# Actions and interactions of estradiol and glucocorticoids in cognition and the brain: Implications for aging women.

Alexandra Ycaza Herrera[a]
Corresponding Author
[a]University of Southern California
3715 McClintock Ave
Los Angeles, Ca 90089
United States
Ycaza@usc.edu
213.821.5703

and

Mara Mather[a]
[a]University of Southern California
3715 McClintock Ave
Los Angeles, Ca 90089
United States
Mara.mather@usc.edu

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**Abstract**

YCAZA HERRERA, A. and M. Mather. Actions and interactions of estradiol and glucocorticoids in cognition and the brain: Implications for post-menopausal women. NEUROSCI BIOBEHAV REV XX(X) XXX-XXX, 2015. Menopause involves dramatic declines in estradiol production and levels. Importantly, estradiol and the class of stress hormones known as glucocorticoids exert countervailing effects throughout the body, with estradiol exerting positive effects on the brain and cognition, glucocorticoids exerting negative effects on the brain and cognition, and estradiol able to mitigate negative effects of glucocorticoids. Although the effects of these hormones in isolation have been extensively studied, the effects of estradiol on the stress response and the neuroprotection offered against glucocorticoid exposure in humans are less well known. Here we review evidence suggesting that estradiol-related protection against glucocorticoids mitigates stress-induced interference with cognitive processes. Animal and human research indicates that estradiol-related mitigation of glucocorticoid damage and interference is one benefit of estradiol supplementation during peri-menopause or soon after menopause. The evidence for estradiol-related protection against glucocorticoids suggests that maintaining estradiol levels in post-menopausal women could protect them from stress-induced declines in neural and cognitive integrity.

*Keywords*: Menopause; Glucocorticoids; Estradiol; Stress; Working Memory; Neurodegeneration; Neuroprotection; Hippocampus; Executive Function

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*Abbreviations*: Glucocorticoids (GC); Hypothalamic-Pituitary-Adrenal (HPA) Axis; Hypothalamic-Pituitary-Gonadal (HPG) Axis; 17β-Estradiol (E2); Trier Social Stress Test (TSST); Cold Pressor Task (CPT); Beta-Amyloid (Aβ); Ovariectomized (OVX); Women's Health Initiative (WHI); Women's Health Initiative Memory Study (WHIMS); Women's Health Initiative Study of Cognitive Aging (WHISCA); Functional Magnetic Resonance Imaging (fMRI); Adrenocorticotropic Hormone (ACTH); Dexamethasone (DEX); Corticotropin Releasing Hormone (CRH)

## 1. Introduction

Women's transition into reproductive senescence is marked by reductions in ovarian function and output, referred to as menopause (Rannevik et al., 1986). However, the dramatic declines in estradiol production and estradiol levels occurring during menopause (Rannevik et al., 1986) may alter more than just reproductive capability. The systems governing stress and fluctuations in female reproductive hormones and the primary hormones of each system (glucocorticoids and estradiol, respectively) intimately interact and influence one another. Thus, as one system changes, the nature of the interactions between them may also change.

Research on how glucocorticoids and estradiol affect the brain, body, and cognition spans a number of species, ranging from rodents to humans. However, how glucocorticoids (GC) and estradiol interact to change the effect and action of the other on the brain, body, and cognition in human females is less studied. Due to the dramatic change in the production and release of estradiol in human females with age, understanding whether and how these systems interact to affect women is of importance.

In addition to interacting, glucocorticoids and estradiol also exert opposing effects on various bodily systems, in males and females. For instance, development of metabolic syndrome (Pasquali et al., 2006; for review see, Rosmond, 2005), unhealthy alterations in fat distribution (Rebuffe-Scrive et al., 1992), promotion of hyperglycemia and hyperinsulinemia (McGuinness et al., 1993; Rebuffe-Scrive et al., 1992), promotion of bone resorption (O'Brien et al., 2004), and maintenance of bone degrading osteoclasts (Jia et al., 2006) have been associated with long-term GC exposure. In contrast, opposite patterns of less unhealthy fat distribution (Green et al., 2004; Musatov et al., 2007), lesser occurrence of hyperglycemia and hyperinsulinemia (Krotkiewski et

al., 1983; Musatov et al., 2007), and promotion and maintenance of bone mineral density (Delmas et al., 1997; Felson et al., 1993; Sowers et al., 1998), have been linked to estradiol, the primary estrogen in females (See Table 1).

Similar contrasting effects of GCs and estradiol occur in neural tissue and cognition, where chronic or extreme GC exposure leads to dendritic retraction, and neuropil and neuron damage or loss (Behl et al., 1997; Filipovic et al., 2013; Hillerer et al., 2013; MacPherson et al., 2005; Magarinos et al., 2011; Stein-Behrens et al., 1992; for review see, Tata and Anderson, 2010; see also, Tombaugh et al., 1992; Tynan et al., 2013; Tynan et al., 2010; Woolley et al., 1990b), and impairments in cognitive performance (Alexander et al., 2007; Duncko et al., 2009; Elzinga and Roelofs, 2005; Luethi et al., 2009; Oei et al., 2006; Schoofs et al., 2009; Young et al., 1999). In contrast, estradiol promotes neural growth and protection (Brinton et al., 2000; Chen et al., 2006; Gerstner et al., 2007; Hao, 2006; Saravia et al., 2007) and improvement of cognitive function (Baker et al., 2012; Krug et al., 2006; Shaywitz et al., 2003; Velázquez-Zamora et al., 2012; Wolf et al., 1999)[1].

Due to the fluctuations and eventual loss of estradiol throughout the adult lifespan of human females, it is important to understand the implications of the opposing effects of stress and estradiol on the brain and cognition. Much of the literature reviewed here will span from basic research findings to findings in human research, and explore patterns of these hormone effects in males and females. We will focus on the negative effects of stress on neural tissue and cognition in both males and females, and discuss whether the opposing effects of estradiol in the same domains may offer some protection against these effects. We propose that estradiol loss after menopause leaves

[1]GCs also are necessary for normal neuronal functioning (Nadeau and Rivest, 2003), and are beneficial for memory of emotional stimuli or events (e.g., Buchanan and Lovallo, 2001). Similarly, estradiol can damage already compromised neural tissue (Chen et al., 2006), and is associated with worse emotional memory (for review see, Sakaki and Mather, 2012).

women more vulnerable to developing dysfunctional stress responses and therefore, larger effects of stress on cognition. We also argue that the loss of estradiol in midlife leaves peri- and post-menopausal women more vulnerable to the negative effects of stress hormone exposure, accelerating age-related declines in neural and cognitive integrity.

## 2. Interactions of the stress and estradiol systems

### *2.1 The "Stress System"*

The hypothalamic-pituitary-adrenal (HPA) axis governs response to stressors. Emotional or physiological challenges cause the paraventricular nucleus of the hypothalamus to release corticotropin-releasing hormone. The portal system carries the neuropeptide to the anterior pituitary, causing release of andrenocorticotropic hormone. Andrenocorticotropic hormone travels via the bloodstream to the adrenal glands, causing release of GCs from the adrenal cortex (the outer layers of the adrenal gland) and the catecholamines epinephrine and norepinephrine from the adrenal medulla (for review see, Lupien et al., 2009). Due to our interest in the effects of GCs, and interactions between GCs and estradiol, we will focus on this portion of the stress response.

During the stress response, GCs assist in the fight-or-flight response by providing immediate energy to the body via assistance converting protein to glucose, fat to usable energy, and shunting blood flow from immediately nonessential systems, such as the gut, to skeletal muscles for energy. Cortisol, the primary GC in humans, also is responsible for terminating the HPA response to a stressor via negative feedback. Glucocorticoids initiate shutdown of the HPA response by exerting direct inhibition of the hypothalamus and pituitary gland, as well as recruiting additional brain regions, particularly the prefrontal cortex and hippocampus, to send inhibitory signals.

### *2.2 The "Estradiol System"*

Unlike the HPA axis, the hypothalamic-pituitary-gonadal (HPG) axis terminates at different targets for males and females, the testes or ovaries, respectively. Here we will focus on the female HPG axis, as we are concerned with estradiol levels pre and post menopause in women.

Like the HPA axis, the HPG axis originates in the hypothalamus. Several subnuclei, including the arcuate nucleus and preoptic area, contain neurons that produce and release gonadotropin-releasing hormone. The portal system delivers gonadotropin-releasing hormone to the anterior pituitary gland, initiating the release of luteinizing hormone and follicle stimulating hormone. Luteinizing hormone and follicle stimulating hormone then act on the ovaries to cause release of estrogens and progestins. Of the three major forms of estrogens (estrone, estradiol, and estriol), estradiol (E2) is the estrogen predominantly responsible for estrogenic effects observed in the brain (McClure et al., 2013; for review see, Purves et al., 2004).

