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The effects of hormone therapy on cognition in breast cancer☆

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Abstract

The use of hormonal therapies for the treatment of breast cancer is common, yet few studies have examined the possible cognitive effects. Several regions of the brain, important in memory and cognition, are rich in oestrogen receptors. As a result, the long-term use of anti-oestrogens may have potential consequences for cognition. This project aims to establish whether significant cognitive deficit exists in women receiving hormone therapy for breast cancer and to develop a cognitive package that is sensitive to the potential effects of oestrogen deficiency on cognition. Cognitive assessments measured a range of memory and attention functions in patient and control groups to identify whether cognitive impairment, if apparent, occurs at a widespread or function specific level. Ninety-four patients from the anastrozole, tamoxifen and combined (ATAC) trial and 35 non-cancer controls were assessed. Groups did not differ significantly in age or estimated full-scale intelligence. The patient group did not differ from controls on measures of working memory, attention and visual memory but was significantly impaired compared to the control group on measures of verbal memory ($P = 0.026$) and processing speed ($P = 0.032$). Cognitive performance in the patient group was not significantly related to length of time on trial or measures of psychological morbidity. As more and more hormonal agents are used in clinical trials of both adjuvant and preventive settings it is of vital importance that any potentially deleterious effects on cognitive function are measured adequately. Preliminary results from this study suggest that anti-oestrogen therapy may cause a specific deficit in verbal memory that corroborates the links between oestrogen levels and verbal memory often reported in studies of the cognitive benefits of hormone replacement therapy.
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1. Introduction

There is substantial evidence that oestrogen may modulate cognitive function, in particular memory (see [1] for a review). In healthy older women endogenous oestradiol levels have sometimes been shown to be associated with better verbal memory performance (total oestradiol) [2] (bioavailable) [3] but not spatial or non-verbal memory [3]. By contrast, Barrett-Connor and Goodman-Gruen [4] found no significant positive association between endogenous oestradiol (total and bioavailable) across a variety of cognitive measures. Yaffe et al. [5] reported that cognitive performance did not differ consistently in relation to total oestradiol. A later study from the same group found that women with high levels of free and bioavailable oestrogen were less likely to develop cognitive impairment [6]. Bioavailable oestradiol may cross the blood–brain barrier more easily and thus, may be more related to cognitive performance.

A large body of research reports comparisons of performance scores between healthy women taking oestrogen replacement therapy and those who are not. A number of observational studies have reported global cognitive benefits of HRT for post-menopausal women [7,8]. More specifically, group differences are most commonly reported on measures of verbal memory in the absence of other cognitive differences [9,10], but this is by no means a consistent finding. One recent study has shown that women who had taken tibolone for 10 years performed worse on three measures of frontal function [11]. Meaningful comparisons between studies are difficult, however, because they vary widely in the assessments used and functions assessed. Sample sizes in many cases are very small and often studies fail to account for mood status, which can affect cognitive performance. Clearer evidence comes from recent imaging studies which suggest that oestrogen replacement has an effect on brain activation patterns [12] and cerebral blood flow [13,14]. In a meta-analysis of eight case-control studies and two prospective cohort studies, Yaffe et al. [15] reported a 29% decrease in the risk of developing Alzheimer's disease

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in oestrogen replacement therapy (ERT) users compared to non-users. Once the disease is established, however, the benefits of ERT are less clear. Several well-conducted randomised trials have found no significant benefit of hormone replacement therapy for established AD (e.g. [16–18]). Four randomised, double blind, placebo controlled trials have reported a significant positive effect of ERT in established Alzheimer's disease [19–22], however, two of these are limited by extremely small patient numbers [19,20] and one uses only a brief mental state measure [22].

