Estrogen, stress and the brain: progress toward unraveling gender discrepancies in major depressive disorder

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Women are twice as likely as men to develop major depressive disorder (MDD) and, while the neurobiological factors underlying this discrepancy are yet to be identified, estrogen almost certainly plays a role. MDD can be precipitated or exacerbated by exposure to stress and there is substantial evidence to suggest that estrogen can interact with stress systems to produce unique stress effects in females. This review integrates current research in animal models regarding estrogen–stress interactions in three areas of the brain known to be relevant to MDD: the hippocampus, the amygdala and the prefrontal cortex. The results from these studies are discussed in the context of MDD, and their implications for future treatment of MDD in women are explored.

**Keywords:** antidepressant • depression • fear • memory • sex difference • stress response • trauma

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Gender differences & major depressive disorder: a role for estrogen?

Major depressive disorder (MDD) is a debilitating and common affliction, affecting at least 15% of the population. It is the number one cause of disability worldwide, costing society an estimated US$43.7 billion annually. Its prevalence is twice as high in women as in men [1], a discrepancy that is also found with respect to attempted suicide [2], assault-related post-traumatic stress disorder [3] and most anxiety disorders [4]. Furthermore, women are prone to longer episodes of depression that are often more severe than those in men [5]. The reasons for this imbalance, are however, unknown.

The possibility that social and cultural factors are primarily responsible for producing this disparity has not been overlooked. There is evidence that women who experience depressive symptoms are more likely than men to seek professional psychiatric help, thus becoming accurately diagnosed as ‘depressed’, while depressed men may tend more towards substance abuse as a means of self-medication and are often labeled ‘alcoholics’ or ‘drug addicts’ [6]. In addition, while certain social sources of security, such as marriage, may render a person more resilient against developing MDD, evidence suggests that this is less effective for women than it is for men [7]. Finally, as a sense of control is critical in protecting an individual from the detrimental effects of stress [8], it is theoretically possible that women simply have less control over the events of their lives.

While these elements undoubtedly contribute to the gender difference in the prevalence of MDD, neurobiological and hormonal variations are also likely to play a role. The most probable of these factors is estrogen, which can have both organizational and activational effects in the brain. Estrogen is known to be responsible for much of the sexual dimorphism in brain development (reviewed in [9]), with sex differences seen in the size and shape of many regions, including the hypothalamus, amygdala and prefrontal cortex (reviewed in [10]). As each of these areas contributes to the regulation of mood, stress response and social functioning, these differences could render women more likely to develop disorders related to such functions.

In addition to estrogen’s actions during development, circulating estrogen probably also contributes to the gender imbalance in MDD. Perhaps most compelling are reports that the
disparity is most robust during child-bearing years [7,11,12]. Further evidence for estrogen’s influence on mood is derived from the phenomena of postpartum depression, a condition often characterized by severe feelings of sadness that often follows the massive drop in estrogen and progesterone after childbirth [13], and premenstrual dysphoric disorder, the severely depressed mood that can occur during the late luteal phase of the menstrual cycle [6]. In addition, administration of estrogen can exacerbate depressive symptoms in young women [14], but not in menopausal women [15] (although it should be noted that these two studies were carried out by different groups). Finally, estrogen has been shown to regulate the expression of serotonin receptors and transporters, which are targets of many commonly used antidepressants [16].

**Stress, MDD & relevant brain regions**

It is well documented that one of the leading risk factors for the development of MDD is exposure to an uncontrollable life stressor [7,16]. Victims of childhood sexual abuse have heightened chances of developing MDD regardless of gender [19], and one in six people who experience a heart attack will develop MDD [20]. Other relevant stressors include the loss of loved ones, ongoing difficulties (such as poverty) and lack of social contact [21].