Estrogens both stimulate and inhibit the HPG axis (for reviews see, Herbison, 1998; Jones, 2009). Throughout most of the monthly menstrual cycle, E2 inhibits release of luteinizing hormone and follicle stimulating hormone by decreasing the sensitivity of neurons regulating these hormones to the effects of gonadotropin releasing hormone. However, large increases in E2 lasting for 2 or more days, such as the increase observed just before ovulation, increases the sensitivity of neurons regulating luteinizing hormone and follicle stimulating hormone to the effects of gonadotropin releasing hormone, stimulating release of the two hormones. Reductions in E2 after this surge return gonadotropin-releasing hormone, luteinizing hormone, and follicle stimulating hormone to more common moderate-to-low levels (for review see, Jones, 2009).

### *2.3 Interactions of the Stress and Estradiol Systems*

It has long been known that the stress and E2 systems influence each other's function (e.g., Selye, 1939) and the complex interactions of these two systems span

beyond what is discussed in this brief section. For instance, there is a large literature examining how interactions between these systems likely affect the development of emotional pathologies, such as depression and post-traumatic stress disorder, predominately in women (for review see, Becker et al., 2007). Additionally, the interactions begin early in development (for reviews see, Dunn et al., 2011; Goel and Bale, 2009; see also, Mueller and Bale, 2007; Mueller and Bale, 2008) influencing the effects of stress throughout the lifespan. Although HPA and HPG interactions during development can alter stress responsiveness later in life, this review focuses on how normal age-related changes in stress-estradiol system interactions may affect women during and after the menopause transition.

One of the first interactions noted between the two systems was the ability of stress to interfere with normal reproductive function (Selye, 1939). Stress-induced interference of HPG function appears to rely on GCs (for review see, Breen and Karsch, 2006), which reduce sensitivity of the ovaries to luteinizing hormone, decrease aromatase activity in ovarian cells (Hsueh and Erickson, 1978), and block ovulation (for review see, Rivier and Rivest, 1991). Furthermore, HPA axis activation is capable of interfering with normal HPG axis activity at every level of the HPG axis, including the hypothalamus and pituitary (for review see, Tilbrook et al., 2000), and the ovaries (for review see, Tetsuka, 2007), where GCs can stop follicle maturation. How and at what level the HPA can disrupt normal HPG function depends on whether stress exposure is acute or chronic (for example, Gore et al., 2006).

On the other side of the interaction, E2 can both reduce and promote HPA function. The majority of circulating GC is often bound to corticosteroid binding globulin, making only 5-10% of the hormone available to enter and act on cells (Burke and Roulet, 1970). One way E2 reduces HPA function is by upregulating corticosteroid binding globulin which decreases exposure to released GCs (for review see, Brien, 1981). On

the other hand, E2 upregulates corticotropin releasing hormone expression in the hypothalamus (Seale et al., 2004a; Seale et al., 2004b), which could result in increased HPA function by stimulating release of the hormone that initiates the HPA response. The bi-directionality of HPA-HPG interactions makes it important to understand whether, and how, these interactions may change when one system is dramatically altered, such as when women go through the menopause transition where E2 levels rapidly and severely decrease.

## 3. Effects of Glucocorticoids and Estradiol on Cognitive Processes

The following sections review effects of GC on cognition and then contrast those with E2 effects on cognition.

### *3.1 Glucocorticoids can Facilitate and Impair Memory Processes*

Exposure to long-term or extreme stress can impair learning and memory. However, stress exposure does not always lead to cognitive impairment. Different factors contribute to whether stress will lead to impairment, such as the type of learning and memory being examined and the amount of stress applied. With regard to the amount of stress applied, effects of stress on learning and memory sometimes follow an inverted-U shaped curve, with too little or too much being related to poor performance and a moderate amount related to peak performance in a variety of tasks from shock avoidance to spatial learning and working memory (Mateo, 2008; Salehi et al., 2010; Yerkes and Dodson, 1908), an effect which also has been observed for measures of neural plasticity (Diamond et al., 1992). Further, what is considered an optimal amount of stress can shift depending on task difficulty (Anderson, 1994; Dodson, 1915; Salehi et al., 2010; for reiview see, Shors, 2004).

Stress can also be beneficial in learning about emotional stimuli. For instance, administration of hydrocortisone (Buchanan and Lovallo, 2001) and stress induction (Payne et al., 2007; Smeets et al., 2006) prior to encoding improved memory for

emotional stimuli while having no effect or even impairing memory for neutral stimuli. However, memory for emotional items is not impervious to stress. Stress applied before retrieval, rather than before encoding, impaired recall of emotional and neutral words (Kuhlmann et al., 2005). Thus, while stress is beneficial to learning and memory in some instances, there are still limitations to when stress can be beneficial, even in these situations.

*3.2 Glucocorticoids Impair Memory Processes in Animals*

With regard to instances of chronic or excessive stress, the animal and human literature is rife with reports of GC- or stress-induced cognitive impairment (for review see, Holmes and Wellman, 2009). In male rodents, eight weeks of daily corticosterone injections resulted in more working memory errors during a Y-maze task (spending equal amounts of time in a familiar and novel arm, instead of spending more time exploring the novel arm) compared with animals receiving a sesame oil control injection (Coburn-Litvak et al., 2003), while nine weeks of corticosterone treatment induced more working memory errors during a radial-arm-maze task (reentering already traversed arms; Arbel et al., 1994), and three weeks of daily corticosterone injections impaired male rodents' reference memory on another measure of working memory, the Barnes maze (Coburn-Litvak et al., 2003).

Similar to effects of exogenous GC administration, cognitive impairments also are observed in animals repeatedly exposed to psychological and physical stressors. For instance, male rats exposed to a cat for six hours then housed with different combinations of 3-4 rats daily over a course of five weeks showed impaired working memory on a radial arm water maze (Park et al., 2001). Males exposed to an unfamiliar environment during a testing delay period for twenty-one days made more working memory errors in a radial arm maze compared with animals housed in their home cages during the delay period (Diamond et al., 1996). Likewise, male rats exposed to restraint

stress for 6 hours/day for 21 days exhibited worse working memory in a Y-maze (Kleen et al., 2006), compared with rats not exposed to restraint stress, with similar results observed in animals trained on a delayed alternation task in a T-maze (Lee and Goto, 2015; See Table 2 for effects of working memory). Shorter stress exposures also can induce cognitive impairments in animals. Four weeks of unpredictable stress resulted in impaired acquisition, working, and reference memory of a modified Morris water maze task and impaired reversal learning in male rodents. The study also found that shorter regimens of six days of unpredictable stress negatively impacted reference memory and reversal learning, while three days of unpredictable stress induced deficits in reference memory on the task (Cerqueira et al., 2007). Similarly, corticosterone administration a mere thirty minutes prior to testing resulted in impaired performance on a delayed alternation task in T-maze in male rodents (Roozendaal, 2004), while fifteen minutes of tail pinch stress increased error rates during a delayed win-shift task in a radial arm maze, an effect blocked in animals given a GC antagonist (Butts et al., 2011).

Interestingly, depending on the type of memory under investigation, these effects of stress on cognition appear more consistently in male animals than female animals (Beck and Luine, 2002; for review see, Beck and Luine, 2010; see also, Bowman, 2003; Bowman et al., 2009; for review see, Luine, 2002). Despite female rodents showing larger HPA responses to a stressor compared with males, E2 may be a possible protective agent in the face of chronic stress, as female animals[2] habituate to chronic stressors sooner than do males (Bowman, 2003; Bowman et al., 2002; Bowman et al., 2009).

*3.3 Glucocorticoids Impair Working Memory and Executive Function in Humans*

[2] "Female animals" here refers to intact females. In many studies, female animals are ovariectomized (ovaries removed) in order to halt endogenous production of sex hormones and allow for experimenters to control levels of ovarian hormones, such as estradiol. If female animals remain intact, then they are still endogenously producing sex hormones, such as estradiol.

Although much of the animal literature focuses on the effects of chronic GC or stress exposure on cognitive processes, most laboratory research with humans focuses on the effects of *acute* stress on cognitive function. Nevertheless, the impairing effects observed in animals also are seen with acute pharmacological, psychological, and physical stress administration in humans. For instance, men treated with acute intravenous (Young et al., 1999) and chronic oral (Lupien et al., 1999) hydrocortisone showed greater working memory errors during a visuospatial sketchpad task (Young et al., 1999) and the Sternberg item recognition task (Lupien et al., 1999), as well as higher error rates in a paired associates task (Young et al., 1999).

With respect to laboratory stressors, one frequently used acute psychological stressor is the Trier Social Stress Test (TSST). The TSST reliably elevates participants' cortisol levels by requiring them to give a speech and perform mental arithmetic in front of an audience (Elzinga and Roelofs, 2005; Oei et al., 2006; Schoofs et al., 2008; Wolf et al., 2009). Completing the TSST resulted in increased reaction times and impairments on tests of working memory given 10-45 minutes later, such as the reading span task (Luethi et al., 2009), the Sternberg item recognition task (Oei et al., 2006), and the N-back task (Schoofs et al., 2008) in men, and the digit span task (Elzinga and Roelofs, 2005) in men and women. The TSST also impairs performance on tests of executive function, or cognitive flexibility. When tested during execution of the social stressor, men and women made fewer correct responses during the compound remote associates test and exhibited increased latencies to complete anagrams (Alexander et al., 2007), and men exhibited impaired performance on a go no-go task (Scholz et al., 2009). Impaired performance on a mental arithmetic task was also impaired in men exhibiting the highest cortisol responses during the task or after a giving a surprise speech (Al'Absi et al., 2002; See Table 3 for effects on executive function and other cognitive processes).