Given the widespread use of anti-oestrogens in the treatment and prevention of breast cancer it is important to consider the effects that such oestrogen deprivation may have on cognition. Selective oestrogen receptor modulators (SERMs) such as tamoxifen and raloxifene are not full oestrogen receptor antagonists in the brain and it is likely that there may be different agonist–antagonist profiles for individual SERMs among different brain areas. The cognitive effects of SERMs have largely been studied in the context of raloxifene for osteoporosis prevention. Currently, there is no evidence that raloxifene has a negative effect on cognitive performance [23] and some indication that it may protect against cognitive impairment in women over 70 years of age [24] or with Alzheimer's disease [25]. Only one study has so far reported long-term cognitive effects of tamoxifen [26]. Women who were past or current users of tamoxifen reported seeing their doctor for memory problems more often than women who were never users. Current tamoxifen users also had lower scores (compared to non-users) on a narrative writing task. No significant difference was found between never and past users, which suggests that any effect may be temporary. Although provocative, the study is problematic since cognitive assessments were limited in their scope and were inappropriately administered, that is sent by post rather than conducted face to face, and consequently the data may be unreliable, particularly as tamoxifen has been found to have a similar effect to HRT on brain metabolism [27].

The impact on cognition of other types of hormone therapy, such as the aromatase inhibitor anastrozole is virtually unknown. Because of the great reduction of circulating oestrogen levels in women taking anastrozole, cognitive assessment may be even more important for this group, particularly as there are currently no data on its potential effects on cognitive function.

This paper reports the results of a pilot study that was designed primarily to assess the suitability and sensitivity of a cognitive assessment package and the acceptability of the assessment to patients, with a view to future studies. The cognitive test battery was administered to a group of women who were receiving hormone therapy for the treatment of breast cancer and a group of women without breast cancer. Patients were on the anastrozole, tamoxifen and combined (ATAC) trial and had been randomised to receive either tamoxifen + anastrozole placebo, anastrozole + tamoxifen placebo or anastrozole + placebo. We used a neuropsychological battery, which involved the assessment of many cognitive domains as well as depression and anxiety but which took just 1 h to administer to avoid fatigue. As a pilot study the data analysis is exploratory in its nature, however, comparisons between the groups provide a timely and important contribution to the growing literature.

2. Method

2.1. Patients

One hundred and eighty-four women taking part in the ATAC trial for the treatment of breast cancer were invited to join the cognitive pilot study. Only patients with no evidence of disease were eligible. Patients were recruited from the Withington Hospital, Manchester. The study had full local ethics committee approval and all participants gave full written consent. One hundred and ten women agreed to participate (60%); the reasons for non-participation included ill health ($N = 14$), transport difficulties ($N = 13$), family problems ($N = 6$) and lack of interest ($N = 35$). Importantly, another six women (8% of those who declined to take part) said that they were anxious about taking the memory tests, either because they feared that they had a very bad memory or because they were afraid of what the results might show.

One hundred and ten women were tested in the hospital clinic between November 2000 and June 2001 but seven women were excluded after assessment due to incomplete data ($N = 103$). The patients' full-scale intelligence quotient (FSIQ) was estimated using the National Adult Reading Test (NART) [28]. The patient group had a significantly higher estimated FSIQ than the published norms ($P < 0.0001$). This is probably the result of a self-selection bias common to research projects of this nature—women who are happy to complete cognitive assessments tend to be intelligent and motivated. As would be predicted from such a high ability group their scores were significantly above published norms for all of the measures (with the exception of immediate verbal memory, which was below). As a result, it was not appropriate to compare their test scores with published norms and we recruited a convenience sample of healthy post-menopausal women to act as a control group ($n = 45$). These women had the same geographical background (many were friends or relatives of the patients) and were comparable in terms of the important predictors age and estimated FSIQ. Ten controls and nine patients who had outlying scores on either of these variables were excluded from the analyses resulting in a patient group of 94 and control group of 35. The patient and control groups were then comparable in age ($t = 1.417$, d.f. $= 127$, $P = 0.159$) and estimated FSIQ ($t = 1.171$, d.f. $= 127$, $P = 0.244$; