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Current Perspective

Does endocrine therapy for the treatment and prevention of breast cancer affect memory and cognition?

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ABSTRACT

Oestrogen receptors have been identified in several areas of the brain important in cognitive performance, including the prefrontal cortex (active during short-term working memory), the hippocampus and related cortical areas (learning and storage of information) and the amygdala (involved in the modulation of memory consolidation). There is much debate as to whether or not a reduction in oestrogen levels results in a corresponding decline in cognitive processing. Arguments for an effect are based on findings from laboratory and hormone replacement studies and the pharmacological actions of breast cancer drugs. However, there are few clinical data substantiating the claim that endocrine therapies used in the treatment and prevention of breast cancer could affect cognition. This paper examines the main evidence associated with this claim and discusses the importance of examining such issues within randomised trials.

1. Introduction

Despite great interest in the effects that factors such as hormone replacement therapy (HRT) and chemotherapy may have on cognition, e.g. 1,2, the impact of endocrine therapies alone in breast cancer treatment or chemoprevention has received less attention. This is intriguing as the mild cognitive deficits found in menopausal women, or women who have had bilateral oophorectomy may be partially explained by the lack of or drop in bioavailable oestrogen. We highlight key findings from cognitive research in the laboratory, HRT, and clinical studies that might elucidate the impact of endocrine therapy on cognitive functioning.

2. Oestrogen and laboratory studies

Oestrogen receptors, ERα and ERβ, have been identified in areas of the brain important in cognitive performance. These include the prefrontal cortex (active during short-term working memory), the hippocampus and related cortical areas (learning and storage of information) and the amygdala (involved in the modulation of memory consolidation).[3,4] The exact role of oestrogen's influence within the memory system is complex but research into Alzheimer's disease (AD) has highlighted its effect on the cholinergic pathway.[5]

Early laboratory work has shown that oestrogen treatment reverses the learning deficits seen in ovarectomised rats on a variety of tests such as T maze avoidance, radial, water maze and place discrimination tasks.[6,7] The usual animal model for this work is young rats, and researchers questioned whether the same effect would occur in an older group[8] thus allowing a more valid comparison with the cognitive problems reported by the majority of post-menopausal women. A series of experiments were conducted that examined this issue and the data have generated further questions about the effect of oestrogen on cognitive processing (see Table 1).[8–10]

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Table 1 – Key findings from laboratory studies highlighting the effect of oestrogen on learning and memory

Author (year)	N	Groups	Relevant finding
Singh et al. (1994)	18	Ovarectomy ± 17β oestradiol versus intact	Impairment of non-spatial learning reversible through oestradiol treatment
O'Neal et al. (1996)	18	Ovarectomy ± polyestradiol-phosphate, 0.5 mg (oestrogen preparation)	Oestrogen treated rats made significantly more correct choices on a delayed matching to sample problem
Markowska and Savonenko (2002)	30	Ovarectomy versus sham surgery	Ovarectomy accelerated rate of cognitive aging on task that placed high demands on working memory
Savonenko and Markowska (2003)	88	Ovarectomy ± 10 μg of 17β oestradiol Sham surgery ± 10 μg of 17β oestradiol	Deteriorating effect of chronic oestradiol treatment in rats with spared ovaries
Daniel et al. (2006)	40	Ovarectomy ± 17β oestradiol Sham surgery ± 17β oestradiol	Chronic oestradiol treatment had positive effect on working memory in middle aged rats when initiated immediately after ovarectomy

In one study two groups of 13-month-old female rats ($n = 10$ sham surgery and $n = 20$ ovarectomised) were repeatedly tested over a nine month period on several tasks.[8] This age group allowed the researchers to examine the natural change in cognition in these animals from "middle age" to "old age". One of the tasks involved a two arm T maze, which tests the animal's rate of finding food by learning to alternate maze arms. In the first trial one arm of the maze was blocked and the rat entered the other arm that had the reinforcement. During the next 10 trials the rat chose either arm and the reinforcement was placed on the side of the arm not visited during the previous trial. During the first testing in this delayed non-matching to position task (DNMP), acquisition training was conducted with an inter-trial delay of 20–25 s and once the criteria of 85% correct choices had been reached longer inter-trial delays were introduced (1, 5, 15 or 30 min). The results from the experiment showed that ovariectomy did not affect the rate of acquisition in the DNMP task. The groups took the same number of sessions to reach the criteria of 85% correct, but the number of correct arm choices as a measure of working memory decreased with aging ($p < 0.01$). As the inter-trial delays increased, placing greater demands on memory, the ovarectomised rats showed a deficit in performance four months after ovarectomy ($p < 0.05$). This decline in processing was later noted (nine months post-ovarectomy) on the trials with shorter time intervals. The efficacy of oestrogen treatment in restoring the deficit in the DNMP task was improved when oestrogen implants were used and primed with repeated injections of 10 μg of 17β oestradiol implants to mimic the natural oestrogen cycle, rather than injections alone.

