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# Estrogen: effects on normal brain function and neuropsychiatric disorders

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Key words: ESTROGEN, BRAIN FUNCTION, NEUROPSYCHIATRIC DISORDERS

## ABSTRACT

Many women complain of memory and other cognitive/emotional difficulties at times that are associated with changes in estrogen levels. However, the biological mechanisms through which estrogen may exert these effects remain poorly understood. The effect of estrogen treatment on cognition and brain function in healthy women, and those with Alzheimer's disease, is controversial. Here we review the evidence that, in healthy women, estrogen affects the dopaminergic, serotonergic, and cholinergic systems, and brain regions crucial to higher cognitive function and mood. We will also present results from recent *in vivo* randomized-controlled neuroimaging experiments in our laboratory demonstrating that, in young females, and those in mid-life: (1) brain function is modulated by normal variation in ovarian function; (2) acute loss of ovarian hormones increases neuronal membrane breakdown; and (3) acute suppression of ovarian function is associated with reduced activation of brain regions critical to memory.

## INTRODUCTION

Many women complain of memory and other cognitive difficulties at times that are associated with changes in estrogen levels, such as pregnancy and perimenopause[1], and postmenopausal women have a higher incidence of Alzheimer's dementia than men[2]. Recent studies have attempted to clarify the nature and degree of these effects and the possible role of estrogen treatment (ET) in preventing dementia. However, the biological mechanisms through which estrogen may exert these effects remain poorly understood. This review will therefore begin by briefly outlining our current understanding of the effects of estrogen on cognition and its role in the prevention of Alzheimer's dementia and subsequently review some of the biological mechanisms that may underlie these effects.

## EFFECTS OF ESTROGEN ON COGNITION AND DEMENTIA

The menstrual cycle has provided a useful non-invasive model to study the modulatory effects of estrogen on cognitive functions (e.g. memory). Although interpretation of the results of these studies has been difficult due to a variety of methodological problems (see reference 3 for review), they suggest that high-estrogen phases of the menstrual cycle are associated with improved performance on verbal tasks and reduced performance on visuospatial tasks[4,5].

This has been supported by some reports of improved verbal memory amongst postmenopausal women taking ET[6–10]. Studies have also suggested that ET has beneficial effects on visual memory, but these effects are less consistent[11]. An inverted U-shaped curve for performance on

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visuospatial performance relative to estradiol levels has also been reported[5], suggesting that optimal performance is achieved at intermediate plasma estradiol concentrations which, if accurate, may account for some of the inconsistencies in the literature.

The role of ET in the prevention of Alzheimer's dementia has not been resolved by studies to date. Meta-analyses of cohort and prospective case-controlled studies of the potential protective effects of ET against Alzheimer's dementia reported risk reductions of up to 34% (relative risk (RR) 0.66; 95% confidence interval (CI) 0.53–0.82)[12]. However, interpretation of these studies is limited by a number of possible confounds (see reference 13 for review).

A recent multicenter, randomized, double-blind, placebo-controlled clinical trial (The Women's Health Initiative Memory Study, WHIMS) attempted to overcome many of these confounds. WHIMS reported that continuous combined estrogen (conjugated equine estrogen, CEE) ± progestin (medroxyprogesterone acetate, MPA) given to women aged over 65 significantly increased the risk for 'all-cause' dementia and cognitive decline[14]. However, it remains unclear to what extent the WHIMS data apply to women prescribed CEE (or other forms of ET) ± MPA immediately postmenopause, which is the time at which it has been suggested ET may have its 'window of opportunity'[2]. Furthermore, the study was unable to determine the effect of ET on Alzheimer's dementia (i.e. as opposed to 'all cause' dementia), as it was underpowered.

Therefore, in summary, some studies suggest that estrogen has modulatory effects on higher cognitive processes in healthy women and ET may delay the onset of Alzheimer's dementia if prescribed during a 'window of opportunity' at the time of the perimenopause; however, *initiation* of ET in women over the age of 65 is associated with increased risk for 'all cause' dementia. We will now consider biological mechanisms that may underlie the putative neuroprotective effects.

## BIOLOGICAL EFFECTS OF ESTROGEN ON THE BRAIN

### Structural (macroscopic) effects

Variation in estrogen (and other hormone) levels during brain maturation may contribute to gender differences in the macroscopic structure and subsequent functioning of the brain. During adolescence, for example, females have been reported to have greater myelination than males in areas such as the superior medullary lamina[15] and the volume of frontal gray matter peaks approximately 1 year earlier in females than male[16]. Furthermore, it has been reported that ventricular enlargement (indicative of brain atrophy) begins in the fifth decade in men compared to the sixth decade in women[17]. However, ventricular enlargement subsequently accelerates faster in women[18], which may be modulated by the decline in estrogen levels around the time of the menopause. We have also reported findings from a magnetic resonance imaging (MRI) study that suggests age-related volume loss in women is significantly greater in areas such as the hippocampus and parietal lobes[19]; this is important as these areas are specifically involved with memory.