Another commonly employed acute laboratory stressor is the cold pressor task (CPT). The CPT is a physical stressor that reliably induces a stress response by requiring participants to hold one of their hands in ice water (Bullinger et al., 1984; Edelson and Robertson, 1986; Lighthall et al., 2009; Lighthall et al., 2011; Mather et al., 2010). Like the TSST, men showed impaired performance on working memory measures such as the operation span task and digit span backward (Schoofs et al., 2009), while a sample of men and women displayed impairment on the Sternberg item recognition task (Duncko et al., 2009) following exposure to the CPT.

The ecological validity of laboratory studies is difficult to assess, however, some work indicates that stressors encountered outside of the laboratory can interfere with cognition in both sexes. For instance, a meta-analysis revealed that intermediate intensity exercise resulted in declines in a range of working memory tasks (McMorris et al., 2011). In other examples, attention-shifting was impaired in students preparing for a major academic exam, and those students' reports of chronic stress on the Perceived Stress Scale predicted their performance on the attention-shift task (Liston et al., 2009). Those experiencing anticipatory stress after being told they would need to give a surprise speech exhibited impaired decision making on the game of dice task (Starcke et al., 2008), while another cohort with high perceived chronic stress also showed poorer working memory than those rating lower perceived chronic stress (Öhman et al., 2007). Even within a population of patients suffering from unipolar major depression, morning cortisol levels were negatively correlated with performance on the Wisconsin Card Sorting Task, a measure of executive function (Egeland et al., 2005).

In sum, pharmacological, physical, psychological, and non-laboratory stressors can interfere with normal, or optimal, cognitive function in animal models and humans. In particular, the evidence suggests that chronic or excessive GC levels impair cognition in tasks requiring executive resources, such as working memory.

*3.4 Estradiol can Facilitate and Impair Memory Processes*

Just as seen with GCs, E2 can exert both negative and positive effects on cognitive function. This dichotomy is highlighted in reports of E2 treatment on cognition in post-menopausal women, with some reporting negative effects (Espeland et al., 2004; Mulnard et al., 2000; Rapp et al., 2003; Resnick et al., 2006; Shumaker et al., 2003) and others reporting benefits (Baker et al., 2012; Duff and Hampson, 2000; Maki et al., 2001; Miller et al., 2002; Smith et al., 2001; Wolf and Kirschbaum, 2002; Wolf et al., 1999), which receive support from basic science reports of estrogenic fortification of the central nervous system (Brinton et al., 2000; Chen et al., 2006; Hosoda et al., 2001; Pike, 1999). To reconcile these mixed reports, Brinton (2005) proposed a healthy cell bias of estrogen action, stating that E2 would be advantageous to a population of healthy cells, but detrimental to a population of declining or already injured cells. To test this hypothesis, Brinton and colleagues compared treatment and prevention models *in vitro*. In treatment models, E2 is applied to neurons either at the time of, or after, application of the deleterious agent (e.g. beta-amyloid; Aβ), whereas prevention models pretreat cells with E2 *before* exposure to the agent. Consistent with the hypothesis, neurons *pretreated* with E2 prior to Aβ protein exposure showed significantly less cell damage and death compared with cultures exposed to Aβ alone. Whereas neurons simultaneously treated with E2 and Aβ protein did not receive any estrogenic protection, nor did neurons exposed to the toxic protein for 1 to 2 days prior to E2 exposure. However, introduction of E2 to the cultures after 5 days of Aβ exposure resulted in greater cell death than the Aβ-alone cultures (Chen et al., 2006). This pattern suggests

that the reports of negative estrogenic effects may be related to the sample population selected; particularly in studies with women many years past menopause (Espeland et al., 2004; Rapp et al., 2003; Resnick et al., 2006; Shumaker et al., 2003), and those using women with documented neural decline (Mulnard et al., 2000)[3].

*3.5 Estradiol Facilitates Memory Processes in Animals*

In contrast to these negative reports of E2 on cognition, E2 often facilitates learning and memory in animals. Ovariectomized (OVX) female animals made fewer working memory errors during a radial arm maze if treated with E2 after OVX compared with OVX females not treated with E2 (Bimonte and Denenberg, 1999; Daniel et al., 1997; Fader et al., 1999). Likewise, females receiving only a sham surgery (ovaries left intact and therefore still producing E2) exhibited a greater number of consecutive correct choices on a radial arm maze, compared with OVX-alone females (Wilson et al., 1999; See Table 2 for effects on working memory).

Benefits of E2 also have been observed in other tasks. Compared with OVX-alone females, ovariectomized animals treated with estradiol benzoate displayed better retention for the location of a hidden platform in a delayed match-to-place task across 10-, 30-, and 100-minute delay intervals (Sandstrom and Williams, 2001). Likewise, E2 treated animals also required less time to reach learning criteria of a delayed-match-to-position task than OVX-alone animals (Gibbs, 1999). The same pattern was observed in an object recognition task. This version of the object recognition task exposed animals to a total of 4 novel objects. Animals were first allowed to explore a pair of 2 novel objects, after some delay they were exposed to another 2 objects (one object from pair #1 and

[3] Negative effects of E2 also have been reported in younger adult women, where E2 levels are negatively associated with memory for emotional items. Attempting to explain this negative association, Sakaki and Mather (2012) proposed that the reported decreased neural activation of the amygdala during *high* E2 phases of the menstrual cycle, relative to low E2 phases (Goldstein et al., 2010; Goldstein et al., 2005), is responsible for the negative relationship between E2 levels and emotional memory.

the third novel object); after a second delay period the animals were exposed to 2 additional objects (one being the second object from pair #1 and the fourth novel object). The animal is said to recognize an object if it spends less time exploring that object compared with time spent exploring the novel object. Ovariectomy followed by 21 days of E2 treatment enhanced retention for the first-tested object after a 3-hour delay and of the second-tested object after a 6-hour delay, compared with non-E2 treated mice (Vaucher et al., 2002; See Table 3 for effects on other cognitive processes).

### *3.6 Estradiol Facilitates Working Memory and Executive Function in Peri- and Post-Menopausal Women*

Akin to the animal studies comparing performance between OVX and OVX + E2 females, the largest effects of E2 are observed in post-menopausal women taking some form of E2 replacement as they no longer produce E2 at the same levels as younger women.

Few studies have examined the cognitive effects of naturally declining E2 levels during menopause in the absence of hormone replacement. In one such study, women within five years of menopause and beyond five years of menopause did not differ on measures of sustained attention, category generation, or episodic memory. However, higher E2 levels in women within five years of menopause were associated with better performance in measures of mental flexibility and planning (i.e., executive function) compared with the steady low E2 levels in the women beyond five years of menopause (Elsabagh et al., 2007), an effect maintained after controlling for age and IQ of women within and beyond 5 years of menopause. Endogenous levels of E2 in postmenopausal women not taking hormone supplements also were positively correlated with performance on the Stroop task, another measure of executive function (Wolf and Kirschbaum, 2002; See Table 3 for effects on executive functions).

When women received 2 weeks of transdermal E2 treatment, those experiencing higher endogenous E2 levels in response to the dosage performed better on the delayed recall portion of a verbal memory test than women experiencing lower dose-induced endogenous E2 levels (Wolf et al., 1999). Women randomly assigned to transdermal hormone replacement experienced improved performance on the Stroop task, spatial working memory (Baker et al., 2012; Krug et al., 2006), digit ordering (Krug et al., 2006), and delayed recall (Baker et al., 2012). Similarly, women already using hormone replacement also made fewer errors on non-spatial working memory (sequential memory of an unfamiliar story, digit ordering and digit span backward) and spatial working memory tasks (Duff and Hampson, 2000), performed better on measures of verbal fluency and working memory (Miller et al., 2002), and displayed better performance on a non-verbal memory task (Smith et al., 2001) compared with women not taking any hormone supplements (See Table 2 for effects on working memory).