As part of a later experiment, the same authors examined the effects of oestrogen manipulations in 20-month-old rats who were randomised into four groups: ovarectomised ($n = 24$), ovarectomised with 17β oestradiol implants ($n = 20$), sham-operated with 17β oestradiol implants ($n = 22$) and sham-operated with spared ovaries ($n = 22$).[10] Performance on a T maze active avoidance task was recorded prior to and following treatment with scopolamine, a muscarinic antagonist known to compromise the cholinergic system. This was conducted in order to estimate the efficacy of oestrogen in counterbalancing the amnesic effects of the drug. The T maze task required the rat to actively avoid a foot shock that was delivered to one of two goal boxes. Training sessions continued until the criteria of five correct avoidance responses in six consecutive training trials were reached. Results from this experiment showed that the sham plus oestrogen group were slower in learning avoidance acquisition ($p < 0.01$). In addition, scopolamine slowed down the avoidance acquisition in the other three groups by increasing the number of errors and number of trials to criteria ($p < 0.0001$). However, regardless of oestrogen treatment both groups of ovarectomised rats showed a significant impairment in avoidance learning after a higher dose of scopolamine ($p < 0.01$). Oestrogen treatment had failed to block the amnesic action of scopolamine. A surprising finding was the deteriorating effect chronic oestrogen treatment had on old rats with spared ovaries. In contrast to the group of old ovarectomised rats where oestrogen did not produce any effect on avoidance acquisition, in rats with spared ovaries the same treatment compromised learning ability. The researchers hypothesised that oestrogen treatment in the old rats activated the release of hypothalamic and pituitary hormones followed by ovarian secretion of progesterone, and that the progesterone negatively affected learning ability. The authors suggested a "time window" during which hormone replacement must be initiated in order for it to be effective. This view is supported by Daniel and colleagues who noted that chronic oestradiol replacement treatment positively affected working memory in middle aged rats when initiated immediately after ovariectomy, but was not effective when initiated after long-term hormone deprivation.[9]

Interpretation of the laboratory findings in relation to the original argument would suggest that a sudden drop in available oestrogen will have an impact on learning, and most at risk would be the younger women who experience an acute menopause.

3. Cognition and changes in hormone levels

3.1. *Surgically induced menopause*

Barbara Sherwin and colleagues conducted a series of early experiments that assessed cognitive functioning in pre-menopausal women pre- and post-oophorectomy for benign disease. The first experiment involved women randomly

assigned to either oestrogen + androgen ($n = 10$), oestrogen alone ($n = 10$), androgen alone ($n = 10$) or placebo ($n = 10$) post-operatively. Scores on a short term verbal memory task were maintained at a pre-operative level compared to those who were assigned placebo.[11] In a second experiment involving 19 women ($n = 10$ oestrogen replacement, $n = 9$ placebo), similar results were reported[12] suggesting that rapid depletion in oestrogen has a direct, albeit, modest effect on verbal learning and memory. Further support came from a study of 19 young women treated with leuprolide acetate depot (LAD), a GnRH agonist for uterine myomas.[13] The levels of all sex hormones decreased after three months of treatment as did scores on neuropsychological tests of verbal memory. The argument for a role of oestrogen in maintaining memory function was strengthened as the deficits reversed in those who received oestrogen treatment (Table 2).

