom score and SST expression in female subjects with MDD but not in males.

Berent, Zboralski, Orzechowska, and Galecki (2014) measured thyrotropin (TSH), free triiodothyronine (FT3), and free thyroxine (FT4) hormone levels, and whereas they observed no differences in TSH and FT4 serum levels, they did find sex differences in FT3, with depressed men showed higher levels of this hormone than depressed women. Furthermore, they observed an overall positive correlation between FT3 levels and clinical improvements.

Regarding HPA axis activity, Chopra et al. (2009) compared the cortisol stress response to the Trier social stress test between subjects with MDD and healthy controls. Salivary cortisol values did not differ between males with MDD and controls but were significantly higher in females with MDD than in control females. Additionally, in females, subjects with MDD had a greater mean area under the curve (AUC), an indicator of the total cortisol excreted in response to stress, than did controls. But women did not differ regarding mean peak percentage change in cortisol (i.e., the percent change from baseline to peak). In contrast, there was no differences in AUC in men, but the mean peak percentage change in cortisol was lower in men with MDD compared to control males. The researchers did not find any significant interaction effect between diagnosis and sex on mean prechallenge cortisol levels, but they did find a negative correlation between age of onset and mean prechallenge cortisol levels in females (but not in males) with MDD. Cortisol did not differ based on menstrual phase in females. On the other hand, Hinkelmann et al. (2012) analyzed cortisol levels at 5 time points during a day and found a Group × Sex interaction such that males with MDD had higher cortisol levels and AUC than control males, while there were no differences between females.

Birur, Amrock, Shelton, and Li (2017) reported higher leptin levels and lower adiponectin levels in depressed women compared with control women, whereas they found no differences in males. A similar comparison between depressed males versus depressed females revealed significantly higher levels of leptin in females. On the other hand, Häfner, Zierer, et al.

(2011) observed that in socially isolated and depressed men leptin levels were significantly increased compared to socially integrated and not depressed men. They saw no significant differences among female study groups.

Within the immune system, Köhler-Forsberg et al. (2017) found a significant positive association between C-reactive protein (CRP) levels and symptom severity among women but not among men. Among women, symptom severity increased for each standard deviation of CRP for observed mood, cognitive symptoms, interest activity, and suicidality. Häfner, Emeny, et al. (2011) studied CRP levels in four subject groups categorized by combinations of depressed mood and social isolation. CRP levels were highest in the group of socially isolated-depressed men. CRP levels were slightly but significantly lower in the group of socially integrated, depressed men compared to the socially integrated, not depressed men. In women, investigators could see no significant differences among the three risk groups and the reference group. Birur et al. (2017) reported higher levels of the cytokines interleukin (IL)-8 and interferon-γ and lower levels of IL-5 in depressed women compared with control women, whereas they found no differences in any measured inflammatory marker between depressed and control men. A similar comparison between depressed males versus depressed females revealed significantly higher levels of IL-6 in females. IL-12 levels negatively correlated with total score on the Montgomery Asberg Depression Rating Scale (MADRS) in depressed males, while IL-1β and tumor necrosis factor (TNF)-α were positively correlated with this score in depressed females. In depressed women, but not depressed men, IL-1β and TNF-α correlated positively with three items on the MADRS, including lassitude, pessimism, and suicidal thoughts.

Discussion

Our findings in the present review indicate there are sex differences in some biological variables in depressive patients. We have summarized the available evidence on different biological variables in depression, focusing on the middle-aged population. Women and men with MDD differ in markers of the monoaminergic system, immune system, and neuroplasticity as well as in some hormones and neurotransmitters. Specifically, women with MDD had higher IL-6, leptin, α-[11C]MTrp, and S100B levels; lower 5-HT1A and FT3 levels; and a slighter reduction in BDNF- and GABA-related genes than men with MDD. Furthermore, there were positive correlations between IL-1β, TNF-α, CRP and BDNF, and symptoms severity and conflicting results regarding the relationship between the duration of illness and levels of neurotrophic factors in women with MDD only. Due to the fact, with the exception of Chopra et al. (2009), these studies did include a determination of gonadal hormone levels, we cannot assess whether the reported biological sex differences were related to sex hormones. Although the wide variability in study designs, populations, and measures make it difficult to compare the study results, the findings may have important implications for the pathophysiology, diagnosis, and pharmacological treatment of depressive disorder in women and men.