However, there also are reports of no effect (Maki et al., 2001; Pefanco et al., 2007; Smith et al., 2001; Yaffe et al., 2006), or negative effects of various E2 supplementation regimens (Espeland et al., 2004; Mulnard et al., 2000; Rapp et al., 2003; Resnick et al., 2006; Shumaker et al., 2003). The tasks in these studies assessed similar cognitive domains as the executive tasks discussed above which benefited from E2 treatment, as well as tasks not involving executive function, such as attention and short-term episodic memory (e.g., Newhouse et al., 2010). The most widely reported negative findings come from the Women's Health Initiative (WHI) studies. At the time of inception, the Women's Health Initiative Memory Study (WHIMS) and Women's Health Initiative Study of Cognitive Aging (WHISCA) were the largest randomized studies testing claims that post-menopausal hormone treatment maintained cognitive function otherwise observed to decline after menopause. However, the WHIMS and WHISCA studies found that conjugated equine estrogens negatively affected performance on

various cognitive measures, such as the California Verbal Learning Test (a measure of verbal retention and recall; Resnick et al., 2006) and the Modified Mini Mental State Exam (a measure of global cognitive function; Espeland et al., 2004; Rapp et al., 2003), as well as increasing the risk of developing dementia (Shumaker et al., 2003). The Alzheimer's Disease Cooperative Study, a randomized, double-blind, placebo-controlled, clinical trial, found similar negative effects of E2 treatment, reporting a faster progression of Alzheimer's in older women with preexisting mild to moderate Alzheimer's disease who were on E2 supplementation (Mulnard et al., 2000).

One key difference between the results of the Alzheimer's Disease Cooperative Study and WHI studies and the positive effects reported above is that, on average, the women reported to experience positive effects began treatment closer to the age of menopause than the women in the Alzheimer's Disease Cooperative Study and WHI studies. For example, E2-associated enhancements in working memory were observed in women who began hormone treatment during peri-menopause or soon after menopause (Duff and Hampson, 2000); those showing benefits in semantic fluency, attention, and working memory were on average 63 years old but had been using E2 supplements for an average of 12 years (Miller et al., 2002), and those displaying better performance on a non-verbal memory task initiated E2 replacement within two years of menopause (Smith et al., 2001).

The above-described findings of E2-induced cognitive impairment were also surprising based on basic science reports of E2-related protection of the central nervous system (Brinton et al., 2000; Chen et al., 2006; Hosoda et al., 2001; Pike, 1999). Together with the proposal for a critical window for E2 treatment initiation (for review see, Maki, 2013; see also, Resnick and Henderson, 2002), Brinton's (2005) healthy-cell bias of E2 action (described above) can account for the disparity between basic science experiments and human studies. Findings that introduction of E2 after 5 days of Aβ

exposure exacerbates Aβ-induced damage (Chen et al., 2006) suggest that E2 treatment would exacerbate existing damage in the neural tissue of participants in both studies, particularly in those women with preexisting Alzheimer's disease, presumably leading to declines in cognitive capacity.

**4. Glucocorticoids and Estradiol Differentially Affect Neuronal Viability and Action**

Consistent with the pattern discussed for cognition, exposure to GCs, either via direct administration or stress exposure, typically results in negative effects such as cell damage or death (Behl et al., 1997; Gerlach and McEwen, 1972; MacPherson et al., 2005; McEwen et al., 1968; Stein-Behrens et al., 1992; Tombaugh et al., 1992; Tynan et al., 2010; Woolley et al., 1990b) whereas E2 exposure results in positive effects such as cell growth and protection (Brinton et al., 2000; Chen et al., 2006; Gerstner et al., 2007; Hao et al., 2007; Saravia et al., 2007; See Table 3)[4]. The following sections review these effects of GC on neuronal viability and action, and then contrast those with the effects of E2.

*4.1 Glucocorticoids Damage Neurons in the Hippocampus and Prefrontal Cortex of Animals*

The hippocampus and prefrontal cortex are the neural regions most sensitive to the deleterious effects of GCs and stress, as might be expected based on the effects of GCs on cognition and these regions' involvement in short-term memory (Alonso et al., 2002; Cabeza et al., 2002), long-term memory (Alonso et al., 2002), and working memory (Cabeza et al., 2002; Curtis and D'Esposito, 2003; for review see, Laroche et al., 2000).

[4] Although chronic or excessive GC exposure is detrimental, it must be noted that GCs are necessary and even beneficial for neuronal proliferation and function when present in basal physiological levels or administered in low doses (Anacker et al., 2012; for review see, de Kloet et al., 1999; see also, Nadeau and Rivest, 2003).

The hippocampus contains a high concentration of GC receptors (Gerlach and McEwen, 1972; McEwen et al., 1968) and is thus highly sensitive to the negative effects of GCs. Exposing the hippocampus to GCs exacerbates damage induced by other neuronal insults, such as Aβ and glutamate (Behl, 1998; for reviews see, Sapolsky, 1990; Sapolsky, 1999, 2000). For example, exposure of embryonic hippocampal neuron cultures to Aβ or glutamate experienced greater rates of cell death if pretreated with dexamethasone (a synthetic GC) or corticosterone (the primary GC in rodents) for 24 hours than cultures not pretreated with GC (Behl et al., 1997). Fetal hippocampal cultures preexposed to corticosterone followed by exposure to hypoxic or hypoglycemic environments (Tombaugh et al., 1992) and adult males preexposed to corticosterone followed by kainic acid exposure (Stein-Behrens et al., 1992) also experienced exacerbated damage (See Table 4 for effects on neuronal survival in concert with other insults).

In addition to exacerbating damage by other insults, GC exposure alone, induced via chronic or severe acute stress exposure, has been shown to upregulate pro-inflammatory cytokines throughout the brain and damage hippocampal neurons. Although normal circulating GC levels have inherently protective anti-inflammatory effects (for reviews see, Chrousos, 2009; Elenkov and Chrousos, 2002; see also, Nadeau and Rivest, 2003), male rats exposed to either severe acute stress (inescapable tail- or foot-shock) or chronic stress (restraint) exhibited increased expression of pro-inflammatory immune-response cytokines such as interleukin-1H (Blandino Jr et al., 2006), interleukin-1β (O'Connor et al., 2003) and activated microglia (Tynan et al., 2010), throughout various brain regions. Increases in microglial markers in response to this type of chronic GC exposure indicate increased inflammation to stressors as part of an immune response (Frank et al., 2007).

Chronic GC and stress exposure also affect neuronal morphology and function in the brain. The hippocampal CA3 region appears particularly susceptible. Male rats experience decreased dendrite length and branch points after twenty-one days of corticosterone injections (Woolley et al., 1990b) and apoptosis and cell damage after dexamethasone administration (Haynes et al., 2003). Male and OVX female rats also experience decreased apical dendrite length and branch points in the region after three weeks of daily restraint stress (Galea et al., 1997; McLaughlin et al., 2010; Watanabe et al., 1992), and male vervet monkeys exposed to chronic social stress exhibited fewer CA3 hippocampal pyramidal cells plus atrophy of dendritic branches of the surviving cells compared with non-stressed cohorts (Uno et al., 1989; See Table 5 for effects on brain tissue).

The same effects have been observed in other regions such as the striatum (Haynes et al., 2003) and layers II and III of the prefrontal cortex (Brown et al., 2005; Cook and Wellman, 2004; Wellman, 2001), where repeated acute and chronic restraint stress decreased apical dendrite branch number and length in male rats. Male rats also displayed decreased volume of layers I and II of medial prefrontal cortex after chronic unpredictable stress, presumably a result of dendritic retraction (Cerqueira et al., 2007). This effect on prefrontal cortical tissue is at least partially a result of GC action, as infusion of the GC receptor agonist RU 28362 into the region interfered with T-maze performance similarly to systemic injection of corticosterone in male rodents (Roozendaal, 2004), but infusion of the GC receptor antagonist RU 38486 into the region blocked stress-induced cognitive interference during a delayed win-shift task in males (Butts et al., 2011). That the medial prefrontal cortex displays the same degree of restructuring after repeated acute stress and not just chronic stress, suggests that this region is highly sensitive to stressful events (for review see, Holmes and Wellman, 2009) and perhaps even more sensitive than the hippocampus. Greater sensitivity of the

prefrontal cortex may explain why cognition related to executive function appears to be more sensitive to the effects of stress or stress hormone exposure than other types of cognition, and why acute stressors in the laboratory can successfully interfere with these cognitive processes in humans.

*4.2 Glucocorticoids and Stress Affect Brain Activity in Humans*

Just as GC and stress can alter neural processes in animals, neuroimaging work in humans also indicates that pharmacological induction of stress and exposure to acute stressors results in marked alterations of brain activity in the aforementioned regions. Typically, men and women activate the dorsolateral and ventrolateral prefrontal cortex during working memory tasks (Cabeza et al., 2002; Owen et al., 2005; Porcelli et al., 2008; Qin et al., 2009). The hippocampus, on the other hand, is significantly co-activated with the default mode network (Greicius et al., 2004), a network of regions active during internally focused tasks that deactivates during tasks requiring external focus, such as working memory tasks (Esposito et al., 2006; Qin et al., 2009). In line with its relation to the default mode network, men experiencing deactivation of the hippocampus during a working memory task exhibited enhanced working memory performance (Cousijn et al., 2012). However, administration of hydrocortisone results in attenuated activation in ventrolateral prefrontal cortex and attenuated deactivation in the hippocampus during performance of a high-cognitive-load n-back task in men and women (Symonds et al., 2012). Similarly, women who viewed aversive video clips prior to performing an n-back task experienced attenuated activation of the dorsolateral prefrontal cortex and attenuated deactivation of the hippocampus during performance of the working memory task (Qin et al., 2009; See Table 6 for effects on brain activation).

