Large-Scale Transcriptomics Studies Provide Insight Into Sex Differences in Depression

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Abstract

Major depressive disorder (MDD) is a leading cause of disability, affecting more than 300 million people worldwide. We first review the well-known sex difference in incidence of MDD, with women being twice as likely to be diagnosed as men, and briefly summarize how the impact of MDD varies between men and women, with sex differences in symptoms, severity, and antidepressant drug response. We then attempt to deconstruct the biological bases for MDD and discuss implications for sex differences research. Next, we review findings from human postmortem studies, both from selected candidate gene studies and from well-powered, unbiased transcriptomics studies, which suggest distinct, and possibly opposite, molecular changes in the brains of depressed men and women. We then discuss inherent challenges of research on the human postmortem brain and suggest paths forward that rely on thoughtful cohort design. Although studies indicate that circulating gonadal hormones might underlie the observed sex differences in MDD, we discuss how additional sex-specific factors, such as genetic sex and developmental exposure to gonadal hormones, may also contribute to altered vulnerability, and we highlight various nuances that we believe should be considered when determining mechanisms underlying observed sex differences. Altogether, this review highlights not only how various sex-specific factors might influence susceptibility or resilience to depression, but also how those sex-specific factors might result in divergent pathology in men and women.

CLINICAL SEX DIFFERENCES IN DEPRESSION

Major depressive disorder (MDD) is a devastating mental illness affecting approximately 350 million people globally (1). In the United States, the economic burden of MDD was estimated at $210.5 billion in 2010 (2). Moreover, patients with mood disorders account for approximately 60% of completed suicides (3). Core MDD symptoms include emotion dysregulation, low mood, flattened affect, and anhedonia. Additional MDD symptoms fall into various dimensions, including cognitive symptoms, physiological symptoms (i.e., altered weight, motor activity, sleep patterns), and comorbid anxiety (4).

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Females are twice as likely as males to have a single MDD episode and 4 times as likely to have recurrent MDD (5,6). This sex difference in MDD incidence may be driven by reporting biases [i.e., women are more likely to seek treatment (7,8)], although it is reported across cultures and in community-based epidemiological studies, suggesting underlying biological differences (9,10). Comparing males and females with MDD, females tend to have more symptoms, higher symptom severity, and more subjective distress (9,11,12). Further, females are more likely to have a comorbid anxiety disorder (13), and males are more likely to have a comorbid substance use disorder (14). Findings suggest that there are sex differences in antidepressant treatment response, but the evidence is not as striking as for the sex difference in MDD incidence. For instance, some studies report that monoamine oxidase inhibitors and selective serotonin reuptake inhibitors may be more effective in female patients (15–17), while male patients respond more favorably to tricyclic antidepressants (17,18) and ketamine (19) [but see (15,20–22)]. Psychotherapy appears similarly effective in men and women (23–26), though women may engage more in psychotherapy (27–30). While there are indeed sex differences in incidence, symptoms, and antidepressant response, evidence suggests that prognosis is similar in men and women once MDD is diagnosed (31).

DECONSTRUCTING THE BIOLOGICAL BASES OF MDD AND IMPLICATIONS FOR SEX DIFFERENCES

Few novel MDD treatments have been developed beyond the serendipitous discovery that agents increasing monoaminergic signaling can reduce mood symptoms, though some studies since then suggest that clinical efficacy of these drugs may include actions that reduce inflammation (32) or increase the formation of new hippocampal neurons (33). Despite wide-spread use, only a third of patients achieve remission with monoamine-targeting treatment (16,34,35). Even when effacious in treating mood symptoms, monoamine-targeting therapeutics do not appear to ameliorate the cognitive deficits associated with MDD (36), and the residual presence of those deficits during remission predicts relapse (37). In sum, although monoaminergic antidepressants provide symptomatic relief in some patients, they might not reverse certain MDD symptom domains.

The categorically defined MDD syndrome may be an imprecise umbrella grouping of multiple clinical symptoms, each of which may have unique and multifactorial etiologies. Indeed, evidence shows that various underlying pathologies occur in depression, including altered excitation-inhibition, reduced neurotrophic support, and inflammation. These pathologies are not systematically observed in MDD and extend to other categorically defined psychiatric disorders and in some cases to neurodegenerative disorders (38). Overwhelming evidence supports a dimensional model, where specificities of symptoms arise from the combination of genetic, environmental, and development risk factors, which may lead to unique brain pathologies.

A dimensional perspective is amenable to biological investigation for pathophysiological mechanisms and the roles of sex. Indeed, pathological entities observed in the human postmortem brain point to specific biological pathways, which in turn can be investigated

in light of multiple factors, including genetic variability, environment, and sex. Here, we review the degree to which evidence stemming from human postmortem brain investigations support either shared or sex-specific pathologies. We then discuss biological factors mediating the role of sex and how their interaction with pathological entities may lead to clinical observations of sex differences in depression.

SEX DIFFERENCES IN MDD: CANDIDATE GENE STUDIES

Gene expression studies in human MDD employing a candidate gene approach have been fruitful in identifying potential drivers for sex differences in MDD. The serotonergic system has been a focus of candidate gene studies because most antidepressants target this system. Interestingly, evidence suggests sex specificity for some serotonin-related alterations in MDD. For instance, levels of the serotonin 1D autoreceptor and serotonin-related transcription factors, NUDR and REST, were higher in dorsal raphe serotonin neurons of female, but not male, subjects with MDD (39). As NUDR and REST act as transcriptional repressors of the serotonin 1A autoreceptor in the dorsal raphe, their increased expression might represent a compensatory attempt to reduce elevated autoreceptors and increase serotonergic transmission. There are also decreased levels of the serotonin 1A receptor and NUDR in the prefrontal cortex (PFC) of depressed women, but not men (40). It is interesting to note that there may be sex-specific MDD alterations to the serotonin system given evidence that selective serotonin reuptake inhibitors may be more efficacious in depressed women compared with other classes of antidepressants (17,41).

Based on evidence suggesting altered excitation and/or inhibition in MDD (42–60), studies have examined alterations in glutamate- and GABA (gamma-aminobutyric acid)-related genes. Some alterations in glutamate-related genes might be sex specific in the dorsolateral PFC (DLPFC). Specifically, depressed females exhibit increased expression of several glutamate receptor genes, including *GRIN1*, *GRIN2A-D*, *GRIA2-4*, *GRIK1-2*, *GRM1*, *GRM4*, *GRM5*, and *GRM7*; only *GRM5* was altered in depressed males, but in the opposite direction compared with females (61). We reported sex-specific MDD alterations in GABA synthesizing enzymes in the basolateral amygdala (BLA) and anterior cingulate cortex (ACC). In the BLA, only depressed females exhibited reductions in *GAD1* and *GAD2*, while in the ACC, only depressed males had reduced expression of *GAD1* and *GAD2* (60,62).

Studies examining expression of GABA subtype–specific markers provide insight into how excitatory pyramidal neurons and inhibitory GABA interneurons are altered in depression, suggesting sex-specific mechanisms of altered excitatory information processing. Somatostatin (SST)-expressing interneurons mainly innervate the distal dendrites of excitatory pyramidal cells, regulating excitatory input and providing feedback inhibition (63–65). Parvalbumin-positive interneurons typically innervate the perisomatic region of pyramidal cells, thereby regulating excitatory output and providing feedforward inhibition (64,65). As *SST* and *PVALB* are activity-dependent regulated genes, alterations in transcript levels in MDD suggest dysfunctions in cellular activity. Furthermore, their pattern of altered expression suggests brain region- and sex-specific changes in information processing by cortical microcircuits in MDD (hypothetical excitation/inhibition balance

in Figure 1A). In the DLPFC, evidence suggests reduced SST, but not parvalbumin, cell activity and thus reduced inhibitory input onto excitatory pyramidal cells in both males and females with MDD (Figure 1B) (62,66). In the ACC, evidence suggests reductions in both SST and parvalbumin cell activities, suggesting reduced inhibitory input and output regulation of excitatory pyramidal neurons (Figure 1C, D). In the ACC, *SST* reductions were more pronounced in depressed females, and *SST* expression was negatively correlated with depressive symptoms only in females with MDD (67). This suggests more profound reduction in inhibitory input onto pyramidal neurons in the ACC of females with MDD (60,67,68). In the BLA, males with MDD do not show alterations in either *SST* or *PVALB*, while females with MDD have reduced SST (Figure 1F), suggesting reduced inhibitory input onto excitatory pyramidal cells in the BLA of females, but not males, with MDD (Figure 1E) (62,69). Differences in input and output of inhibitory regulation of excitatory signal will affect information coding and propagation, respectively. Region and sex specificities in altered information processing may affect cognition and emotion, providing a potential pathophysiological substrate for sex differences in symptoms. While evidence from animal studies suggests that alterations in GABA neurons affect relevant behaviors (70), it is unclear whether sex differences observed in humans have clinical consequences. For instance, it is possible that these brain region–specific molecular alterations converge on similar clinical outcomes in males and females.

SEX DIFFERENCES IN MDD: EVIDENCE FROM TRANSCRIPTOMICS STUDIES

Early transcriptomics investigations of MDD included both sexes but were often skewed toward males and not powered to investigate sex differences. Conclusions from these studies could be biased toward results driven by male-specific alterations; indicate alterations that are consistent between males and females if the cohort is relatively sex balanced but is not powered to detect sex differences; or show no differences if biological disturbances are in opposite directions between men and women. We summarize results of transcriptomics investigations in Table 1, providing information on whether both sexes were represented. Very few studies were fully powered to detect sex differences. These studies have used similar approaches, and results were validated across cohorts.