How exposure to stress might lead to mental illness is a subject of much investigation, with substantial focus on the ability of stress to alter brain structure and connectivity. Notably, significant morphological differences between depressed patients and healthy controls have been observed in the hippocampus, the prefrontal cortex and, to a somewhat lesser extent, the amygdala [22]. Hippocampal volume in depressed patients has been reported not only to be smaller than in controls, but also to be negatively correlated with likelihood of relapse [23]. By contrast, the amygdala is reported to be increased in size and activity in first-episode depressed patients when compared with controls [24]. Finally, imaging studies reveal reduced volume of the medial prefrontal cortex (mPFC) in depressed patients [25], as well as suppressed mPFC activity compared with controls [26]. The fact that these regions are each key mediators of emotion, learning and mood regulation suggests that symptoms of MDD may derive from suboptimal functioning due to compromised structural integrity.

It has been hypothesized that stress may induce changes in brain structure and size through neurotoxic effects of glucocorticoids (GCs). During stress, GCs are released throughout the brain and, in excess, can activate neurochemical signaling cascades that can result in programmed cell death. Thus, repeated stress may lead to neuronal loss, which then translates to reduced volume in the hippocampus and prefrontal cortex (reviewed in [27]). This process may be exacerbated by a stress-induced reduction in neurotrophic factors, which could help to counter the neurotoxic effects of GCs. Indeed, reduced levels of neurotrophic factors have been observed in post-mortem tissue from suicide victims, and antidepressant treatment has been shown in animal models to restore neurotrophic factor levels after stress (reviewed in [28]).

When taken together with the difference in the prevalence of MDD in men and women, such reports lead to the question of whether women and men have distinct neurobiological responses to stress and, if so, how might estrogen be involved in promoting these differences? Animal models of stress have been eminently useful in beginning to answer these questions. Stressors such as footshock, restraint and anxiogenic drugs produce neurochemical and psychological profiles in animals that mimic the stress response in humans [29]; thus, findings from animal work that illuminate the mechanisms underlying stress effects can help us understand these processes in humans. Such studies have produced a growing literature demonstrating that estrogen can interact with stress to induce a unique response to stress in females (Table 1). The effects of these interactions appear to be remarkably specific, however, and whether the effects are ‘beneficial’ or ‘detrimental’ appears to depend on the stress regimen employed, brain region studied and measures used.

**Estrogen–stress interactions in the hippocampus**

The hippocampus has been extensively studied and is known to mediate functions involving plasticity, learning, long-term memory and particularly spatial memory (reviewed in [30]). As mentioned earlier, hippocampal volume is reduced in depressed patients [23], a phenomenon that has been reported to be more profound in men than in women [31]. In animal models, the hippocampus has been shown on many levels to be sensitive and vulnerable to stress-induced changes in both males and females [32]. Behaviorally, hippocampal function can be measured using a learning task, such as classical eye-blink conditioning, or spatial memory tasks such as the Y-maze or Morris water maze. Acute stress has been shown to have opposing effects in male and female rats on performance of these tasks; while exposure to a brief series

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of foot shocks causes enhanced eye-blink conditioning in male rats, it leads to impairment in females. Interestingly, this interaction is most robust when females are in the proestrus phase of the estrus cycle, when estrogen levels are at their highest [6]. This work suggests that estrogen might render the hippocampus more sensitive to the detrimental effects of stress; however, the story is not so simple.

In tests of hippocampus-mediated spatial memory, stress has an impairing effect on males’ performance, but has either no effect or performance-enhancing effects in females. Specifically, exposure to acute restraint stress has been shown to reduce accuracy in the Y-maze task in males but to facilitate performance in females [33]. Although estrus cycle phase did not modulate the stress effect in this study, animals in pro-estrus had a significantly higher corticosterone response to the stress exposure. Studies using repeated or chronic stressors produce similar results. In males, exposure to chronic restraint stress can cause impaired performance on the radial arm maze (reviewed in [34]), a spatial task known to require hippocampal integrity [35]. However, this same regimen has been shown to have beneficial effects on spatial memory in female rats in proestrus [36]; since estrogen levels are at their peak during this phase, stress-induced enhancement of performance may indicate a positive stress–estrogen interaction. Work in ovariectomized (OVX) rats is consistent with these findings, demonstrating stress-enhanced radial arm maze performance in estrogen-replaced animals, but not in animals that remained estrogen depleted [37].