These studies show that GC exposure alters brain activity in prefrontal cortex and hippocampal regions during working memory tasks, indicating that GC impairs executive control mechanisms critical for maintaining and accessing information in

memory via altering brain activation patterns observed in non-stressful situations. Taken further, the results in animals suggests that prolonged exposure to stress may result in more than just altered brain activation, but to more long-lasting consequences such as neural damage.

*4.3 Estradiol Protects Neurons in the Hippocampus and Prefrontal Cortex of Animals*

Although E2 can increase tissue vulnerability to a population of already damaged cells, in the absence of preexisting toxicity and damage E2 promotes neurogenesis and is neuroprotective. For instance, fetal primary hippocampal neurons exposed to conjugated-equine estrogens (Brinton et al., 2000) or E2 (Chen et al., 2006) showed increased number, and length, of neurites, as well as increased secondary branching and branch length when compared with cultures free of any estrogenic compounds (See Table 4 for effects on neuronal survival in concert with other insults).

E2 also promotes neurogenesis in mature animals (See Table 5 for effects on neuronal morphology). E2 treatment increased cell proliferation and decreased cell death in the dentate gyrus region of the hippocampus of middle-aged male mice (Saravia et al., 2007), essentially slowing down the rate of age-related declines in cell proliferation of this hippocampal region. Estrogenic promotion of cell proliferation in the hippocampus could aid in the maintenance of hippocampal-dependent learning and memory processes. For instance, in adult animals mature granule cells appear to only respond to specific stimuli or stimuli ranges, while new granule cells have a lower threshold for response to a wider range of stimuli (Marin-Burgin et al., 2012) possibly allowing them to better form new connections as learning occurs.

In addition to promoting neurogenesis and maintaining neural integrity, E2 also is neuroprotective. *In vitro* studies find that pretreatment of hippocampal fetal neurons with either E2 (Chen et al., 2006) or conjugated-equine estrogens (Brinton et al., 2000) blocked the neurodegeneration caused by Aβ exposure, decreased the degree of

apoptosis, and attenuated the Aβ-induced decrease in ATP levels. Similar estrogenic protection has been reported against hydrogen peroxide challenge and glutamate excitotoxicity (Brinton et al., 2000). Estradiol also protects oligodendrocytes, the glial cells responsible for myelinating axons within the central nervous system, from hyperoxic insults in rat pups, suggesting E2 can act as a line of defense against insults threatening proper myelination during development (Gerstner et al., 2007).

*In vivo* studies report similar patterns of neuroprotection by E2 in hippocampus and entorhinal cortex, as well as neurogenesis in prefrontal cortex. Estradiol pretreatment blocked the marked dose-dependent neuron loss in the entorhinal cortex and hippocampus induced by kainic acid in OVX-alone females (Hoffman et al., 2003). In males, intracerebroventricular injection of E2 ten minutes prior to quinolinic acid injection protected the CA1 region of the hippocampus (Kuroki et al., 2001). Estradiol pretreatment also protected male mice from the stereotypical motor deficits accompanying methylmercury exposure and reduced the amount of lipid peroxidation in the cerebellum (Malagutti et al., 2009), suggested to be a result of E2's protection of the antioxidant glutathione (Malagutti et al., 2009). Estradiol may also protect the brain from age-related declines; ovariectomy followed by cyclic E2 replacement increased dendrite spine density in layer III of dorsolateral prefrontal cortex in young-adult female rhesus monkeys and restored density in aged female monkeys, compared with female rhesus monkeys not treated with E2 (Hao et al., 2007).

These findings indicate that E2 protects the brain via at least 3 mechanisms: 1) regulation of excitatory ion influx, 2) antioxidant systems, and 3) maintaining proper energy metabolism despite facing trauma. Furthermore, E2 appears to make use of various sub-mechanisms in modulating these protective effects. Molecular mechanisms of E2 protection include 1) upregulation of extra-cellular signal-regulated kinase (ERK) phosphorylation in the face of quinolinic acid exposure, as blockade of E2-induced

upregulation of ERK phosphorylation made E2 ineffective at inhibiting quinolinic acid damage (Kuroki et al., 2001), 2) E2 reduction of oxidative stress and maintenance of respiratory capacity of mitochondria faced with various mitochondrial-specific toxins (Yao et al., 2011), and 3) blockade of glutamate-induced and hydrogen peroxide-induced cell loss by increasing nitric oxide synthesis (Andozia et al., 2010; Mannella et al., 2009).

Other ways E2 limits excitotoxicity include 1) enhancing the transport of extra-cellular lactate into neurons in the face of glutamate challenge (Mendelowitsch et al., 2001), 2) blockade of NMDA-induced rises of calcium influx via direct (versus genomic) inhibition of NMDA receptors (Weaver Jr et al., 1997), 3) reductions in hydrogen peroxide- and glutamate-induced cell death (Singer et al., 1998; Zhao et al., 2004) and cerebral ischemia-induced cell death (Dubal et al., 1999) via upregulation of the anti-apoptotic protein bcl-2, 4) protection against A$\beta$ exposure associated with upregulation of another anti-apoptotic protein from the bcl family, bcl-$x_L$ (Pike, 1999), 5) blockade of glutamate-induced and A$\beta$-induced cell damage by increasing the tolerance of mitochondria to calcium and lengthening the time of mitochondrial tolerance through upregulation of bcl-2 (Nilsen and Brinton, 2003; Nilsen et al., 2006), and 6) blockade of glutamate-induced cell death via inhibition of the excitotoxic levels of calcium influx associated with exposure to high levels of glutamate (Andozia et al., 2010; Mannella et al., 2009; Nilsen et al., 2002).

*4.4 Estradiol Affects Brain Structure and Activity in Humans*

Women exhibit natural fluctuations of circulating E2 levels during the monthly menstrual cycle, and dramatic decreases in E2 levels during menopause. Notably, E2 is produced not only in the reproductive tract but also in various brain regions, including the hippocampus (Mukai et al., 2006)[5]. This begs the question of whether and how brain

[5] One source of local E2 production in the brain is aromatization of testosterone to estradiol (Simpson, 2003; Simpson, 2002).

levels of E2 relate to levels circulating elsewhere in the body. Rodents either left intact or gonadectomized followed by E2 replacement or vehicle showed treatment-dependent levels of E2 in the hippocampus (Barker and Galea, 2009), suggesting that local production of E2 in the hippocampus is influenced by circulating levels of the hormone. In addition, there is intriguing initial evidence that hippocampal volume fluctuates along with E2 levels during the menstrual cycle (Protopopescu et al., 2008). In this study, women showed greater gray matter volume in the right anterior hippocampus (overlapping with anterior parahippocampal gyrus) during the high E2, low progesterone, late follicular phase (10-12 day after the onset of menses) than during in the high progesterone, low E2, late luteal phase (1-5 days before the onset of menses; See Table 5 for effects on neuronal morphology).

Given that hippocampal dendrite spine density (Gould et al., 1990; Woolley et al., 1990a; Woolley and McEwen, 1993) and synapse density (Woolley and McEwen, 1992) are modulated by E2 levels, as a function of NMDA receptor activation (Woolley and McEwen, 1994), E2 should be able to modulate the ability of the hippocampus to exhibit long-term potentiation during these different E2 phases. However, this may be disrupted in post-menopausal women, who no longer produce significant levels of E2. Evidence that E2 level within the hippocampus is influenced by circulating E2 levels in the body (Barker and Galea, 2009) suggests that post-menopausal women may produce less E2 in the hippocampus as a result of decreased circulating levels of E2[6]. Coupled with evidence for E2-related hippocampal neuroprotection, loss of E2 after menopause may make the hippocampus more vulnerable to degeneration. Thus, application of E2 close to the time of menopause may help maintain E2 production in the hippocampus, thereby prolonging the integrity of the structure and aiding in maintenance of cognitive function.

[6] Prior to menopause, both circulating levels and local production via aromatization should influence local levels of E2 in women's brains. The loss of one source of E2 after menopause might then result in lower levels of the hormone in the brain as only one source of E2 remains.

Neuroimaging studies in human females support the basic science findings of estrogenic neuroprotection (for review see, Smith and Zubieta, 2001). In a structural magnetic resonance imaging study, post-menopausal women using unopposed E2 for 20+ years experienced less ventricular enlargement and white matter loss than women who did not use E2 (Ha et al., 2007), possibly partially resulting from the estrogenic protection of oligodendrocytes and subsequent promotion of myelination observed in developmental animal models (Gerstner et al., 2007).