The above gender differences are, however, likely to be partly attributable to a number of other factors (e.g. X-chromosome effects). Research that has specifically analyzed the actions of estrogen on brain anatomy is limited to several studies of ET in postmenopausal women. The earliest study reported an absence of significant differences in the volumes of total gray and white matter, or in regional brain volumes, in long-term users of ET compared to age-matched non-users[20]. More recent studies have yielded conflicting reports. One study has reported significantly greater right hippocampal volume in women treated with ET compared to an untreated group[21], but this was not supported in a subsequent study by the same group[22].

### Cellular (microscopic) effects

There have been a greater number of studies into the effects of estrogens at the cellular level. These studies have reported a multitude of specific effects which are likely to be important to brain maturation and higher cognitive function; these are considered below.

#### *Neurotrophism and neurogenesis*

*In vitro* studies of cultured hippocampal neurons have reported that estrogen induces filipodial outgrowth and increases neuron number and branching complexity[23]. This is important because the hippocampus, as stated above, plays a key role in memory processing. Rat hippocampal dendritic spine density has also been reported to increase in association with high-estrogen phases

of the estrous cycle[24,25] and similarly hippocampal neurogenesis has been reported to significantly reduce following oophorectomy (and subsequently increase with ET)[26]. Furthermore, it has been reported in rats that estrogen-induced changes in hippocampal dendritic spine density are associated with improved performance on a delayed-matching-to-place task, suggesting that these local changes may have significant effects on higher cognitive processes.

### *Neuronal and glial integrity*

Neuronal and glial function can be studied using a neuroimaging technique called proton magnetic resonance spectroscopy ($^1$H MRS). We have previously reported a significant age-related increase in right parietal and hippocampal choline-containing compounds (Cho) in postmenopausal women who had never used ET compared to long-term ET users[27]. Cho is a marker of membrane metabolism[28] that has been reported to increase with age[29]. Our findings therefore suggest that ET may reduce the normal age-related increase in neuronal membrane breakdown. These findings have been supported by a more recent MRS study which has reported reduced *myo*-inositol (MI) concentrations in women treated with ET compared to untreated women[30]. MI modulates neuronal signal transduction and cellular osmolarity[31], is amyloidogenic in animal models, has been reported to increase with age[32] and be further increased in people with Alzheimer's disease.

### *Antioxidant and anti-apoptotic properties*

Reactive oxygen species (ROS), produced during the course of normal cell metabolism, have the capacity to cause significant cellular damage. The brain contains a number of defences against ROS (e.g. enzymes that catalyze their breakdown). Estrogen has antioxidant properties that may be increased *in* vivo via a synergistic interaction with glutathione (an intracellular reducing agent)[33]. The importance of ET as a defence against ROS may increase with age, as animal studies suggest a decline in other antioxidant defences in older animals[34].

## Functional effects

Research into the effects of estrogen on brain function may be divided into studies of pre- and postmenopausal women.

### *Premenopausal women*

A functional magnetic resonance imaging (*f*MRI) study across the menstrual cycle has reported increased brain activation, associated with high estrogen levels, in regions implicated in verbal and visuospatial memory processing. These areas included the inferior and medial frontal and postcentral gyri during a mental rotation task and the superior parietal cortex during a word-stem completion task[35]. These data therefore suggest that estrogen modulates brain activation in brain regions implicated in tasks.

This has been supported by a more recent *f*MRI study of the brain regions involved in a semantic decision task across the menstrual cycle[36]. This study reported greater activation in temporal and medial superior regions during the mid-luteal (high estrogen and high progesterone) phase of the menstrual cycle. In addition, there were significant correlations between the extent of activation and serum estrogen (and progesterone levels). These data suggest that neural recruitment during a semantic decision task is modulated by naturally occurring fluctuations in gonadal steroids.

Acute ovarian steroid suppression (using a gonadotropin releasing hormone (GnRH) analogue) has also been used to study the effects of estrogen withdrawal on brain function in young women. An early positron emission tomography (PET) study[37] reported a significant reduction in blood flow in brain regions known to be involved in a modified version of the Wisconsin Card Sorting Test (WCST) (i.e. dorsolateral prefrontal and parietal cortex) following a GnRH analogue and this was subsequently restored with estrogen (and progesterone) add-back. These findings have been supported by a recent unpublished *f*MRI study by our group. We report an encoding specific effect at the prefrontal cortex, cingulate and insula in a verbal episodic memory task.

### *Postmenopausal women*

Several observational studies have reported a significant effect of ET on brain function. One early PET study[38] compared ET users (ET+) to non-users (ET−) and reported significant differences in the relative regional cerebral blood flow in brain regions known to be important in memory, including frontal and parahippocampal gyri, in a delayed verbal recognition task, and parietal and parahippocampal cortices, in a delayed figural recognition task. The behavioral data also suggested that ET+ women performed

better on these tasks, suggesting that the regions differentially activated between groups were involved in the modulation of the effects of estrogen on verbal and figural recognition.