Estrogen–stress interactions in the hippocampus have also been explored at the cellular level. While exposure to a single stressor can cause an increase in dendritic spine density in the CA1 region in male rats, this same treatment causes a decrease in spine density in female rats in pro-estrus [38]. Spine density levels are normally higher during pro-estrus than during other estrus phases (and higher than in males) and, thus, it appears that stress prevents this estrogen-mediated increase. By contrast, when animals are chronically stressed, male rats demonstrate a decrease in dendritic arborization, while females demonstrate no dendritic atrophy (although these rats did demonstrate a decrease in basal dendrite branch points, indicating a change in arbor complexity) [39]. In addition, it has been reported that estrogen treatment in OVX rats protects the hippocampus from neuronal loss due to chronic stress exposure [40].

Taken together, these studies demonstrate that the interaction of estrogen and stress in the hippocampus is not a singular process, but a complex set of responses that depend on the duration of the stressor and the level of analysis. Overall, evidence suggests that estrogen can protect the hippocampus from both behavioral and structural changes observed in male animals after stress exposure. The eyeblink conditioning and spine density studies appear to be exceptions; however, in both cases, females in proestrus had baseline levels higher than those of males and the apparent decrease in performance or density in fact reflected a leveling of these measures to match those of males, thus complicating interpretation.

**Estrogen–stress interactions in the amygdala**

It is well documented that the amygdala plays an integral role in mediating the processing, memory of and response to negative, emotionally salient stimuli [41,42], functions clearly relevant to MDD. In animal models, amygdala function is most commonly measured using the conditioned-fear paradigm, in which, after repeated pairings of a neutral stimulus (such as an auditory tone) with an aversive stimulus (usually footshock), an animal will display fearful behavior to the presentation of the neutral stimulus alone, indicating that the animal has learned the association between tone and shock [43]. This behavior can then be suppressed by repeated presentation of the neutral stimulus without subsequent shock, in a process known as extinction (reviewed in [44]).

Surprisingly, little is known regarding the functional effects of estrogen in the amygdala and the limited studies that have been carried out with female rats in fear-conditioning paradigms are inconsistent in their findings. Sex differences have been reported in the acquisition [45] and extinction [46] of contextual fear, but the role of estrogen in mediating these differences remains to be determined. It has recently been observed that estrogen-treated female rats are impaired at extinguishing a previously conditioned fear response [47], an effect that has also been reported in cycling women [48]. The effects of stress on these processes are also somewhat unclear and have only just begun to be investigated. Recent work has demonstrated that while exposure to chronic restraint stress can impair extinction recall in male rats, it instead impairs conditioning recall in female rats [49]. Although estrogen’s involvement in this discrepancy has not been directly tested, there is some evidence that it may be involved, offering encouraging potential for therapeutics.

One research group has designed a viral construct that combines the GC-binding domain of the GC receptor with the DNA-binding domain of the estrogen receptor. GCs are released during stress and are thought to contribute to many of the effects of stress in the brain [50]. When this construct is administered to an animal that is subsequently stressed, what would normally be GC effects then become estrogen effects [51], which, as described above, can often be beneficial. Accordingly, this construct can reverse stress-induced impairments in hippocampally mediated cognitive tasks observed in males [52]. Furthermore, animals administered the construct before fear conditioning demonstrate suppressed recall for conditioning [53], consistent with the sex differences in the study described earlier. As GCs have been shown to enhance memory for conditioned fear [54], these studies together suggest that estrogen is in a position to negate some of the potentially harmful effects of stress in the amygdala by suppressing the strengthened memory. Prolonged or enhanced memory for an aversive event can lead to inappropriate responses to relevant cues in the future, when no real danger exists. Such responses are ordinarily inhibited by the projection pathway from the mPFC to the amygdala, but should this circuit become compromised, pathology may arise.

**Estrogen–stress interactions in the mPFC**

The symptoms of MDD include poor concentration, prolonged sadness, impaired verbal fluency and recurring negative thoughts, all of which are implicative of dysfunction in the
mPFC. Moreover, depressed patients are impaired at tasks known
to demand optimal mPFC function [55], such as the Wisconsin Card Sort Task and the Stroop Task. The mPFC governs much of
the brain’s executive function, integrating input from subcortical
and other cortical areas. It regulates behavior, thought and affect
using working memory [56], enabling us to plan and organize our
behavior and emotions effectively [57]. In animal models, mPFC
function is measured using delayed-response tasks, which require
an animal to continually update information and suppress previously
rewarded, but inappropriate, responses. Acute stress has
been shown to reliably induce impairment in these tasks in both
monkeys and rodents, effects that are due largely to excess release of
catecholamines in the mPFC [58].