In 2017, Labonte *et al.* (71) published the first well-powered, large-scale transcriptomics study to directly assess sex differences in the brains of subjects with MDD, focusing on the DLPFC, orbitofrontal cortex, ACC, anterior insula, nucleus accumbens, and ventral subiculum. The authors found very little overlap of genes differentially expressed in both men and women with MDD and used network-based approaches to zero in on potentially relevant gene targets. Weighted gene coexpression network analysis identified gene modules exhibiting sex-specific patterns of gain and loss of connectivity in MDD. This analysis suggests that some molecular pathways implicated in MDD might be affected in a sex-specific manner. Examination of gene modules identified relevant sex-specific hub genes, which, when manipulated in mice, produced sex-specific stress vulnerability. Downregulation of the female MDD–specific gene, *DUSP6*, promoted stress vulnerability in females only, potentially by increasing pyramidal neuron excitability via activation of

ERK signaling. Additionally, overexpression of the male MDD–specific gene, *EMX1*, promoted stress vulnerability in males only. Using differential expression analysis combined with network-based methods, this study narrowed down their gene hits and zeroed in on potentially relevant sex-specific hub genes that might drive sex differences in depression (71).

Recently, we used large-scale transcriptomics, combined with meta-analysis across mood-related brain regions (DLPFC, ACC, BLA), to investigate sex-specific alterations in MDD (72). We replicated the findings of Labonte *et al.* (71), showing little overlap in differentially expressed genes between men and women with MDD. Brains from our study were from a different brain bank than Labonte *et al.* (71), suggesting the sex-specific transcriptional signature of depression may be a generalizable biological phenomenon. We found more than 1000 transcripts with significant interactions of sex and disease, and these transcripts were affected in opposite directions in men and women with MDD (i.e., upregulated in one sex, downregulated in the other sex). While this was initially quite surprising, we replicated this result using the data of Labonte *et al.* (71), hence confirming the presence of opposite patterns of gene changes across cohorts obtained from different brain banks. We found that men with MDD have decreases in markers of synapses and increases in markers of microglia and inflammation (72), suggesting that men with MDD have decreased dendritic spines and more reactive microglia. This result in men with MDD is consistent with previous reports of reduced dendritic complexity in the ACC, reduced dendritic processes and spine synapses in the DLPFC (73), and increased reactive microglia in the ACC in MDD (74). Chronic stress in male rodents recapitulates the dendritic pathology observed in MDD (75,76), and it is hypothesized that dendritic spine alterations contribute to MDD symptoms (77,78). These changes in MDD are consistent with a model in which reactive microglia may participate in excessive pathological removal of synapses (79–81).

However, as more than 70% of subjects in previous studies of dendritic morphology and microglia reactivity in MDD were male, it is unclear if females with MDD exhibit a similar pathology. Surprisingly, we found opposite gene expression changes in women with MDD, with increased synapse-related genes and decreased expression of microglia-specific genes (72). Our results in men and women with MDD are consistent with rodent studies demonstrating that stressed male mice have decreased dendritic spine complexity and increased reactive microglia, but the opposite pattern occurs in stressed females (75,82). Together, these cross-species studies of putative interactions between microglia and dendrites suggest sex-specific pathways for divergent pathologies relevant to information processing mediated by spines on excitatory pyramidal neurons (Figure 2).

Another exciting contribution was added in 2020 by Issler *et al.* (83). Using the Labonte *et al.* (71) dataset, the authors focused on long noncoding RNAs (lncRNAs), as these represented approximately 30% of the differentially expressed transcripts. Through various roles, including as signals, scaffolds, enhancers, and decoys, lncRNAs play key roles in regulating transcription of other genes. Identified lncRNAs might be key drivers of the sex-specific transcriptional profile of MDD. Similar to the pattern of results for protein-coding genes reported by Labonte *et al.* (71) and Seney *et al.* (72), there was little overlap in differentially expressed lncRNAs between men and women with MDD. The authors

then zeroed in on *LINC00473*, as this transcript is of high abundance, exhibits lower expression only in depressed women, and is expressed in neurons and neural progenitor cells. Interestingly, *LINC00473* is associated with several genes previously implicated in MDD, including the female MDD–specific gene, *DUSP6*, identified by Labonte *et al.* (71). When expression of *LINC00473* is induced in mice, it promotes female, but not male, resilience to stress, potentially via its effect on electro-physiological properties of pyramidal neurons in females. When *LINC00473* expression is induced in human-derived neuroblastoma cells, it binds to relevant depression and anxiety-related genes, including *CREBBP*, *MAP2*, and *ERBB4*. Thus, *LINC00473* may be an upstream regulatory driver of female-specific MDD mechanisms. Exactly why changes in levels of this same lncRNA do not produce effects in males is currently unknown.

