> "Both society (gender) and biology (sex) are equal determinants of emotion. Of the three categories of drive required for survival, important differences in males and females exist in agonistic and reproductive drives which influence emotional circuitry across core limbic structures: amygdala, hypothalamus, and hippocampus. The challenge for the future is to determine when a sex/gender difference makes a difference."

Gender/sex differences in emotions

by G. Einstein, J. Downar, and S. H. Kennedy, *Canada*

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Biological sex differences begin in utero and continue to develop throughout life, based on biology and experience. The concept of gender requires disentangling biological (sex) and social (gender) constructs as well as considering the role that hormones and genes play in establishing emotional differences, especially those due to the sexual differentiation of the fetus and the reproductive cycle. Increasingly sophisticated functional neuroimaging techniques highlight what is known about brain sex differences, and its influence on different expressions of emotions. There is also limited evidence of difference in symptoms of depression between men and women, and conflicting reports about differential antidepressant response in men and women with major depressive disorder.

Medicographia. 2013;35:271-280 (see French abstract on page 280)

Since the mid-20th century, women have been viewed as the "expressive" experts and men the "instrumental" experts.[1] Emotional competencies are so embedded in our popular notions of what it is to be female or male, that tests of gender role identification use emotion items as key components to identify a person as feminine and not masculine[2] and there is a strong current of thinking that females have greater access to their emotions.[3] However, while much of the popular imagination continues to maintain this divide between male and female emotions, the scientific literature has moved toward an understanding that there is a filigreed intertwining of biological, social, and interpretive dimensions that influences an individual's emotional repertoire, leading to individual differences being greater than differences between sexes. These potential differences have implications when it comes to the etiopathology and treatment of psychiatric disorders, such as major depressive disorder (MDD), which include aberrant emotional function as a key component of the illness.

Sex and gender

"Sex" is indicative of the biological characteristics of the organism, while "gender" refers to the social situation of that phenotype—whether a person is interpreted by themselves and others as male or female. Gender operates at many levels—the personal, social, and institutional.[4] One may have the biological characteristics of a male (XY), but want to be part of the gendered world of a female (XX). One's gendered experience of being treated as male affects one's biology to conform more closely to what is considered "maleness." These experiences will shape neural circuits that will, in turn, mediate one's actions and perceptions of the world.[5]

Sexual differentiation

The first step toward establishing sex differences occurs in the developing embryo. If the fetus is XY, there is a region on the short arm of the Y-chromosome, containing the gene SRY, that when switched on leads the indifferent gonad to develop into the testes. The testes begin to produce androgens in the sixth week of gestation and this has repercussions for each body system, including the nervous system. It is well understood from rodent studies that estrogen via testosterone synthesis early in development sets the neural circuitry in the XY brain on a course that differentiates it from female neural circuitry, especially in the areas of the brain that mediate sexual reproduction.[6] Since the XX fetus does not have SRY, the indifferent gonad follows a developmental path toward becoming ovaries which do not secrete appreciable estrogen until much later in development and so with respect to brain development, the male brain sees testosterone and estrogen early and often, while the female brain develops essentially in their absence. The production of follicle-stimulating hormone (FSH) is thought to play a key role in the development of the ovaries. Both androgens and estrogens will affect neural circuits throughout life and are essentially growth factors causing dendrites and axons to grow[7] as well as synapses and neural connections to form.[8]

Hormonal and social effects on sex differences in emotion

◆ *Hormones during reproductive cycle*

The cyclic release of hormones in the ovarian cycle and the menstrual cycle has been viewed as sources of mood differences between females and males. It has not gone unnoticed that some neuropsychiatric disorders seem to be in synchrony with phases of the ovarian cycle and are so named: premenstrual dysphoric disorder (PMDD; low estrogen), catemenial epilepsy (high estrogen), and menstrual migraine (low estrogen). However, these conditions are very rare. While the prevalence of PMDD has been estimated to occur in 3% to 9% of the adult female population, a recent community study reported 1.3%,[9-11] Since mood disorders are nearly twice as prevalent in females as in males,[12,13] a discrepancy that begins at puberty and dissipates following menopause,[14] it has been difficult to move away from hormonal explanations for women's moods as opposed to men's, with the late luteal or premenstrual phase perceived as a time of increased irritability and negativity, leading to the broader lay concept of premenstrual syndrome (PMS[15,16]).