3.2. *Hormone replacement therapy*

Early evidence that HRT might have a protective effect on or even improve cognitive performance in post-menopausal women (for review see 14) is weakened by the results from the Women's Health Initiative Memory Study (WHIMS). WHIMS was a double blind randomised placebo controlled trial that enrolled a subgroup of women from the Women's Health Initiative (WHI) to examine the effect of HRT on the incidence of mild cognitive impairment and dementia. In total 4532 women aged 65 years and older were randomised to take combined therapy (conjugated equine oestrogen and medroxyprogesterone aceta (CEE + MPA)), unopposed oestrogen or placebo. Cognitive assessment was performed annually using the Modified Mini Mental State Examination (3MSE). Women who exhibited evidence of cognitive impairment were subjected to further extensive neuropsychological testing. The clinical trial was discontinued prematurely due to the increased risk of stroke, heart disease, breast cancer and pulmonary embolism. However, the data collected indicated that women in the combined therapy group were twice as likely as those receiving placebo to develop probable dementia,[15] although there were no significant between-group differences in the rate of cognitive decline nor diagnosis of AD.[1,15] In addition, data from the oestrogen-alone arm of the trial revealed a negative but non-significant trend of a risk of probable dementia compared with placebo ($p = 0.18$).[16] Another article from the group that elaborated further their previous results suggested that the combination arm had a negative impact on verbal memory ($p \leqslant 0.01$) and a trend to a positive impact on figural mem-

Table 2 – Key findings from HRT and surgical menopause studies highlighting the effect of oestrogen on cognition

Author (year)	N	Design	Groups	Relevant finding
Shumaker et al. (2003)	4532	Randomised Clinical Trial (RCT)	Post-menopausal women conjugated equine oestrogen + medroxyprogesterone aceta (CEE + MPA) versus placebo (P)	Women in CEE + MPA group were twice as likely as those receiving placebo to develop dementia
Rapp et al. (2003)	4532	As above	Same study as above	CEE + MPA group declined in 3MSE examination total score compared to placebo but no group differences in diagnosis of Alzheimer's disease
Shumaker et al. (2004)	2947	As above	Post-menopausal women CEE alone versus placebo	Negative but non-significant trend of a risk of probable dementia compared with placebo
Resnick et al. (2006)	1416	As above	Subgroup from CEE + MPA versus P study	Effects on memory evident only after long term therapy and more pronounced in women with lower cognitive functioning
Joffe et al. (2006)	52	RCT	Peri and post-menopausal women oral oestrogen versus dermal patches for 12 weeks	Compared with placebo women who received oestrogen had fewer errors of perseveration on verbal recall
Sherwin (1988)	40	Prospective cross-over design random allocation	Pre-menopausal women allocated oestrogen-androgen, oestrogen, androgen or placebo post-ovarectomy	Scores on four memory measures from women treated with all preparations higher than placebo group
Phillips and Sherwin (1992)	19	Repeated measures random allocation	Pre-menopausal women allocated oestrogen or placebo post-ovarectomy	Oestrogen group maintained baseline scores on a delayed verbal recall task whereas placebo group deteriorated significantly
Sherwin and Tulandi (1996)	19	Double blind oestrogen or placebo	Women with uterine myomas allocated oestrogen or placebo following 12 weeks GnRH treatment	Scores on verbal memory decreased from pre- to post-treatment. Findings reversed in group receiving oestrogen treatment

ory ($p = 0.012$) over time compared with placebo, but other cognitive domains were not affected. The effects on memory were evident only after long-term therapy and more pronounced in women with lower cognitive functioning at baseline.[17] These somewhat counter-intuitive and conflicting results require explanation.

Some authors have suggested that HRT initiated in women over 65 years of age may increase risk for non-specific dementia through cerebral vascular events.[18] Another possible reason for the variation in findings is due to the timing of oestrogen treatment. Sherwin[19] postulates that studies reporting an improvement in cognitive function were assessing women who received oestrogen supplementation at the time of menopause, whereas those studies reporting no improvement such as the WHIMS involved women who were receiving HRT many years after the menopause. Further support for this theory comes from a review of endocrine therapy and age at initiation of treatment that showed beneficial effects of unopposed oestrogen on certain aspects of cognition in younger women (<65 years), but no benefit for older women.[20]