Although the majority of work elucidating the effects of stress
on mPFC structure and function has been carried out in male
animals, there are several recent studies investigating these pro-
cesses in females. The results from these studies suggest that,
unlike in the hippocampus and amygdala, estrogen can amplify
the effects of stress in the mPFC, thus making females more vul-
nerable to the detrimental consequences of stress exposure. It has
been observed that female rats are more sensitive to the mPFC-
impairing effects of acute stress (i.e., less stress is required to
induce cognitive impairment), but only when estrogen levels are
high – either during proestrus or in OVX animals with estrogen
replacement. Females either in the estrus phase or OVX with no
hormone replacement are as vulnerable to stress-induced mPFC
impairments as males [59]. This phenomenon has been observed using several different forms of stress [60], indicating that these
estrogen–stress interactions are products of the stress response
in general and not an artefact of the particular paradigm used.

The neurotransmitter systems underlying estrogen’s media-
tion of stress-induced mPFC impairment have just begun to be
investigated. As stated earlier, it is known from work in male
animals that stress-induced mPFC impairment is due in large part
to catecholamine release. Specifically, it has been shown that the
mPFC becomes dysfunctional when the dopamine D1 receptor
or the norepinephrine (NE) α-1 receptors are activated; however,
stimulation of the NE α-2 receptor can restore mPFC function
during stress [58]. By contrast, females demonstrate impairment
reversal after NE α-2 stimulation only in OVX animals; OVX
animals with estrogen replacement are unresponsive to this treat-
ment and remain impaired [61]. This work suggests that estrogen
may promote sensitivity to stress-induced mPFC impairment by
blocking the protective effects of the NE α-2 receptor.

In addition to mediating the effects of acute stress on mPFC
function, estrogen has also been shown to influence the response
of the mPFC to chronic stress at the cellular level. As in the
hippocampus, the male mPFC undergoes dendritic retrac-
tion after exposure to chronic restraint stress. It has recently
been reported, however, that mPFC neurons that project to
the amygdala are protected from stress-induced atrophy, sug-
ning that the effects of stress may be circuit specific [62].
In females, however, the effects of chronic stress are reversed.
While mPFC neurons in females appear to be generally resil-
ent against stress-induced morphological changes, the mPFC
neurons that project to the amygdala are only sensitive to the
effects of stress in estrogen-replaced OVX female. While OVX
animals without estrogen replacement demonstrate no changes
in dendritic length with stress, neurons in this pathway in OVX
animals also administered estrogen undergo stress-induced
dendritic expansion, which could enable possible overstimula-
tion and subsequent dysfunction of the circuit [Shansky RM et al.,
Manuscript Submitted].

Together, these studies suggest that if an animal is stressed
under conditions of high estrogen, the mPFC may respond in a
maladaptive, rather than adaptive manner. Dysfunction of the
pathway connecting the mPFC to the amygdala could result in
a release of mPFC inhibition of amygdala activity, thus enabling
inappropriate ‘negative’ behavior, as is characteristic of MDD
symptoms. This work indicates possible processes that may
contribute to the higher prevalence of stress-related and mPFC-
compromised mental illnesses in women, and an understanding of
the mechanisms by which estrogen modulates the stress response
may lead to better-designed treatments for these diseases.

Expert commentary: implications for MDD treatment
The fact that the effects of estrogen can be both beneficial and
detrimental to an animal’s stress response certainly complicates
the question of how to approach antidepressant development, as
it is clear that the idea of estrogen being simply ‘good’ or ‘bad’
for women is unrealistic. Ideally, one would harness the protective
effects that estrogen has in the hippocampus and amygdala, while
inhibiting its actions in the mPFC, to most effectively prevent or
reverse the negative consequences of stress. Unfortunately, the
mechanisms by which these effects take place are currently only
crudely understood.