Attempts to correlate female gonadal hormones with women's mood in both women with PMDD and women without disorders have been largely inconclusive. Studies on the effects of exogenous hormone administration on mood in menopausal women also reveal contradictory results; estrogen administration has been shown to reduce, increase, or have no significant effect on negative mood: "Studies conducted, however, have overwhelmingly refuted the presumption that gonadal steroid levels are abnormal in women with PMDD."[17] In studies of randomly recruited, non-help-seeking women, who were blinded to the purpose of the study, no correspondence was observed either between menstrual phase[18,19] or ovarian steroids and either negative or positive mood.[19] Rather it was psychosocial factors—stress and physical health—that were most highly correlated with mood *(Figure 1).*[19] Thus, despite reports of a link between menstrual phase and self-reported mood, a direct relationship between ovarian hormones and mood is not well established (for review, see reference 20).

◆ *Hormones and life changes during pregnancy and postpartum*

Much has been written about the moods of women during pregnancy and delivery, especially with respect to depression and anxiety.[21] The postpartum period is seen as a particularly vulnerable time for women, especially if there is prior depression or psychosis.[22] What is not known is how much of postpartum mood depends on hormonal fluctuations and how much depends on the enormity of the undertaking of parenthood, societal expectations, and sleep deprivation. Robinson and Stewart[23] suggest that the postpartum period is a time when family roles are reevaluated, often becoming more traditional with women taking on the greater load of household and childcare responsibilities. Changing roles and sleep deprivation may be strong drivers for mood shifts. These can be seen as affecting men as well; consequently, men may also be vulnerable to paternal postpartum depression, with rates ranging from 10.4%-25.6%.[24] Thus, in the period when women most commonly suffer postpartum depression, significant numbers of men do as well. Since many studies show that children are affected by depression in fathers as well as mothers,[25] this is an important, but as yet understudied aspect of men's moods.

◆ *Sex differences in "emotion behavior"*

From a behavioral perspective, at least one approach has served to delineate emotions so the permutations and com-

SELECTED ABBREVIATIONS AND ACRONYMS

ACC	anterior cingulate cortex
CRESCEND	Clinical RESearch CENter for Depression
CYP	cytochrome P450
DBS	deep brain stimulation
fMRI	functional magnetic resonance imaging
MAOI	monoamine oxidase inhibitor
MDD	major depressive disorder
NCS	National Comorbidity Survey
PMDD	premenstrual dysphoric disorder
rTMS	repetitive transcranial magnetic stimulation
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
vmPFC	ventromedial prefrontal cortex

Figure 1. *Linear mixed models of mood items with* t*-statistics of mood variables.*

*All models include measures of E1G, PdG, weekly social support, and subjective stress and physical health (*P<0.05, **P<0.01, ◊P<0.0001). **(A)** Model of composite positive mood with E1G and PdG measured the same day. Composite positive mood is the average of happiness, confidence, enjoyment, energy, feeling of being on top of things, and motivation. Only perceived stress and physical health contributed significantly to the model (P<0.0001). **(B)** Model of composite negative mood with E1G and PdG measured the same day. Composite negative mood is the average of irritability, sadness, anxiety, and difficulty coping. Only perceived stress and physical health contributed significantly to the model (P<0.0001). **(C)** Model of irritability with E1G and PdG measured 1 day prior. PdG (P=0.0048), stress (P<0.0001), and physical health (P=0.0120) contributed significantly to the model.*

Abbreviations: *E1G, estrone glucuronide; PdG, pregnanediol-3 glucuronide.*

After reference 19: *Schwartz et al.* Horm Behav. *2012;62(4):448-454. © 2012, Elsevier Inc.*

binations can be viewed as "mixed and matched" by the sexes.[26,27] This framework addresses: (i) overt actions; (ii) subjective reports, and (iii) physiological responses. When emotion is deconstructed into these components, studies that only focus on sex differences do not account for the complexity of emotional processes.[28] With respect to overt actions, while men and women both report feeling sadness at the same levels, women tend to display overt signs of sadness while men tend to withdraw. However, this difference in behavioral repertoire may be situational, with women believing that they should verbally express their emotion while men do not. Both feel more expressive when talking with a woman.