Altogether, recent large-scale transcriptomics studies have provided strong evidence for sex-specific molecular signatures of MDD. These studies also delve deeper into mechanisms, point toward potential key drivers influencing sex-specific MDD vulnerability (e.g., *DUSP6*, *EMX1*, *LINC00473*), and suggest opposing brain pathological changes in depressed men and women.

HUMAN POSTMORTEM BRAIN RESEARCH CHALLENGES AND RECOMMENDATIONS FOR PATHS FORWARD

Studies of postmortem human brain are essential to identify disease- and sex-specific molecular, cellular, and circuitry alterations characteristic of MDD. Completion of such studies and interpretation of results require consideration of factors largely unique to human postmortem brain research, and these have been comprehensively reviewed [e.g., (84)]. Here, we discuss 5 aspects of postmortem human brain study design of particular consideration for investigations of the MDD disease process and suggest paths forward for thoughtful design of future studies.

One consideration is the potential effect of comorbid diagnoses to influence, or be influenced by, the MDD disease process on the measures of interest. MDD is often comorbid with anxiety disorders, and this is especially pronounced in women (13). Whether MDD disease processes include molecular, cellular, or circuitry alterations that trigger anxiety disorder pathogenic processes or whether each disorder has an independent and additive effect on a dependent measure can be informed by postmortem human brain studies. For example, a finding that the magnitude of the MDD female-specific effect on GABA synthesizing enzyme levels in the BLA (69) is even greater in female subjects with MDD and a comorbid anxiety disorder would suggest a shared and additive effect of both disorders on this measure. In contrast, the presence of this effect in female subjects with MDD and a comorbid anxiety disorder, but not in subjects with only an MDD or an anxiety disorder diagnosis, suggests that a sex-specific aspect of the MDD disease process contributes to the development of an anxiety disorder.

A second consideration is the potential effect of symptom heterogeneity on the measures of interest within subjects with MDD. Indeed, although many psychiatric illnesses have heterogeneous diagnostic symptoms, MDD is particularly diverse (85). For example,

individuals with symptoms including weight gain or loss, insomnia or hypersomnia, psychomotor agitation, or retardation all may meet criteria for an MDD diagnosis (85). Depending on the disease-related experimental question, this heterogeneity may be critical to consider during study design to produce results that can inform how brain alterations may map onto MDD symptoms. For instance, a study of the MDD disease effects in a sleep-relevant brain region (e.g., lateral hypothalamus) is strengthened by inclusion of MDD subjects with one type of sleep disturbance (e.g., insomnia) or equal numbers of MDD subjects with insomnia or hypersomnia. This consideration may be especially relevant in the study of sex differences in MDD, as there is evidence for different symptom profiles in men and women (11).

A third consideration is the potential effect of death by suicide. On average, approximately 60% of individuals who died by suicide had a prior mood disorder (86). Notably, women report a greater frequency of suicidal thoughts and attempts than men, but men die by suicide more commonly than women (87,88). Neural alterations associated with death by suicide in individuals with MDD may index disease severity, reflect the influence of certain suicide and MDD risk factors such as early childhood adversity, and/or represent a suicide-specific and diagnosis-independent finding (89–94).

A fourth consideration is the potential effect of treatment by antidepressant medications on the measures of interest. The efficacy of these medications may include mechanisms that alter neural functioning in a manner that obscures or eliminates the MDD disease effect on molecular-, cellular-, or circuitry-dependent measures. For instance, subjects with MDD not taking antidepressants have lower striatal levels of dihydroxyphenylacetic acid and higher PFC binding levels of β_1 adrenoreceptors (95), suggesting that these alterations are related to MDD disease processes rather than effects of antidepressants. The triangulation method, which uses 3 different approaches to disentangle medication and disease effects, is one effective strategy previously used in postmortem human brain studies [e.g., (96–99)]. In the first approach, the dependent measure is compared between subjects with MDD on and off antidepressant medications at the time of death. A finding of no difference suggests that the medications do not affect the measure of interest. In the second approach, the dependent measure is compared between subjects with MDD and subjects with a different psychiatric illness also treated with antidepressant medications. A finding in antidepressant-treated subjects with MDD, but not antidepressant-treated subjects with a different psychiatric illness, suggests that the medications do not affect the measure of interest. In the third approach, the dependent measure is quantified in animal models that mimic treatment in humans. A finding of no effect suggests that the medications do not affect the measure of interest. Consistency of results across each of the 3 approaches strongly supports that the finding in subjects with MDD reflects a factor related to the disease process and not antidepressant medications.