The most popular and commonly used antidepressants, selective
serotonin-reuptake inhibitors (SSRIs), function by blocking sero-
tonin transporters, thus enabling more of the neurotransmitter sero-
tonin to remain in the synapse. Estrogen has been shown to regulate
the expression of both serotonin transporters and receptors [16],
which may contribute to reports that women are more responsive
than men to both SSRI treatment [63] and tryptophan (a precursor
to serotonin) depletion [64]. In animal models, females have been
shown to have unique responses to various antidepressants: female
rats have a more pronounced increase in serotonin turnover after
administration of clomipramine, a tricyclic antidepressant [65],
and display a greater antidepressant response to transcranial magnetic
stimulation than males [66]. Finally, fluoxetine (a SSRI) has been
shown to be effective in reversing the effects of acute stress on
aversive learning in females, but not in males [67], again suggesting
distinct sex differences in response to antidepressants.

Unfortunately, none of these studies controlled for estrogen
levels and, thus, estrogen’s role in manifesting the sex differences
observed is not yet known. This is a crucial next step in our
progress toward developing better antidepressant treatments for
women. Since manipulating hormone levels in women of child-
bearing age presents a potential ethical dilemma, it is imperative
that we understand the downstream mechanisms of estrogen’s
effects so as to craft more nuanced interventions.
Estrogen, stress & the brain: unraveling gender discrepancies in MDD

Five-year view
For several decades, studies of stress effects in the brain were performed almost exclusively in males, for the simple reason that it was easier that way. Recently, however, more scientists are extending the breadth of their research to females as well and finding compelling evidence that not only do the sexes differ profoundly in their response to stress, but that ovarian hormones can mediate these differences. The field still has substantial ground to make up, however, a significant part of which can be covered in the next 5 years.

The groundwork has been laid. We now know that three brain regions relevant to MDD respond differently to stress in females compared with how they do in males and that these responses may be modulated by estrogen. Researchers will next ask how estrogen does this. What neurotransmitter systems does estrogen interact with to produce either stress-induced enhanced or impaired cognitive abilities? How do estrogen and stress work together with structural proteins to cause morphological changes? And, perhaps most importantly, what pharmacological manipulations can mimic the beneficial and protective effects of estrogen, but block the detrimental effects? Of course, not all of these questions can be conclusively answered in the next 5 years, nor will we probably have new, female-specific antidepressants on the market in that time period. However, the field is currently poised to make significant breakthroughs into furthering our understanding of estrogen–stress interactions and the neurobiology underlying women’s greater prevalence of MDD. Thus, the next 5 years should be remarkably fruitful.

Key issues
- Major depressive disorder is twice as prevalent in women as in men and can be brought on or worsened by exposure to stress.
- Sex can induce changes in memory, emotion and behavioral control, as well as in neuronal morphology.
- Sex differences in the stress response abound in the brain, with compelling evidence that estrogen might mediate these differences.
- Estrogen–stress interactions can produce adaptive or maladaptive effects, depending on the brain region being studied.
- Understanding the mechanisms by which estrogen modulates the stress response will be critical in developing better antidepressant treatments for women.

References
Perspective

Shansky


27 Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Arch. Gen. Psychiatry* 57(10), 925–935 (2000).


34 Bowman RE. Stress-induced changes in spatial memory are sexually differentiated and vary across the lifespan. *J. Neuroendocrinol.* 17(8), 526–535 (2005).

35 Mair RG, Burk JA, Porter MC. Lesions of the frontal cortex, hippocampus, and intralaminar thalamic nuclei have distinct effects on remembering in rats. *Behav. Neurosci.* 112(4), 772–792 (1998).


47 Toufexis DJ, Myers KM, Bowser ME, Davis M. Estrogen disrupts the inhibition of fear in female rats, possibly through the antagonistic effects of estrogen receptor α (ERα) and ERβ. *J. Neurosci.* 27(36), 9729–9735 (2007).


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Perspective

58 Arnsten AF. Catecholamine and second messenger influences on prefrontal cortical networks of "representational knowledge": a rational bridge between genetics and the symptoms of mental illness. *Cereb. Cortex* 17(Suppl. 1), i6–i15 (2007).


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