Some may argue that the positive impact of oestrogen therapy, observed in younger women, is simply a function of a reduction in vasomotor symptoms and improved sleep. Hot flushes and night sweats are rated amongst the most distressing of post-menopausal symptoms that interfere with quality of life.[21] The suggestion that vasomotor symptoms impact on cognitive processes was examined in a randomised double blind placebo controlled study of oestrogen therapy in peri and post-menopausal women.[22] In this study 52 women were randomly assigned to oestradiol 0.05 mg/day ($n = 26$) or placebo dermal patches ($n = 26$) for 12 weeks. They completed tests of memory, learning and executive functioning at baseline and at the end of the study. The results showed that compared with placebo, those women who received oestrogen therapy had fewer errors of perseveration on verbal recall but no other differences were found in cognitive performance. Although oestrogen therapy reduced the number and severity of hot flushes, this was not associated with an improvement in sleep. One may argue that the longer a woman has been post-menopausal, the less likely it is that antioestrogen treatment (which has an opposite action to HRT) would impact upon cognition.

4. Evidence that endocrine therapy may interfere with cognition

4.1. *Selective oestrogen receptor modulators (SERMs)*

The SERM tamoxifen, a mixed agonist/antagonist, binds to the oestrogen receptors ERα and ERβ amongst others, but there is conflicting evidence as to whether it acts as an agonist or an antagonist in the brain. Ernst and colleagues examined the impact of tamoxifen and oestrogen on brain metabolism in 43 elderly women (65–80 years) compared with 33 matched controls.[23] The data suggested that tamoxifen had a similar effect to oestrogen: both resulted in lower concentrations of myo-inositol, described as a putative glial marker whose levels reflect glial content or activity. This finding was opposite to what would be expected in normal aging and suggests that tamoxifen may have a favourable effect on the aging brain and would not interfere with cognition.

It is proposed that the lack of agreement on the role of tamoxifen is dependent on the pathway of oestrogen action, which can result in tamoxifen having both an agonist effect and an antagonist effect.[24] Raloxifene, a benzothiophene member of the SERM class of compounds used in the treatment and prevention of osteoporosis, mimics the effects of oestrogen in the brain by promoting neurone outgrowth in cells expressing both ERα and ERβ.[25] Data from animal studies showed that ovariectomised rats receiving tamoxifen or raloxifene demonstrate increased Choline Acetyltransferase (ChATa) activity in the hippocampus, which contains ERα and ERβ receptors, suggesting that both act as oestrogen-agonists in this area of the brain. Raloxifene also has been shown to affect brain activation patterns during a memory task in 20 post-menopausal women.[26] Functional magnetic resonance imaging (fMRI) was performed before and after 3 months of daily treatment with 60 mg of raloxifene or placebo. Although there was no difference in mean recognition scores between the groups, those receiving raloxifene showed a change in brain activation pattern upon visual encoding in areas associated with cognitive functioning. Unfortunately, no definite conclusion could be drawn on whether these would result in positive or negative changes to cognition in the long term.

Further clues as to the type and severity of cognitive impairment that may occur from endocrine therapies come from the Multiple Outcomes of Raloxifene trial (MORE). This was a randomised clinical trial of raloxifene (60 or 120 mg) versus placebo in $n < 7000$ post-menopausal women. Although there was a trend towards a decline in performance on verbal memory and attention tasks, there were no significant differences between women receiving raloxifene and those receiving placebo. Subsequent analyses of 744 women with suspected dementia revealed that women receiving 120 mg of raloxifene were at significantly lower risk (33%) of developing mild cognitive impairment compared with the placebo group. There was a lower though not significant risk of developing Alzheimer's disease in the group treated with 120 mg of raloxifene (Table 3).[27]

Another study, Co-STAR, is comparing the effects of tamoxifen and raloxifene on age associated decline in memory and other cognitive abilities in women aged 65 years and older. Results will be compared with HRT data from the Women's Health Initiative Study of Cognitive Aging (WHISCA). The results, which are not yet published, will provide insight into the effects of SERMS and HRT on cognitive function.