A fifth consideration is the potential confounding effect of inadequate tissue preservation. Key measures reflecting tissue quality include 1) postmortem interval, the amount of time between death and brain preservation; 2) RNA integrity number, a measure of RNA quality and concentration; and 3) brain pH, which is correlated with RNA yield and quality. Matching subjects across diagnostic groups as closely as possible on these factors minimizes

sources for technical variability and helps to ensure that findings are not confounded by inferior tissue quality in one subject group. Further, rigorous experimental design to identify sex-specific MDD disease effects ensures that these factors are similarly represented in male and female subjects both within and across diagnostic groups.

In conclusion, accurate mapping of the neural alterations that contribute to sex-specific brain dysfunction in MDD requires postmortem human brain studies that take into consideration these clinical and technical aspects. Although tissue quality measures are routinely determined for postmortem human brain samples, the clinical considerations require a systematic and comprehensive characterization that identifies each individual's comorbid diagnoses, MDD symptom profile, and treatment at time of death (100). Studies of clinically well-characterized subjects can provide key insights into how brain pathological alterations map onto MDD symptoms. These studies can also provide results meaningful for the development of novel, personalized, and evidence-based therapeutics. Indeed, studies investigating whether distinct molecular phenotypes are present in subjects with distinct symptom phenotypes hold promise for the development of personalized therapeutics (101–103).

BIOLOGICAL FACTORS UNDERLYING THE ROLE OF SEX

Alterations observed in the human brain do not necessarily drive sex differences in MDD. For instance, sex differences may reflect compensatory mechanisms, may be due to unknown confounds, or may be downstream of primary pathology. Studies in model systems are therefore key to determining causation. While many previous studies used rodent stress paradigms designed for males, recent studies have established paradigms that also work in females (104–107), thus providing a preclinical venue to compare the transcriptional alterations observed in MDD. While beyond the scope of this review, Rainville and Hodes provide a thorough review of rodent literature related to sex differences in stress response and discuss peripheral mechanisms that might drive sex differences in MDD (108). We highlight various nuances to consider when determining mechanisms underlying observed sex differences.

As genetic sex (XX or XY) is inextricably linked to gonadal sex (ovaries or testes) in humans, it is challenging to determine the underlying causes of sex differences (hormones vs. sex chromosomes). Except for rare genetic conditions, XY individuals have testes, and XX individuals have ovaries. XY individuals have male-like circulating hormones in adulthood that may influence the sex difference (i.e., acute, activational effect of hormone) and also are exposed to male-like circulating hormones during sensitive developmental periods (109). While many sex differences are caused by acute hormone effects, there are instances where hormone exposure during sensitive periods cause permanent sex differences (i.e., organizational hormone effect) (110,111). The sensitive developmental window varies based on the trait examined (112) and can extend from the prenatal period through puberty (113–115). In support of a role of gonadal hormones, many sex differences in the human brain and behavior appear at puberty and are correlated with gonadal hormone levels (116–118). Permanent sex differences are challenging to investigate in humans, as it is not possible to determine gonadal hormone levels during sensitive periods, as some occur

prenatally. Evidence also suggests that genetic sex, independent of gonadal hormones, influences social behavior (119,120), alcohol abuse (121), habit formation (122), aggressive and parenting behavior (123), and gene expression (124–129). Given complications in disentangling effects of genetic sex, developmental gonadal hormone exposure, and adult hormone exposure, it is often necessary to move to animal models. There are comprehensive reviews on this topic (130–133).

While an identified sex difference may be caused by a single sex-related factor, it is possible that multiple mechanisms work in tandem to create the sex difference. The sum of these sex-biased effects on gene networks and cells is referred to as the sexome, which is reviewed by Arnold and Lusis (134). For instance, organizational effects of hormones often interact with adult circulating hormones for full expression of the sex difference. In other words, acute hormonal effects in adulthood may occur only if proper hormones were present during sensitive developmental periods.

Although one might predict that sex-related factors work together to promote a sex difference (i.e., two factors push the sex difference in the same direction), this is not always the case. In fact, two sex-related factors might work in opposite directions, sometimes even to eliminate a sex difference, a phenomenon termed compensation (135). Examples of compensation are that male-typical hormones (androgens) increase weight and adiposity, but male genetic sex (XY) decreases them; removing androgens amplifies the XY genetic sex effect, as the opposing factor is not present to balance it (136,137); or, conversely, XY genetic sex increases anxiety-like behaviors, which are compensated by adult circulating testosterone (127). Additionally, males and females might arrive at the same trait via different mechanisms (e.g., XX effect in females, testosterone effect in males).

Altogether, various strategies can be employed in animal models to disentangle mechanisms underlying sex differences observed in humans (131–133). However, it is often not as simple as one factor working independently to cause a sex difference. Rather, many factors may work together or in opposition.