A subsequent observational study using PET analyzed regional cerebral glucose metabolism during performance of a continuous word recognition task in ET+ and ET− postmenopausal women and women with Alzheimer's disease[39]. ET− women were reported to have metabolic ratios that were intermediate to ET+ women and Alzheimer's disease patients in cortical regions that are characteristically hypometabolic in Alzheimer's disease (including the dorsolateral prefrontal, middle temporal, and parietal cortices). Although the behavioral performance did not differ between ET+ and ET− women, it was suggested that the relative hypometabolism in ET− women might be an early indicator of future cognitive decline.

The above findings have been supported by a placebo-controlled, cross-over study using *f*MRI[40] which reported altered activation in the superior frontal gyrus during storage of verbal material and decreased activation in the inferior parietal lobule during storage of figural material in ET+ compared to ET− women.

## Effects on neurotransmitter systems

Animal and human studies suggest that estrogen can affect cholinergic, dopaminergic and serotonergic systems. These systems will therefore be considered separately.

### *Cholinergic system*

In rat studies, estradiol has been reported to:

(1) Enhance cholinergic muscarinic receptor density[41];
(2) Enhance high-affinity choline uptake and the activity of choline acetyltransferase (ChAT) in the basal forebrain and two of its projection areas (the CA1 region of the hippocampus and the frontal cortex)[42];
(3) Modulate acetylcholine release[43]; and
(4) Ameliorate a scopolamine-induced memory deficit[44].

Furthermore, several studies have reported that the effects of estradiol on the cholinergic system and cognitive function diminish with time following loss of ovarian function[45–47].

We have reported greater responsivity to a cholinergic challenge in postmenopausal women on long-term ET[48]. We have also recently reported higher muscarinic (m1/m4) receptor density in long-term ET users versus never-users in the left striatum, hippocampus, lateral frontal cortex and thalamus, which correlated with plasma estradiol levels in the left hippocampus and temporal cortex. This is supported by an earlier single-photon emission tomography (SPET) study that reported an increased index of cortical cholinergic nerve terminal concentrations with increasing years of ET use in healthy postmenopausal women[49].

### *Dopaminergic system*

Estrogen deprivation for 30 days has been reported to lead to loss of over 30% of dopaminergic cells in the substantia nigra of non-human primates[50], and chronic ET has been demonstrated to restore striatal dopaminergic function in ovariectomized rats[51]. However, the length of time of ET administration may affect dopaminergic responsivity, as acute ET administration has, for example, been reported to convert high D2 dopamine receptor binding sites to low affinity sites[52]. Similarly, the dose and time of testing (relative to the last exposure to ET) may also be important. Rats tested 48 h or more after exposure to high doses of estradiol have been reported to exhibit dopamine receptor hypersensitivity[53], whereas lower doses have been reported to lead to dopamine receptor hyposensitivity[53,54].

In humans, dopamine D2 receptor concentration reduces significantly with increasing age, especially in frontal and basal ganglia regions[55], with a more pronounced decline observed in women than in men[56]. The response to a dopaminergic challenge is increased in women taking the combined oral contraceptive pill[57], at high-estrogen phases of the menstrual cycle[58], and on the fourth day postpartum in women at risk of puerperal psychosis compared to controls[59]. We have also reported greater responsivity to a dopaminergic challenge in postmenopausal women on long-term ET[60]. To date, there is an absence of neuroimaging studies into the interaction between estrogen and the dopaminergic system.

### *Serotonergic system*

Rat studies suggest that short- and long-term ET in ovariectomized rats leads to regulation of 5-$HT_1$ receptor density[61,62].

In healthy premenopausal women, responsivity to a serotonergic challenge test has been reported

to vary across the menstrual cycle, with greatest responsivity when estrogen levels are high[63]. Furthermore, we have reported greater responsivity to serotonergic challenge in postmenopausal women on long-term ET[64]; similar findings have been reported in women following short-term ET[65,66]. PET and SPET studies suggest that short-term ET is associated with a widespread increase in cortical $5HT_{2A}$ receptor availability in postmenopausal women[67]. We have recently reported that long-term ET is associated with lower 5-$HT_{2A}$ receptor availability in hippocampus. This may indicate that up-regulation of post-synaptic 5-$HT_{2A}$ receptors is associated with short-term use, followed by down-regulation with chronic use. This could be clinically relevant, as total cortical 5-$HT_{2A}$ binding potential has previously been reported to be negatively correlated with delayed verbal memory.

## CONCLUSION

There is increasing evidence to suggest that estrogen modulates cognitive function and that ET may protect against Alzheimer's disease if it is initiated during a 'window of opportunity' at the onset of the menopause. Although the biological mechanisms underlying these effects remain poorly understood, this review has examined some of the putative neuroprotective effects of estrogen at the macroscopic, microscopic, functional and neurotransmitter levels.

Further studies are still required to determine, first, the cognitive outcome of modulating variables that are clinically relevant when prescribing ET (e.g. dose/type of ET and delay in taking ET after the menopause onset) and, second, other biological mechanisms that may underlie estrogen's effects on cognition and dementia during female brain maturation.

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