In the case of alexithymia, a personality construct that is characterized by impoverishment of imagination, poor capacity for symbolic thought, and inability to experience and describe feelings,[29] neither subjective reports nor physiological response differs between the sexes. Numerous studies have failed to find a reliable sex difference.[30-32] In subjective reports, men and women report experiencing anger with equal intensity and frequency.[2] Physiological responses reveal that men tend to make evident more responses than women; however, with regard to fear, for example, there are no specific fear-related differences in autonomic response between females and males.[28] Work on emotional regulation also belies the traditional stereotypes. Emotion regulation as defined by Nolen-Hoeksema and Aldao[33] consists of many types of coping: adaptive (eg, active coping, positive reappraisal) and maladaptive (eg, avoidance and self-blame). Interestingly, women reported using self-blame as a strategy more than men only in studies in which women appraised the stressor as more severe than men did, suggesting that sex differences might actually be in the domain of stressor appraisal. Additionally, women reported using a wider range of strategies than men, including rumination, reappraisal, active coping (or problem solving), acceptance, and social support. Importantly, this sex difference was significant, even when self-reported depressive symptoms were controlled for, suggesting that this difference in coping strategies is not simply a reflection of women's greater tendency toward depressive symptoms. There were sex differences in rumination, suppression, and social support seeking that were not moderated by stressor appraisal and these are more strongly related to depressive symptoms than adaptive strategies *(Table I, page 274).*[33]

Emotional regulation strategies vary with age in older women, but not so in men; use of acceptance did not decrease with age for women. Older men made the fewest reports of reappraisal, active coping, and acceptance. This suggests that men may find it harder than women to assume a positive, efficacious, or accepting attitude toward problems that arise in older age. Lack of acceptance, active coping, or reappraisal was not associated with depressive symptoms in the oldest age group as they were with the younger adults.[33] When taken together, these studies and others suggest that individual variation in emotion and its expression depend more on the

	Women			Men		
	Young adults	Middle-aged adults	Older adults	Young adults	Middle-aged adults	Older adults
Depressive symptoms	5.50 (0.27)	4.94 (0.26)	4.10 (0.33)	4.29 (0.28)	4.24 (0.27)	3.60 (0.37)
Rumination	2.04 (0.02)	1.90 (0.02)	1.65 (0.03)	1.98 (0.03)	1.85 (0.02)	1.58 (0.03)
Suppression	1.95 (0.04)	1.97 (0.04)	2.31 (0.05)	2.03 (0.04)	2.03 (0.04)	2.09 (0.06)
Reappraisal	2.85 (0.05)	2.81 (0.05)	2.67 (0.07)	2.70 (0.06)	2.57 (0.05)	2.22 (0.07)
Active coping	2.91 (0.05)	2.93 (0.05)	2.65 (0.07)	3.01 (0.05)	2.84 (0.05)	2.32 (0.07)
Acceptance	3.02 (0.05)	3.22 (0.05)	3.14 (0.06)	3.04 (0.05)	3.07 (0.05)	2.76 (0.06)
Social support	3.05 (0.06)	3.03 (0.05)	2.65 (0.07)	2.78 (0.06)	2.66 (0.06)	2.24 (0.08)

Notes: Means for emotion regulation strategies are adjusted for depressive symptom scores: numbers in parentheses are standard deviations for depressive symptoms and standard errors for emotion regulation strategies.

Table I. *Descriptive statistics for all variables by gender and age.*
After reference 33: *Nolen-Hoeksema and Aldao.* Pers Individ Dif. *2011;51:704-708. © 2011, Elsevier Ltd.*

nature of the emotional stimulus, mental health status, context, age, and the response format. This complex pattern of findings is best accounted for by acknowledging that both society (gender) and biology (sex) are equal determinants of emotion: emphasizing sex differences in emotionality imposes a framework on the patient that might burden psychotherapy with stereotypes.