SUMMARY

Recent advances in basic neuroscience knowledge and the development of novel investigational tools are now merging with a renewed interest in understanding the biological bases of the well-characterized clinical differences in depression between men and women. We have highlighted candidate gene and large-scale transcriptomics studies suggesting divergent pathologies in depressed men and women. We discussed challenges encountered when performing human postmortem brain studies in MDD and propose paths forward for future studies. Approaches in model systems are highlighting the complexity of examining mechanisms underlying sex differences. These novel perspectives are generating hypotheses and tools to investigate the putative roles and interactions of factors underlying the biological bases of sex differences in depression.

ACKNOWLEDGMENTS AND DISCLOSURES

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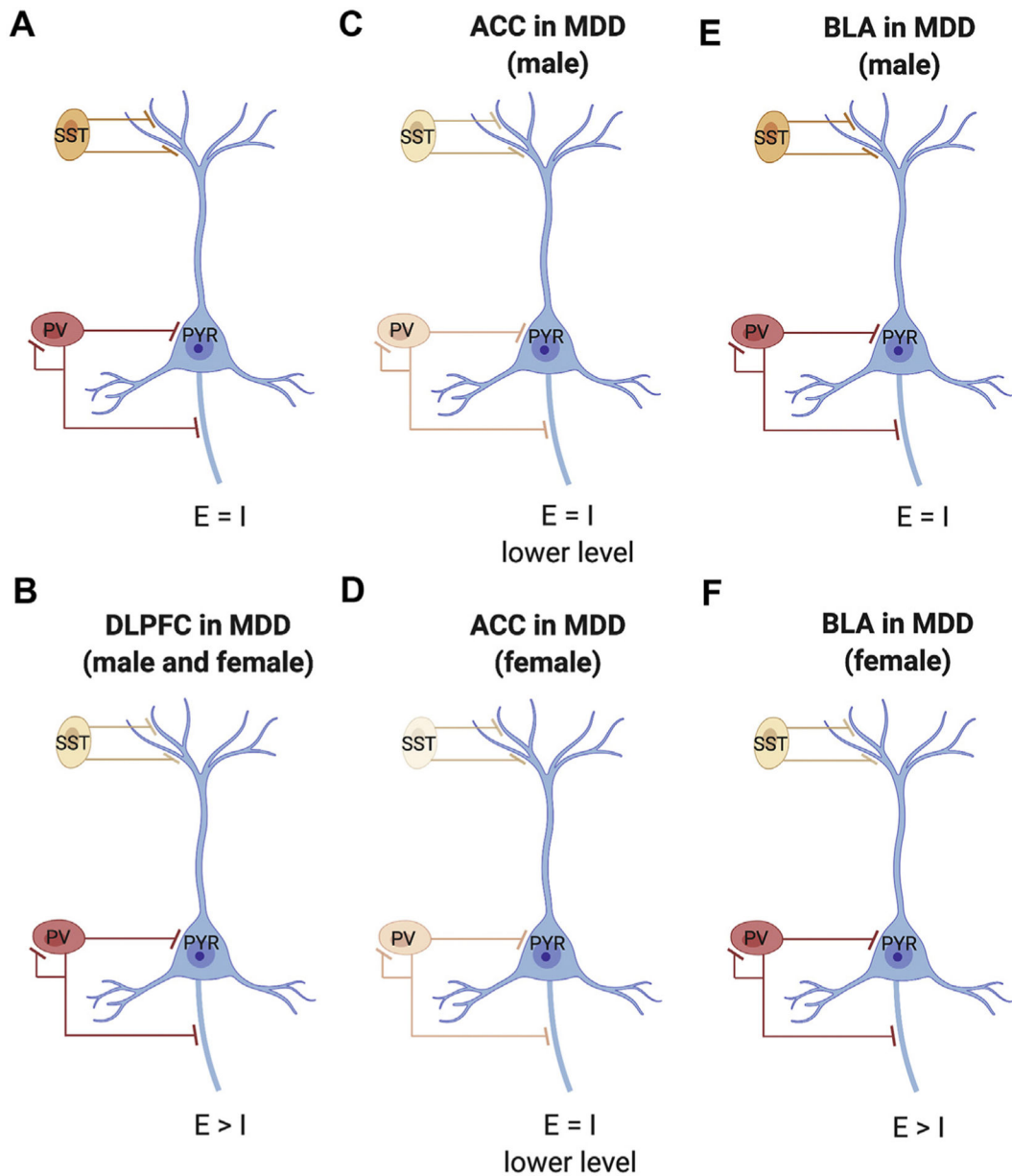
Figure 1.

Schematic of neocortical microcircuitry and associated dysfunction in major depressive disorder (MDD). **(A)** Canonical microcircuitry in healthy control subjects with excitation (E)/inhibition (I) balance. **(B)** In the dorsolateral prefrontal cortex (DLPFC) of male and female subjects with MDD, there is lower expression of somatostatin (SST) (indicated by lighter color), but no change in parvalbumin (PV), suggesting reduced inhibition of input of pyramidal cells (PYR). **(C)** In the anterior cingulate cortex (ACC) of male subjects with MDD, there is moderately lower expression of both SST and PV, suggesting reduced inhibition of input and output of pyramidal cells, i.e., lower E/I balance. **(D)** In the ACC of female subjects with MDD, there is a robust reduction in expression of SST and moderately lower PV, suggesting strong inhibition of input and reduced inhibition of output

of pyramidal cells, suggesting E/I imbalance. **(E)** In the basolateral amygdala (BLA) of male subjects with MDD, there are no differences in SST or PV, suggesting conserved E/I balance. **(F)** In the BLA of female subjects with MDD, there is reduced expression of SST, but not PV, suggesting reduced inhibition of input of pyramidal cells and altered E/I balance.
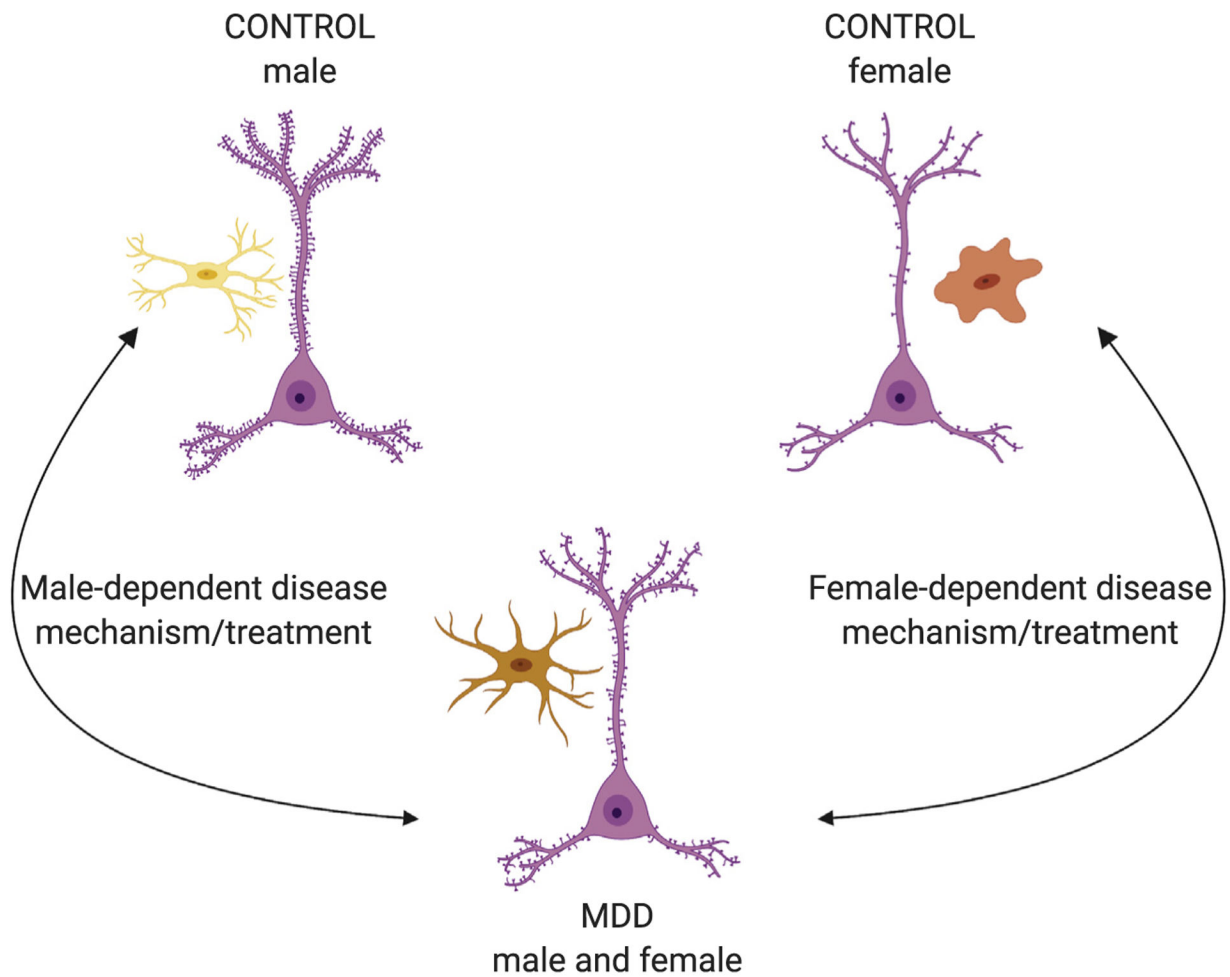
Figure 2.
Proposed model of sex-specific major depressive disorder (MDD) mechanism involving
dendritic spines and microglia. Male control subjects have more dendritic spines and fewer
activated microglia than male subjects with MDD, but female control subjects have fewer
dendritic spines and more activated microglia than female subjects with MDD. MDD effects
appear to be opposite in male and female subjects, converging on a similar MDD phenotype
across sexes. Successful treatment would push male and female subjects back to their sex-
specific baselines, which would require opposite effects on microglia. Further, it is possible
that a successful treatment in one sex might push the other sex further from their sex-specific
baseline, which could be detrimental. Pyramidal cells are in pink. Ramified microglia are in
yellow, reactive/amboid microglia are in red, and intermediate microglia are in orange.