Functional magnetic resonance imaging (fMRI) studies have also reported greater activity in regions associated with the specific tasks being tested (See Table 6 for effects on brain activation). Women who began combination E2/progestin treatment during peri-menopause performed better on a verbal recognition task, which was associated with greater activation in the hippocampus compared with nonusers (Maki et al., 2011). Ten years of uninterrupted combination hormone treatment, initiated within two years of menopause, also was associated with greater frontal cortex and hippocampal activation during a visual working memory task performed during an fMRI scan, which positively correlated with performance on the task, compared with never-users (Berent-Spillson et al., 2010).

Other post-menopausal women following the same treatment guidelines as in Berent-Spillson et al. (2010) exhibited higher cholinergic activity in the hippocampus and posterior cingulate at rest, compared with never-users (Smith et al., 2011). Maintenance of cholinergic activity has important implications for cognitive preservation since the neurotransmitter is intimately involved in attention, learning and memory (for reviews see, Klinkenberg et al., 2011; Micheau and Marighetto, 2011).

Although reintroduction of E2 after onset of Alzheimer's disease can exacerbate symptoms, early initiation of hormone treatment might protect carriers of the ApoE-e4 allele, an allele associated with greater risk for Alzheimer's, from developing the disease.

E2 use in post-menopausal women, both with and without the ApoE-e4 allele, prevented declines in glucose metabolism in the posterior cingulate (Rasgon et al., 2005), an area associated with early declines in metabolic function for those with preclinical Alzheimer's disease (Minoshima et al., 1997), relative to carriers and non-carriers of the e4 allele not on an E2 regimen.

**5. Interactions between Estradiol and Glucocorticoids in Neurons and the Stress Response**

Thus far we have reviewed findings from cell-, animal-, and human-based research in order to understand how E2 and GCs affect neuronal integrity and function, as well as cognition. In this section we will discuss how E2 may modulate the effect of GC in the brain and stress response. However, it should be noted that the physiological response to stress differs between female rodents and women. For instance, female rodents display larger GC responses to stressors than males (for review see, Handa et al., 1994; see also, McCormick et al., 2002; Seale et al., 2004a; Seale et al., 2004b; Suzuki et al., 2001), attributed to a combination of excitatory actions of estradiol on the stress response system in females (Burgess and Handa, 1992; Suzuki et al., 2001; Weiser and Handa, 2009) and inhibitory actions of testosterone on the stress response system in males (Bingaman et al., 1994; Suzuki et al., 2001), while women tend to display smaller GC responses than men (Dixon et al., 2004; Kirschbaum et al., 1999; Kirschbaum et al., 1992; Kudielka et al., 2004; Kudielka et al., 1998; Kudielka and Kirschbaum, 2005). The contradicting GC response profiles of rodents and humans limits the translational generalization of stress response profiles and suggests the way in which the two systems interact to affect cognition may differ across species. Thus, discussion of E2 influences on the stress response, and implications for peri- and post-menopausal women, will be limited to studies with humans. However, we will begin with

a review of cell and animal research examining how E2 and GCs interact to change the effect of one another on neurons.

*5.1 Estradiol Offers Protection Against Glucocorticoid Damage*

In isolation, E2 exerts protective effects in the same regions where GCs are damaging; furthermore, E2 can directly protect neural tissue from the damaging effects of GC exposure in male and female rodents (See Table 7). Males pretreated with E2 prior to dexamethasone administration exhibited attenuated apoptosis and cell damage in the striatum and hippocampus than those not receiving pretreatment (Haynes et al., 2003). Males also experienced hippocampal protection and possible protection of learning and memory processes from stress such that hippocampal slices from males exposed to a stressor prior to termination displayed greater long-term potentiation when bathed in a medium containing E2 than slices bathed in a control solution of artificial cerebrospinal fluid (Foy et al., 2008). Similar protective trends were seen in intact females compared with intact males exposed to chronic restraint stress. Despite exhibiting higher corticosterone responses to the stressor and less success at habituation, stressed females experienced less neuronal damage in the CA3 region of the hippocampus than males. Stressed females experienced loss of basal branch points, but not branch length, while stressed males experienced a significant loss of both apical branch points and length, compared with control animals (Galea et al., 1997). In OVX females, chronic restraint stress decreased cell number (Takuma et al., 2007) and apical dendrite complexity (McLaughlin et al., 2010) in the CA3 region of the hippocampus and layers II and III of the medial prefrontal cortex (Garrett and Wellman, 2009), effects prevented by E2 replacement after OVX (Garrett and Wellman, 2009; McLaughlin et al., 2010; Takuma et al., 2007).

One mechanism of action for the estrogenic neuroprotection against GC exposure may be the ability of E2 to regulate GC receptor concentration. Typically,

chronic stress or stress hormone administration results in downregulation of GC receptors (Ferrini et al., 1995; Herman et al., 1989; Sapolsky et al., 1984; for review see, Seckl and Olsson, 1995). The resulting reduction of receptors leads to an inability to accurately detect GC levels, hindering the ability of the HPA axis to shut down the stress response (Sapolsky et al., 1986). E2 administration, however, upregulates GC receptors both in the absence of stress (Ferrini and De Nicola, 1991), and in the face of chronic corticosterone administration (Ferrini et al., 1995). Estrogenic upregulation of GC receptors should allow the brain to better detect lower levels of GC, making the HPA axis more responsive, thereby leading to more rapid discontinuation of the stress response, and thus to neural protection by way of reducing exposure time to GC.

*5.2 Estradiol and Stress Response Interactions in Humans*

In humans, sex differences provide one line of evidence for estrogenic blunting of HPA axis activation, as women display dampened HPA responses to stressors. Naturally cycling young-adult women (i.e., not using hormone contraception) show lower adrenocorticotropic hormone (ACTH) (Faraday et al., 2005; Kirschbaum et al., 1999; Kudielka et al., 1998) and biologically active free cortisol (Davis and Emory, 1995; Kirschbaum et al., 1999; Kirschbaum et al., 1992; Kudielka et al., 2004; Kudielka et al., 1998) responses compared with young-adult men. Likewise, women tested during the high E2 phase of the menstrual cycle showed lower stress-related activation of the anterior cingulate gyrus, orbitofrontal cortex, medial and ventromedial prefrontal cortex, amygdala, and hippocampus than men (Goldstein et al., 2010), with similar activational differences in women tested during the low E2 versus higher E2 phases of the menstrual cycle (Goldstein et al., 2005). Furthermore, women using hormone contraception show additionally blunted cortisol responses compared with naturally cycling women, possibly as a result of the ethinyl estradiol in these forms of contraception (Kirschbaum et al., 1999; Nielsen et al., 2014; Nielsen et al., 2013). Evidence in young-adult men also

suggests that E2 dampens sympathetic responses to a stressor, with just one day of E2 treatment resulting in blunted systolic blood pressure, pulse rate, epinephrine, and norepinephrine responses to a mental stressor (Del Rio et al., 1994).

Similar dampening of the stress response has been observed in post-menopausal women on E2 treatment. Transdermal or oral E2 interventions spanning 1 day (Del Rio et al., 1998), 3 weeks (Ceresini et al., 2000), 1 month (Puder et al., 2001), 6 weeks (Lindheim et al., 1992), and 8 weeks (Komesaroff et al., 1999) reduced the epinephrine (Ceresini et al., 2000; Del Rio et al., 1998), norepinephrine (Ceresini et al., 2000), diastolic blood pressure (Ceresini et al., 2000; Komesaroff et al., 1999; Lindheim et al., 1992), systolic blood pressure (Komesaroff et al., 1999; Lindheim et al., 1992), ACTH and cortisol (Puder et al., 2001) responses to various stressors, such as mental stressors (Ceresini et al., 2000; Del Rio et al., 1998; Lindheim et al., 1992), the cold pressor task (Lindheim et al., 1992), and an endotoxin challenge (Puder et al., 2001).

Together, the findings indicate that E2 blunts the magnitude of the HPA axis response to stressors in women. Taking into account the negative effects of prolonged or heightened stress hormone exposure, the loss of E2 during and after menopause may put post-menopausal women at greater risk of experiencing stress-induced alterations in cognitive function, as a result of dramatically reduced E2 levels. However, the use of hormone supplements during and after the menopause transition should alleviate the potential increased negative effects of stress exposure on cognitive function.

**6. Estradiol May Counteract Negative Effects of Glucocorticoids in Middle-Aged and Older Females**

Aging is associated with a number of bodily changes. Among these changes are alterations in the function of the stress response system, particularly the HPA axis. A common paradigm for testing HPA axis sensitivity to stressors in aged subjects is to administer real or synthetic GCs and measure how quickly the HPA axis responds to

and adjusts subsequent hormone release. In one model, animals are given injections of dexamethasone (DEX), which activates the negative feedback system of the HPA axis, and reduces subsequent release of the animal's endogenous corticosterone response to a stressor. In young-adult animals, this procedure results in a significant reduction of corticosterone release in response to a stress, however, aged male rodents fail to show this DEX-induced corticosterone suppression to a stressor, (Ferrini et al., 1999; Riegle and Hess, 1972). This age-related failure to inhibit HPA axis reactivity also is observed in female rhesus monkeys subjected to corticotropin releasing hormone (CRH), ACTH, and DEX tests (Goncharova and Lapin, 2002) and in a CRH test performed in male and female dogs (Reul et al., 1991). Additionally, aged male rats also displayed prolonged corticosterone secretion after termination of an acute stressor compared with young animals (Ferrini et al., 1999; Sapolsky et al., 1983), with similar results observed in older male and female rodents exposed to chronic stress (Riegle, 1973; Sapolsky et al., 1983).

One possible explanation for the heightened and prolonged stress response in aged animals may be age-related downregulation of GC receptors in the brain, particularly in the hippocampus (Ferrini et al., 1999; Mizoguchi et al., 2009; Sapolsky et al., 1986). Loss of GC receptors in the aged hippocampus, a structure intimately involved in termination of the stress response, leads to a failure to accurately detect circulating GC levels and thus a failure to downregulate the HPA axis during and after stress exposure. The resulting excess GC exposure leads to hippocampal damage and subsequent loss of more GC receptors, leading to a cycle of more GC exposure, damage, and receptor loss (Sapolsky et al., 1986).

Consistent with this pattern, some reports indicate older adult humans also exhibit higher basal cortisol, and potentiated and prolonged stress responses as measured by various biomarkers, such as cortisol and salivary alpha amylase (a

biomarker for norepinephrine; Almela et al., 2011; for salivary alpha amylase as a marker for norepinephrine response see, Chatterton et al., 1996; see also, Dodt et al., 1991; Wilkinson et al., 2001). While human studies on brain levels of GC receptor concentration are few and far between, there is preliminary work showing older adults do experience GC receptor downregulation in both the brain and bloodstream. For instance, older adults had reduced levels of GC receptor mRNA in plasma compared with younger adults (Grasso et al., 1997), and showed lower GC receptor concentration in the dorsolateral prefrontal cortex than the expression displayed in the brains of adolescents and adults in a postmortem study (Perlman et al., 2007). Reductions of GC mRNA in plasma and the brain may explain failures of older adults to downregulate the HPA axis after a brief stressful event.

Women, however, may experience protection from this cycle of decline in GC receptor concentration, HPA hyperactivity, and ensuing neural damage, by extending E2 presence and action beyond menopause. The loss of E2 after menopause likely leads to potentiated age-related changes in HPA axis function due to the loss of estrogenic protection. However, prolonging E2 exposure beyond menopause will likely maintain proper HPA axis function. For instance, recall that E2 administration upregulated GC receptors in the hippocampus of older male rats, compared with older animals not treated with E2 (Ferrini et al., 1999). This type of estrogenic upregulation of GC receptors in the hippocampus could help prevent or reverse the age-related hyperactivity of the HPA axis as more receptors would be available to detect circulating GC levels and spare the hippocampus, and other brain regions, such as the prefrontal cortex, from further damage.

Importantly for human females, E2 has been shown to counter each of the age-related dysfunctions (e.g., hippocampal damage, receptor downregulation, and HPA axis hyperactivity) described above. Yet, despite the protective effects of E2 treatment after

menopause, and the attenuating effects of E2 on the stress response, Newhouse et al. (2010) reported worse performance on various measures of attention and for memory of hard word pairs in a verbal paired associates task in women assigned to three months of E2 treatment, compared with women who had been assigned to placebo, after completion of the TSST. However, similar to the WHI study, some caveats apply. Women assigned to E2 were an average age of 65.18 years old, with an age range of 52-83, and years since menopause averaged 14.57 years, with a range of 1-31 years. Thus, while the age and time-since-menopause ranges surely captured some women within the first years since their last menses, it also captured women well beyond the climacteric transition. Similar to the WHI studies, the inclusion of women outside the critical window (for review see, Maki, 2013; see also, Resnick and Henderson, 2002) could have activated effects of the healthy cell bias (Brinton, 2005) and resulted in less protection from stress and greater impairments in attention and short-term episodic memory.

Insofar as E2 protects the hippocampus and prefrontal cortex, and consequently the negative feedback system of the HPA axis, extension of E2 exposure past menopause may be a possible mechanism for the relatively enhanced cognitive function observed in post-menopausal women who initiated hormone treatment close to the time of menopause.

**7. Conclusion**

Stress is encountered by all people on a daily basis. With regard to women, there is clear evidence that the systems governing stress and sex hormones intimately interact and even exert opposing effects on various bodily systems. Given the countervailing effects of the two hormones, the decline in proper GC regulation with aging, and the ability of E2 to directly mitigate potential negative effects of GC exposure, there is the potential for increased and/or accelerated neuronal and cognitive decline post-

menopause due to increased HPA reactivity to stress exposure and lack of E2 protection.

This line of research is relevant to half of the global population, as all women should eventually experience menopause, and while the exact parameters of if and when E2 replacement is suitable vary from woman to woman, it is nonetheless important to understand all potential benefits and risks of E2 replacement, such as whether E2 can limit age-related changes in the stress response system. There are also many questions that remain to be answered. One such question, discussed here, is when estradiol replacement should begin relative to menopause in order to enhance potential benefits and limit potential dangers. Others needing to be addressed and discussed elsewhere in relation to other domains, include whether different forms of estrogens follow different time and dose curves before affecting the domain of interest, or whether some forms of estrogens and estradiol lead to negative versus positive effects (Barha et al., 2010; for review see, Barha and Galea, 2010; see also, Barha and Galea, 2013; Barha et al., 2009; McClure et al., 2013). These points illustrate how the current state of estradiol-treatment research is incomplete and in need of more intensive research. Working toward uncovering how the interaction between GC and E2 changes after menopause, and the implications of these changes elsewhere in the peri- and post-menopausal woman's body, is necessary for providing the most complete understanding of how estradiol treatment may affect women's health.

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TABLE 1: Effects of Glucocorticoids and Estradiol in the Body

| **Metabolic Syndrome and Related Indices in Animal Models** | | | |
|---|---|---|---|
| **Species** | **Index** | **Effect of, or relationship with, Glucocorticoids** | **Effect of, or relationship with, Estradiol** |
| **Human** | Metabolic Syndrome | ↑ (Pasquali et al., 2006; Rosmond, 2005) | / |
| | Abdominal visceral fat | ↑ (Green et al., 2004) | / |
| | Triglyceride, Glucose, and Insulin | / | ↓ (Krotkiewski et al., 1983) |
| | Bone Mineral Density | / | ↑ (Delmas et al., 1997; Felson et al., 1993; Sowers et al., 1998) |
| **Rat & Mouse** | Metabolic Syndrome | ↑ (Musatov et al., 2007) | / |
| | Intraabdominal fat | ↑ (Rebuffe-Scrive et al., 1992) | / |
| | Insulin | ↑ (Rebuffe-Scrive et al., 1992) | / |
| | Osteoblasts | ↓ (O'Brien et al., 2004) | / |
| | Osteocytes | ↓ (O'Brien et al., 2004) | / |
| | Osteoclasts | ↑ (Jia et al., 2006) | / |
| **Dog** | Glucose and Insulin | / | ↓ (McGuinness et al., 1993) |

"/" indicates unknown, or not investigated in cited articles

TABLE 2: Countervailing effects of glucocorticoids and estradiol on working memory

| **Working Memory** | | | |
|---|---|---|---|
| **Species** | **Task** | **Effect of Stress or Glucocorticoid On Performance** | **Effect of Estradiol On Performance** |
| **Human** | Digit Ordering | / | ↑ (Females)<br><br>(Duff and Hampson, 2000; Krug et al., 2006) |
| | Digit Span | ↓ (Males & Females)<br><br>(Elzinga and Roelofs, 2005; Schoofs et al., 2009) | ↑ (Females)<br><br>(Miller et al., 2002) |
| | N-Back | ↓ (Males)<br><br>(Schoofs et al., 2008) | / |
| | Reading Span | ↓ (Males)<br><br>(Luethi et al., 2009) | / |
| | Sternberg Item Recognition | ↓ (Males)<br><br>(Duncko et al., 2009; Lupien et al., 1999; Oei et al., 2006) | / |
| | Visuospatial Sketchpad | ↓ (Males)<br><br>(Young et al., 1999) | / |
| | Trail Making Test B | ↓ (Males & Females)<br><br>(Öhman et al., 2007) | / |
| **Rat** | Delayed Match-to-Place<br>&<br>Delayed Match-to-Position | / | ↑ (Females)<br><br>(Gibbs, 1999; Sandstrom and Williams, 2001) |
| | Radial Arm Maze<br>&<br>Delayed Win-Shift Task | ↓ (Males)<br><br>(Arbel et al., 1994; Butts et al., 2011; Diamond et al., 1996) | ↑ (Females)<br><br>(Bimonte and Denenberg, 1999; Daniel et al., 1997; Fader et al., 1999; Wilson et al., 1999) |
| | Radial Arm Water Maze<br>&<br>Morris Water Maze | ↓ (Males)<br><br>(Cerqueira et al., 2007; Park et al., 2001) | / |
| | Y-Maze<br>&<br>T-maze (delayed alternation) | ↓ (Males)<br><br>(Coburn-Litvak et al., 2003; Kleen et al., 2006; Lee and Goto, 2015; Roozendaal, 2004) | / |