Neural effects on sex differences in emotion

How, and why, might emotions differ across sex? An "adaptationist perspective" affirms that the body's individual organs serve several functions. Although there is an overlap in critical survival functions across sex, there are also important distinctions among several organ systems, namely, reproductive, endocrine, cardiovascular, digestive, and the central nervous system.

Three categories of drive are required for survival of any organism: homeostatic (maintaining key internal parameters in safe ranges), agonistic (self-preserving behaviors against hostile conspecifics or predators, and self-advancing behaviors against prey or rivals), and reproductive (finding suitable mates, birthing, nurturing, and defending young). For at least the latter two categories of drive, important differences exist between the males and females in nearly every species, including humans. These differences are reflected in the emotional circuitry of the brain, most notably in the so-called core limbic structures: the amygdala, hypothalamus, and hippocampus.

The emerging field of affective neuroscience has made rapid progress in delineating the neural substrates of emotion.[34] The core limbic structures are essential for the generation of integrated emotional states such as fear, anger, or sadness. Other, more caudal, regions of the neuraxis, such as the brainstem, the periaqueductal gray, and ventrolateral medulla coordinate the outward expression of emotional states, while peripheral autonomic pathways generate visceral responses and provide interceptive input about the inner state of the body. Rostrally, the limbic sensory cortex in the insula integrates this input into the "feel" of emotions, while the limbic motor cortex of the anterior cingulate cortex (ACC) and ventromedial prefrontal cortex (vmPFC) generate appropriate somatic markers or "visceral feelings" to guide complex behavior and decision-making. The ventral striatum and limbic nuclei of the thalamus provide key outputs from core limbic structures to cortex, essential for weaving the survival functions of emotion into everyday perception and action. Finally, a network of prefrontal regions including the dorsomedial, ventrolateral, ventromedial, and frontopolar cortices are critical for the process of reappraisal: adjusting emotional states based on cognition and context.[35]

All of these structures show varying degrees of sexual dimorphism. Structurally, total brain volume is approximately 10% higher in males,[36] while the gray-white matter ratio is similar in both females and males.[37] Voxel-based morphometry (VBM) studies have shown subtly larger gray matter volume in the amygdala, hippocampus, and parahippocampal cortex in males, as well as increased white matter volume in the anterior temporal lobes, which connect densely to the amygdala.[38] Females have slightly larger gray matter volumes in the ventrolateral and lateral orbitofrontal cortex,[37] which play critical roles in reappraisal of emotional stimuli,[39] as well as in the superior temporal sulcus (STS), which plays a critical role in social cue perception.[40]

Functional imaging positron emission tomography (PET) studies have shown slightly higher metabolic activity in the male anterior temporal lobe as well as in the amygdala, hippocampus, and orbitofrontal cortex, consistent with volumetric findings. Females have shown lower activity in posterior and midcingulate regions.[41] However, there is considerable variability in results among studies, with some studies showing opposite

effects in the same regions,[42-44] and some smaller studies find no significant differences in resting metabolic activity between males and females.[45,46] Functional magnetic resonance imaging (fMRI) studies have found no sex differences in the functional connectivity of resting-state networks for the "default mode" of introspection and self-reflection, the "executive control" network engaged during cognitive tasks, or the "salience network" activated by potentially relevant events in the sensory environment.[47]

◆ *Sex differences in hemispheric asymmetries in emotion pathways*

In a majority of studies to date, sex differences in raw structural and functional neuroanatomy are consistently identified, but they are subtle in magnitude. A major exception is a well-replicated sex difference: asymmetry of emotional functions across the two hemispheres of the brain *(Figure 2).* For example, on resting-state fMRI, the left amygdala shows markedly stronger and more widespread functional connectivity to the rest of the brain in women; conversely, the right amygdala shows stronger connectivity to the rest of the brain in men.[48] During emotional provocation, there is a three-way interaction between sex, hemisphere, and emotional valence. In women, negative stimuli activate the left amygdala, hippocampus, hypothalamus, vmPFC, and ACC,[49] while in men, it is positive emotional stimuli that activate a left-sided network of limbic structures (including amygdala, orbitofrontal cortex, uncus, and temporal pole). Likewise, males show greater activation of the right amygdala in response to sad faces.[50] Subjective sadness is correlated with right amygdala activation in males, but not females.[51]

Sex differences in asymmetry are also apparent in studies of emotional memory. Men watching emotional slides or film clips show strongly lateralized right, but not left amygdala activation which is associated with enhanced memory of the emotionally arousing scenes. Women demonstrate left, but not right amygdala activation associated with better memory for the emotional scenes.[52,53]

Sex differences in limbic activity are also apparent during more complex emotion-driven prosocial behavior. For example, the anterior insula activates not only during pain, but also empathetically, when witnessing others in pain.[54] In women, this empathetic response is reduced if the other person had previously acted unfairly in a social exchange. However, in men witnessing unfair individuals in pain, the empathetic insular response is abolished entirely. Additionally, in these men, the reward circuitry of the left ventral striatum was also activated asymmetrically. No such "vengeful" response was seen in women, in either hemisphere.

Lesion studies confirm sex differences in functional asymmetry of limbic regions. Among men, right vmPFC lesion caused profound impairments in social and emotional functioning as well as in decision-making, akin to those of the famous case of Phineas Gage. Left-sided lesions produced mild or no impairment.[55] In contrast, among women, it was lesions of the left vmPFC that led to profound social and emotional impairment, while right vmPFC lesions were relatively benign.[56] The same type of sex difference has been observed for the amygdala, with social and emotional deficits arising from right-sided, but not left-sided, lesions in men and left-sided, but not right-sided, lesions in women.[57]

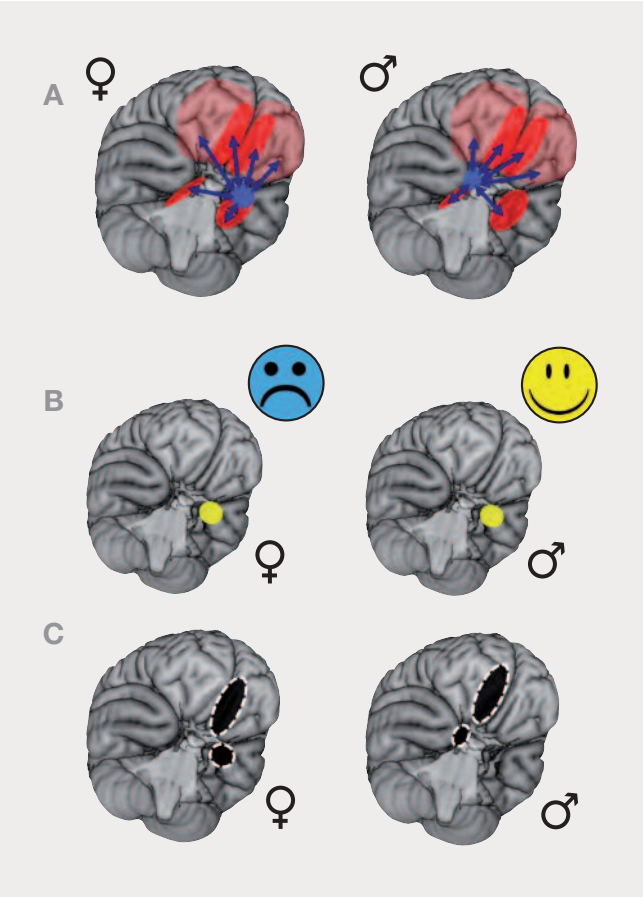

Figure 2. *Gender-dependent hemispheric asymmetries in emotion regulation pathways.*
(A) *In females, the left, but not the right, amygdala shows strong resting-state connectivity to a widespread network of ventral prefrontal, temporal, and parahippocampal regions. In males, the reverse is true.* ***(B)*** *The left amygdala is activated by negative emotional stimuli in females, but by positive emotional stimuli in males.* ***(C)*** *Major deficits in social, emotional, and decision-making functions arise from left-hemisphere lesions of the amygdala or ventromedial prefrontal cortex in females, but from right-hemisphere lesions of these structures in males.*

Sex differences in MDD symptom presentation

The case for sex differences in psychiatric illnesses has attracted increasing attention in recent years.[58] Beginning in adolescence, women have a twofold greater risk for MDD compared with men.[59] Although men and women report similar depressive symptoms,[60] women are more likely to recall their symptoms and also experience a greater number of recurring depressive episodes.[61] Classically, atypical (reversed) neurovegetative symptoms are more prevalent in women com-

pared with men.[62] Evidence to support higher rates of atypical depression in women is derived from studies of twins and sibling pairs.

An evaluation of more than 200 opposite-sex dizygotic twin pairs who met lifetime criteria for MDD showed that fatigue, hypersomnia, and psychomotor retardation were more prevalent in females, while insomnia and agitation were more likely to occur in males.[63] The authors suggested that both sex and gender played a role in differential recall as well as hormonal and sociocultural variables.

In an assessment of 94 female twin pairs, Kendler and colleagues identified "severe typical" and "atypical" depression groups. The "severe typical" group was characterized by comorbid anxiety and panic symptoms, greater functional impairment, and a longer episode duration, while the atypical group reported increased eating, hypersomnia, and more frequent, but shorter episodes. Interestingly, neither neuroticism nor anxiety symptoms were prevalent in the atypical group. However, the absence of male comparison twins limits any conclusions about apparent sex differences in depressive symptoms. This finding was supported by results from a Canadian community epidemiology study which examined the symptom presentation of recurrent depressive episodes in over 650 cases. The authors reported persistent atypical presentation in only 11% of cases, while the majority were either "typical" or did not firmly belong in either category. In both typical and atypical groups, women represented 77% and 75% of the sample, respectively.[64]

Using a different technique, Moskvina and colleagues[65] compared symptom presentation in more than 400 sibling pairs who met criteria for MDD across European centers. They confirmed a higher frequency of atypical symptoms (fatigue, increased appetite, weight gain, and hypersomnia) in women, who also had higher rates of tearfulness, pathological guilt, morning severity, and loss of reactivity. Female siblings also reported an earlier age of onset and prolonged episode length compared with male siblings. There was also a significant correlation in symptom profiles between female sibling pairs, but not between male sibling pairs or in male-female sibling pairs.

While most studies captured data from white samples, Lai,[66] examined male-female differences in 146 Taiwanese patients: women had greater frequency of sleep disturbance (time to onset and total sleep time), somatic complaints (chest pain, headaches, and appetite loss), as well as sadness and nervousness. Women were also more likely than men to report a reduction in sexual interest, function, and overall satisfaction. In the largest clinical cohort to date of depressed patients participating in a treatment study, 63% were women and they reported greater severity of depressive symptoms, comorbidity of anxiety disorders, binge eating, and somatoform disorders as well as hypersomnia and rejection sensitivity, but less suicidal ideation compared with men.[67] Men reported a greater number of depressive episodes as well as alcohol and substance use.[67]

In contrast, Silverstein and colleagues[68] found that in both the National Comorbidity Survey (NCS14) and the Zurich study,[69] "pure depression" was comparable in frequency between men and women, while anxious somatic depression was twice as frequent in women. These authors concluded that atypical depressive symptoms did not contribute to male-female differences.

Sex differences in antidepressant treatment response

The presence of differing symptom distributions and potential depressive subtypes in men and women suggests that response to antidepressant treatment may also display sex differences.[70] However, publications in this area provide contrasting results *(Table II)*.[70-85]

◆ *Response to tricyclic antidepressants and monoamine oxidase inhibitors*

Reports from the pre–selective serotonin reuptake inhibitor (SSRI) era suggest that men have higher response rates than women to tricyclic antidepressants (TCAs).[86-88] A subsequent publication by Quitkin in 2002[70] used retrospective data to analyze differences in treatment response to TCAs by categorizing participants according to age (<50 years of age and >50 years of age) and sex. A survival analysis indicated that there was no difference in TCA treatment response between older men and older women. However, older women had superior response rates to TCAs when compared with younger women. These results were also replicated in a study by Grigoriadis and colleagues who found that older women responded more favorably to the TCA desipramine than younger women with response rates of 62% and 34%, respectively.[84]

Quitkin and colleagues[70] also evaluated sex differences in response to monoamine oxidase inhibitor (MAOI) therapies. While there was no difference in antidepressant response between older men and older women, there was a difference in response rates between sexes which was accounted for by younger women having a superior response to MAOIs compared with younger men.[70] These findings contrast with results from a large naturalistic study which concluded that men and women were equally likely to respond to SSRI, TCA, MAOI, and serotonin norepinephrine reuptake inhibitor (SNRI) antidepressants.[77]

◆ *Response to SSRIs and SNRIs*

In a study of chronic depression involving 235 men and 400 women, Kornstein and colleagues[71] identified sex differences in antidepressant response to sertraline and imipramine. There was a statistically significant interaction between sex and treatment, with women having a more favorable response to ser-

traline than imipramine (57% vs 46%), while men were more likely to respond to imipramine than sertraline (62% vs 45%). Moreover, compared with men, women had a greater likelihood of achieving remission over the 12-week treatment period. The inferior response to imipramine compared with sertraline in premenopausal women was attributed to higher attrition among younger women who received the TCA.[71]

Using data from the 9-year, multicenter, prospective trial CRESCEND (the Clinical RESearch CENter for Depression), based in South Korea, Yang and colleagues[85] found that women were more likely to respond to SSRIs,[70,71] supporting previous findings that atypical symptoms are more prevalent in women and respond better to SSRIs.[89] There were no significant differences in response rates between sexes when

Author, Year	Treatment	Study type	n	Findings
Kornstein et al,[71] 2000	Sertraline, imipramine	12-Week double-blind trial	635	Women had a superior response to sertraline, men to imipramine
Martenyi et al,[72] 2001	Fluoxetine, maprotiline	6-Week double-blind trial	105	Women were more responsive to fluoxetine than maprotiline; no difference in men
Entsuah et al,[73] 2001	Venlafaxine, SSRIs	8 Double-blind, active controlled, randomized trials (4 were placebo controlled)	2045	No sex differences
Quitkin et al,[70] 2002	TCAs, MAOIs, fluoxetine	8 Placebo-controlled trials and 1 open-label study	1746	Older women had a more favorable response to TCAs than younger women; women had a statistically superior response to MAOIs
Parker et al,[74] 2003	TCA, SSRI	1 Retrospective study 1 Prospective study	346 162	No sex differences
Hildebrandt et al,[75] 2003	TCA, SSRI, MAOI	3 Double-blind, randomized controlled trials	292	No sex differences
Grigoriadis et al,[76] 2003	SSRI, nefazodone, or venlafaxine	8-Week double-blind study	201	Younger compared with older women were more responsive to serotonergic antidepressants
Scheibe et al,[77] 2003	TCAs, SSRIs, SNRIs, MAOIs, RIMAs	Retrospective study	385	No sex differences
Wohlfarth et al,[78] 2004	TCAs	30 Randomized, placebo controlled trials	3886	No sex differences
Cassano et al,[79] 2004	Fluoxetine	8-Week open-label study	320	No sex differences
Khan et al,[80] 2005	SSRIs, SNRIs	15 Randomized placebo-controlled trials	323	Women responded better to SSRIs and SNRIs than men
Kornstein et al,[81] 2006	Duloxetine	7 Randomized, double-blind, placebo controlled trials	896	No sex differences in antidepressant response, but women on duloxetine compared with placebo had a significant reduction in pain severity
Grigoriadis et al,[82] 2007	TCAs, SSRIs, SNRIs	8-Week, open-label, flexible-dose trial	205	Men responded more favorably to SSRIs and venlafaxine than women
Young et al,[83] 2009	Citalopram	12- to14-Week, open-label, flexible dose study	2876	Women were significantly more likely to achieve remission than men during citalopram treatment
Grigoriadis et al,[84] 2010	Desimpramine	8-Week, double-blind, flexible-dose study; women only	113	No sex differences; older women showed better response to desimpramine than younger women (trend)
Yang et al,[85] 2011	SSRIs, newer dual antidepressants, other antidepressants	12-Week naturalistic cohort study	723	Women were significantly more likely to respond to SSRIs than men

Table II. *Sex- and age-related differences in antidepressant treatment response.*

Abbreviations: *MAOI, monoamine oxidase inhibitor; RIMA, reversible inhibitor of monoamine oxidase A; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake.*