Table 1.

Results of Transcriptomics Investigations

Reference	Brain Regions	Key Findings	Males and Females in Cohort
Evans et al., 2004 (138)	DLPFC, ACC (BA 24)	FGF-related genes	Control males: 6 Control females: 1 MDD males: 7 MDD females: 2
Iwamoto et al., 2004 (139)	PFC (BA 10)	*AQP4, LIM*	Control males: 9 Control females: 6 MDD males: 6 MDD females: 5
Choudary et al., 2005 (140)	DLPFC, ACC (BA 24)	GABA-, glutamate-related genes	Control males: 6 Control females: 1 MDD males: 7 MDD females: 2
Aston et al., 2005 (141)	Temporal cortex	Oligodendrocyte-, myelination-related genes	Control males: 9 Control females: 5 MDD males: 9 MDD females: 3
Kang et al., 2007 (142)	DLPFC	FGF-, immune-related genes, *FOXD3, UCN3*	Control males: 11 Control females: 3 MDD males: 10 MDD females: 4
Sequeira et al., 2007 (143)	Amygdala, hippocampus, ACC (BA 24), BA 29	GABA-, neurotransmission-related genes	Control males: 13 MDD males: 18
Tochigi et al., 2008 (144)	PFC (BA 10)	Cell proliferation-, FGF-related genes	Control males: 9 Control females: 6 MDD males: 6 MDD females: 5
Klempan et al., 2009 (145)	PFC (BAs 44, 45, 46, 47)	GABA-related genes	Control males: 13 MDD males: 16
Sequeira et al., 2009 (146)	17 cortical and subcortical regions	GABA-, glutamate-related genes	Control males: 13 MDD males: 16
Sibille et al., 2009 (62)	ACC (BA 25), AMY (lateral/basolateral/basomedial)	Oligodendrocyte-, neuronal-related genes in AMY	Control males: 14–16 MDD males: 14–16
Lalovic et al., 2010 (147)	Frontal cortex (BAs 8/9, 11, 47)	Lipid metabolism-, immune responserelated genes	Control males: 6–13 MDD males: 10–15
Bernard et al., 2011 (148)	Locus coeruleus	Glutamate-, growth factor-, astrocyterelated genes	Control males: 8 Control females: 1 MDD males: 11 MDD females: 1

Reference	Brain Regions	Key Findings	Males and Females in Cohort
Sequeira *et al.*, 2012 (149)	DLPFC, ACC (BA 24), NAc	Suicide-associated alterations in serotonin-and metallothioneinrelated genes	MDD males: 8–13 MDD females: 3
Guilloux *et al.*, 2012 (69)	AMY (lateral/basolateral/basomedial)	BDNF-, GABA-related genes	Control females: 21 MDD females: 21
Duric *et al.*, 2013 (150)	Dentate gyrus, CA1	Glutamate- and synapse-related genes	Control males: 9 Control females: 6 MDD males: 9–10 MDD females: 5–6
Labonte *et al.*, 2017 (71)	DLPFC (BA 8/9), OFC (BA 11), ACC (BA 25), aINS, NAc, vSUB	Sex-specific signatures of MDD; *DUSP6* as female-specific; *EMX1* as male-specific	Control males: 13 Control females: 9 MDD males: 13 MDD females: 13
Seney *et al.*, 2018 (72)	DLPFC, ACC (BA 25), AMY (lateral/basolateral/basomedial)	MDD males: decreased synapse-, increased immune-related genes MDD females: increased synapse-, decreased immune-related genes	Control males: 26 Control females: 24 MDD males: 26 MDD females: 24
Issler *et al.*, 2020 (83)	DLPFC (BA 8/9), OFC (BA 11), ACC (BA 25), aINS, NAc, vSUB	Sex-specific alterations in lncRNAs; LINC00473 as female-specific	Control males: 13 Control females: 9 MDD males: 13 MDD females: 13

ACC, anterior cingulate cortex; aINS, anterior insula; AMY, amygdala; BA, Brodmann area; BDNF, brain-derived neurotrophic factor; DLPFC, dorsolateral prefrontal cortex; FGF, fibroblast growth factor; GABA, gamma-aminobutyric acid; lncRNA, long noncoding RNA; MDD, major depressive disorder; NAc, nucleus accumbens; OFC, orbitofrontal cortex; PFC, prefrontal cortex; vSUB, ventral subiculum.