"/" indicates unknown, or not investigated in cited articles

TABLE 3: Countervailing effects of glucocorticoids and estradiol on executive function and other cognitive processes

| **Executive Processes** | | | |
|---|---|---|---|
| **Species** | **Task** | **Effect of Stress or Glucocorticoid On Performance** | **Effect of Estradiol On Performance** |
| **Human** | Cognitive Flexibility, Mental Flexibility, & Planning | ↓ (Males & Females) (Alexander et al., 2007) | ↑ (Females) (Elsabagh et al., 2007) |
| | Go No-Go | ↓ (Males) (Scholz et al., 2009) | / |
| | Stroop Task | / | ↑ (Females) (Baker et al., 2012; Krug et al., 2006; Wolf and Kirschbaum, 2002) |
| | Verbal Fluency | / | ↑ (Females) (Miller et al., 2002) |
| | Mental Arithmetic | ↓ (Males) (Al'Absi et al., 2002) | / |
| | Attention Shift | ↓ (Males & Females) (Liston et al., 2009) | / |
| | Decision Making | ↓ (Sex not stated) (Starcke et al., 2008) | / |
| | Wisconsin Card Sorting Task | ↓ (Males & Females) (Egeland et al., 2005) | |
| **Rat** | Reversal Learning | ↓ (Males) (Cerqueira et al., 2007) | / |
| **Other Cognitive Processes** | | | |
| **Human** | Delayed Recall | / | ↑ (Females) (Baker et al., 2012) |
| | Paired Associates | ↓ (Males) (Young et al., 1999) | / |
| | California Verbal Learning Test | / | ↓ (Females) (Resnick et al., 2006) |
| | Modified Mini Mental State Exam | / | ↓ (Females) (Espeland et al., 2004; Rapp et al., 2003) |

| | | | |
|---|---|---|---|
| **Rat** | Object Recognition | / | ↑ (Females)<br><br>(Vaucher et al., 2002) |
| | Reference Memory | ↓ (Males)<br><br>(Cerqueira et al., 2007) | / |

"/" indicates unknown, or not investigated in cited articles

TABLE 4: Effects of Glucocorticoids and Estradiol on Neuronal Viability

| **Effects of Glucocorticoids and Estradiol on Neuronal Survival After Exposure to Insults** | | | | |
|---|---|---|---|---|
| **Species** | **Neural Region or Neural Tissue** | **Insult** | **Effect of Glucocorticoid with other Insults** | **Effect of Estradiol with other Insults** |
| **Mice** | Cerebellum | Methylmercury | / | ↑ (Males)<br><br>(Malagutti et al., 2009) |
| **Rat** | Fetal Hippocampal Cultures | Aβ | ↓<br><br>(Behl et al., 1997) | ↑<br><br>(Brinton et al., 2000; Chen et al., 2006) |
| | | Hypoxia | ↓<br><br>(Tombaugh et al., 1992) | / |
| | | Hypoglycemia | ↓<br><br>(Tombaugh et al., 1992) | / |
| | | Hydrogen Peroxide | / | ↑<br><br>(Brinton et al., 2000) |
| | | Glutamate Excitotoxicity | / | ↑<br><br>(Brinton et al., 2000) |
| | Hippocampus | Kainic Acid | ↓ (Males)<br><br>(Stein-Behrens et al., 1992) | ↑ (Females)<br><br>(Hoffman et al., 2003) |
| | | Quinolinic Acid | / | ↑ (Males)<br><br>(Kuroki et al., 2001) |
| **Rhesus Monkey** | Prefrontal Cortex | Aging | / | ↑ (Females)<br><br>(Hao et al., 2007) |

"/" indicates unknown, or not investigated in cited articles

TABLE 5: Effects of Glucocorticoids and Estradiol on Neuronal Morphology

| **Effects of Glucocorticoids and Estradiol on Neuronal Morphology** | | | | |
|---|---|---|---|---|
| **Species** | **Neural Region or Neural Tissue** | **Outcome of Interest** | **Effect of Glucocorticoid or Stress on Neural Tissue** | **Effect of Estradiol on Neural Tissue** |
| **Rat** | Various regions | Inflammatory Markers | ↑ (Males)<br><br>(Blandino Jr et al., 2006; MacPherson et al., 2005; O'Connor et al., 2003; Tynan et al., 2010) | / |
| | Hippocampus or Fetal Hippocampal Cultures | Dendrite Length | ↓ (Males & Females)<br><br>(Galea et al., 1997; McLaughlin et al., 2010; Watanabe et al., 1992; Woolley et al., 1990b) | ↑ (Fetal Cultures)<br><br>(Brinton et al., 2000; Chen et al., 2006) |
| | | Dendrite Branch Points | ↓ (Males & Females)<br><br>(Galea et al., 1997; McLaughlin et al., 2010; Watanabe et al., 1992; Woolley et al., 1990b) | ↑ (Fetal Cultures)<br><br>(Brinton et al., 2000; Chen et al., 2006) |
| | | Dendrite Spine Density | / | ↑ (Females)<br><br>(Gould et al., 1990; Woolley et al., 1990a; Woolley and McEwen, 1993) |
| | | Synaptic Density | / | ↑ (Females)<br><br>(Woolley and McEwen, 1992) |
| | | Neuron Number | ↓ (Males)<br><br>(Haynes et al., 2003) | ↑ (Males & Fetal Cultures)<br><br>(Brinton et al., 2000; Chen et al., 2006; Saravia et al., 2007) |
| | Striatum | Neuron Number | ↓ (Males)<br><br>(Haynes et al., 2003) | / |
| | Prefrontal Cortex | Dendrite Length | ↓ (Males)<br><br>(Brown et al., 2005; Cook and Wellman, 2004; Wellman, 2001) | / |

| | | | | |
|---|---|---|---|---|
| | | Dendrite Branch Points | ↓ (Males)<br><br>(Brown et al., 2005; Cook and Wellman, 2004; Wellman, 2001) | / |
| **Vervet Monkey** | Hippocampus | Neuron Number | ↓ (Males)<br><br>(Uno et al., 1989) | / |
| | | Dendrite Branch Points | ↓ (Males)<br><br>(Uno et al., 1989) | / |
| **Human** | Hippocampus | Area Volume | / | ↑ (Females)<br><br>(Protopopescu et al., 2008) |

"/" indicates unknown, or not investigated in cited articles

TABLE 6: Effects of Glucocorticoids and Estradiol on Brain Function

| **Effects of Glucocorticoids and Estradiol on Brain Function** | | | | |
|---|---|---|---|---|
| **Species** | **Neural Region or Neural Tissue** | **Outcome of Interest** | **Effects of Glucocorticoids on Brain Function** | **Effects of Estradiol on Brain Function** |
| **Human** | Prefrontal Cortex | Increased BOLD activation during working memory task | ↓ (Males & Females) (Qin et al., 2009; Symonds et al., 2012) | / |
| | Hippocampus | Decreased BOLD activation during working memory task | ↓ (Females) (Qin et al., 2009; Symonds et al., 2012) | / |
| | | BOLD activation during a verbal recognition task | / | ↑ (Females) (Maki et al., 2011) |
| | | Cholinergic activity | / | ↑ (Females) (Smith et al., 2011) |

"/" indicates unknown, or not investigated in cited articles

TABLE 7: Estrogenic Modulation of Glucocorticoid Effects

| **Modulation of the Glucocorticoid or Stress effects on Neural Tissue by Estradiol** | | | |
|---|---|---|---|
| **Species** | **Neural Region** | **Effect of Glucocorticoid Exposure** | **Modulated Effect by Estradiol** |
| **Rat** | Hippocampus | ↓ (Males)<br><br>(Haynes et al., 2003) | Blocked<br><br>(Haynes et al., 2003) |
| | | ↓LTP (Males)<br><br>(Foy et al., 2008) | Attenuated<br><br>(Foy et al., 2008) |
| | | ↓ Dendritic Complexity (Males & OVX Females)<br><br>(Galea et al., 1997; McLaughlin et al., 2010) | Attenuated or Blocked (Intact Females & OVX+E2 replacement)<br><br>(Galea et al., 1997; McLaughlin et al., 2010) |
| | | ↓ Cell Number (OVX Females)<br><br>(Takuma et al., 2007) | Blocked<br><br>(Takuma et al., 2007) |
| | Striatum | ↓ (Males)<br><br>(Haynes et al., 2003) | Blocked<br><br>(Haynes et al., 2003) |
| | Prefrontal Cortex | ↓ (OVX Females)<br><br>(Garrett and Wellman, 2009) | Blocked<br><br>(Garrett and Wellman, 2009) |

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