The pathophysiological mechanisms explored in the reviewed studies are integrally related to and interconnected with sex hormones. Accumulating evidence suggests that cortisol can have both permissive and stimulatory effects on the immune system under specific conditions (Bellavance & Rivest, 2014), and at the same time, inflammation causes HPA axis hyperactivity. Both of these mechanisms reduce neurogenesis and affect neurochemical pathways, including the monoamines, glutamate, and BDNF, suggesting that all of these systems are interrelated (Dean & Keshavan, 2017). Furthermore, there is a reciprocal relationship between the variables mentioned above and sex hormones. Thus, estrogen and androgen signaling in the limbic brain may influence the regulation of HPA axis function, perhaps contributing to the dysregulation seen in patients with affective disorders and the underlying susceptibility of some individuals to affective disorders (Fernández-Guasti et al., 2012). Estrogen influences neurotransmitter activity, neurogenesis, and neurotrophic factor expression as well as many aspects of glial function (Borrow & Cameron, 2014; Karki, Smith, Johnson, & Lee, 2014; Licznerski & Duman, 2013). In particular, estradiol increases BDNF levels within the brain and alters serotonergic expression in a 5-HT1A receptor-specific manner (Borrow & Cameron, 2014). Furthermore, some authors have suggested that estrogen facilitates the excitatory glutamate response (Smith & Woolley, 2004). On the other hand, testosterone can influence dopamine, GABA, and serotonin release, but the biochemical mechanisms of these interactions remain poorly understood (McHenry et al., 2014). Finally, interactions among the HPA axis; neurotrophic factors; fluctuations in ovarian steroids, metabolic factors, and inflammatory cytokines can also increase susceptibility to depression (Duman, Aghajanian, Sanacora, & Krystal, 2016). The authors of a recent review (Dean & Keshavan, 2017) affirm that focusing on any one of these mechanisms as the main cause of depression is far too reductionist. Rather, all of these mechanisms occupy a position in a complex interactive matrix of pathophysiological factors such that a functional alteration in any point of the system can lead to malfunction of the entire matrix, with the end product being a depressive syndrome.

MDD is a major public health problem with substantial economic and social effects worldwide. Women are approximately 2 times more likely than men to present with a lifetime history of MDD. Thus, understanding the pathophysiology of this disorder and the mechanisms involved in sex differences in the development of MDD has important implications for the psychopharmacologic, hormonal, and immunoregulatory treatment and prevention of MDD.

One limitation of the present review is the potential bias resulting from the wide variability in study design, sample size, sex ratio, age range, and measures across studies that make them difficult to compare. In addition, authors either did not specify pharmacological treatment or it was heterogeneous within studies, which could affect the biological measures.

Several studies did not report the ethnicity or other socioeconomic characteristics of their samples. Notably, a number of studies did not present results regarding the interaction between sex and depression factors.

In conclusion, this systematic review provides an up-to-date summary of the recent literature regarding sex differences in different biological variables in patients with depressive disorder. The findings show important differences between sexes in the pathophysiology of depression, suggesting the necessity for studying all the mechanisms involved in these sex differences. A better understanding of these mechanisms would allow clinicians to identify both women and men who are at increased risk for depression, as well as to identify sex-specific biomarkers for this disorder (Strawbridge, Young, & Cleare, 2017). Future studies should include large samples and samples comprising drug-naive depressed patients, make comparisons based on sex, control for fluctuations in sex hormones and for pharmacological treatment, and use standardized criteria for evaluating MDD. The ultimate goal of such research would be to provide the information necessary for nurses in the clinical setting to care for the increasing number of depressive patients using an individualized biopsychosocial approach.

Author Contributions

A. Labaka contributed to conception, design, data analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be held accountable for all aspects of work ensuring integrity and accuracy. O. Goñi-Balentziaga contributed to design, acquisition, and analysis; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be held accountable for all aspects of work ensuring integrity and accuracy. A. Lebeña contributed to conception, acquisition, and analysis; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be held accountable for all aspects of work ensuring integrity and accuracy. J. Pérez-Tejada contributed to conception, design, acquisition, data analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be held accountable for all aspects of work ensuring integrity and accuracy.

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