4.2. *Aromatase inhibitors (AIs)*

Aromatase, needed for the synthesis of oestrogen, is also found in numerous sites in the brain, particularly the hippocampus and the cortex.[28] However, the biochemical changes occurring as a result of the introduction of aromatase-inhibiting (AIs) drugs and the subsequent consequences for cognition are not known. As far as the authors are aware, there is only one published study that

Table 3 – Key findings from treatment studies highlighting the effect of oestrogen on cognition

Author (year)	N	Design	Groups	Relevant finding
Ernst et al. (2002)	76	Observational	Post-menopausal tamoxifen or HRT or control proton magnetic resonance spectroscopy	Reduced concentrations of myo-inositol in the brains of patients of tamoxifen and HRT groups suggest that tamoxifen has an effect similar to oestrogen
Neele et al. (2001)	20	RCT	Post-menopausal women whole brain fMRI conducted before and after 3 months of daily treatment with 60 mg raloxifene	Raloxifene group showed a change in brain activation pattern upon visual encoding associated with cognitive functioning. No definite conclusions
Yaffe et al. (2005)	5386	Randomised trial post-menopausal women	Raloxifene 60 mg or 120 mg versus placebo	No significant differences on cognitive test but subsequent analysis of $n = 744$ women with suspected dementia revealed that 120 mg group were at a significantly lower risk compared with placebo group
Jenkins et al. (2004)	129	Cross-sectional study	Subgroup of post-menopausal women in ATAC trial versus control group	Significantly poorer performance on tasks of verbal memory and processing speed compared to control group

has examined this issue. This involved 100 post-menopausal breast cancer patients who were participating in the Anastrozole, Tamoxifen Alone or Combined (ATAC) clinical trial.[29] These women had been on the trial for a median of 36 months, and had not received chemotherapy. Performance on a series of standardised cognitive tasks was compared with an age-matched control group. The results from this cross-sectional study revealed a significantly poorer performance on tasks of verbal memory and processing speed in the breast cancer patients compared with controls. However, the numbers of patients allocated to the different treatment arms were too small to conduct any between-group analyses to determine whether tamoxifen or anastrozole or the combination was implicated. Also there was no pre-treatment baseline assessment of the patients' performance to be able to establish whether or not the effect was due to endocrine therapy.

5. Conclusions and future research

Much of the literature that exists examining the effects of endocrine therapy on cognition in breast cancer patients has been confounded by prior chemotherapy treatment. Although many authors have attempted to tease out the effects, there is no conclusive evidence of a detrimental effect.[30,31] The lack of consistency in the literature is exacerbated by methodological inconsistencies. Differences in sample sizes, assessment tools including the use of subjective reports of cognitive functioning, approaches to determining meaningful change, timing of follow-up, absence of pre-treatment data and whether women were pre- or post-menopausal have hindered the interpretation of findings.[32] In addition, consideration has not always been given to factors such as depression and anxiety and the role they have in moderating the effects of treatment on cognition.[2] The earlier HRT observational studies are a prime example of the types of misleading interpretations that can be made and show the importance of conducting robust, longitudinal research which may provide counter-intuitive information.

5.1. *IBIS-II cognitive sub-protocol*

An opportunity to address some of these issues is present in the cognitive sub-protocol of the International Breast Cancer Intervention Study (IBIS-II) trial, prevention arm (anastrozole versus placebo). The IBIS-II trial provides the ideal platform from which to explore whether endocrine therapy impairs cognitive processes in post-menopausal women. The advantages of this study over previous investigations are that participants do not have breast cancer, will not have received chemotherapy and as it is a placebo controlled trial the effect, if any, of anastrozole will be evident. The cognitive sub-protocol involves $n < 200$ women from 5 participating centres in the UK. Cognitive assessments are conducted on these women at baseline (pre-trial drug), 6 months and 2 years later. The assessment comprises a piloted battery of standardised neuropsychological tasks used in previous studies and measures of quality of life and psychological morbidity.[29,31] In addition, a subjective measure of cognitive performance is obtained as participants are interviewed about whether or not they have noticed any changes in their memory and/or attention. Considering the evidence from initial studies of hormones on cognition, it is reasonable to predict that anastrozole might have an adverse effect on cognitive functioning in the younger pre-menopausal rather than post-menopausal women. However, given the recent evidence that anti-oestrogen treatments such as tamoxifen and raloxifene may be beneficial to women, it is possible that AIs could demonstrate a similar relationship.

Conflict of interest statement

All authors confirm that they do not have a conflict of interest to state.

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