Updated from reference 82: *Grigoriadis et al.* J Clin Psychopharmacol. *2007;27(1):95-98. © 2007, Lippincott Williams & Wilkins.*

data from seven randomized double-blind, placebo-controlled trials of duloxetine were pooled. On the other hand, compared with men, duloxetine-treated women showed a greater reduction in overall pain severity scores.[81]

◆ *Other medications*

Data are limited on sex differences in response rates to newer antidepressants and augmentation therapies for depression. Recent evidence suggests that agomelatine, which is a novel melatonergic antidepressant with good tolerability has equal efficacy in men and women.[90]

◆ *Limitations*

Gonadal hormones, specifically estrogen, which is a substrate for cytochrome P450 (CYP) 3A4 and CYP1A2 as well as an inhibitor of CYP1A2, may impact antidepressant metabolism by enhancing response to SSRIs or inhibiting response to TCAs.[91] However, failure to demonstrate differences may also relate to methodological limitations in published studies. Not all studies stratified their samples according to the hormonal status of women (pre/perimenopausal vs postmenopausal); several studies were underpowered due to small sample size.[70]

◆ *Neurostimulation therapies*

Sex differences may also be relevant in response to anatomically targeted device therapies such as repetitive transcranial magnetic stimulation (rTMS)[92] and deep brain stimulation (DBS). Given the differential roles of left- and right-hemisphere limbic structures in negative emotions in men and women, tailoring the parameters of rTMS according to the sex of the patient could potentially improve antidepressant efficacy. In DBS for MDD, electrodes are typically implanted bilaterally in the subgenual cingulum, an area of the vmPFC that is densely connected with the amygdala. Stimulation is typically bilateral. Although DBS is effective in many refractory depression cases, approximately one-third still do not respond to treatment.[93] Again, based on the lesion and neuroimaging evidence above, adjusting stimulation laterality for sex could improve the response rates.

Conclusion

We have reviewed key studies looking at sex differences in emotional behavior, brain circuits, and response to treatment. It seems that gender—or the social expectations of both patient and therapist—plays a role in establishing differences where differences have been established. In terms of brain circuits, sex differences are particularly prominent in limbic structures relevant to the generation and expression of emotional states, such as the amygdala, insula, and medial prefrontal cortex. The most striking differences appear as an interaction between sex, hemisphere, and emotional valence. For negative emotions, men preferentially recruit right hemisphere structures, while women depend more on left hemisphere structures. However, these data are still controversial and without clear replication. This suggests that individual differences may be extremely important, especially for the success of some of the newest brain-targeting therapies. These individual differences may also be at play in the noted therapeutic efficacies of different treatment classes of antidepressants. Importantly, however, with the exception of the behavioral work which has a long history, serious exploration into sex differences in brain and treatment response are emerging fields. As such, they will need to develop awareness in experimental design regarding the age of participants, sex, and reproductive life stage as well as, within that stage, reproductive status and hormonal levels. Gender expectations may also need to figure into any cellular and genetic research as the emerging field of epigenetics suggests that social location will also affect biology. The challenge for the future is to determine when a sex/gender difference makes a difference. ■

Acknowledgments: The authors would like to thank Anna Cyriac for her contribution to this manuscript.

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Keywords: *antidepressants; emotion; gender differences; major depressive disorder (MDD); neurobiology; neuroimaging; sex differences; symptom presentation; treatment response*

DIFFÉRENCES ÉMOTIONNELLES SELON LE SEXE ET LE GENRE

Les différences sexuelles biologiques commencent in utero *et se développent tout au long de la vie en fonction des processus biologiques et de l'expérience. Le concept de genre nécessite de séparer les constructions biologiques (sexe) et sociales (genre) et de s'intéresser au rôle joué par les hormones et les gènes dans la mise en place des différences émotionnelles, et plus particulièrement de celles qui sont dues à la différenciation sexuelle du fœtus et au cycle reproductif. Des techniques de neuro-imagerie fonctionnelles de plus en plus sophistiquées mettent en évidence les différences sexuelles cérébrales et leur influence sur les différentes expressions des émotions. Il existe peu de preuves démontrant des différences de symptômes entre les hommes et les femmes dans la dépression et les données sur les différences de réponse aux antidépresseurs selon le sexe dans la dépression majeure sont contradictoires.*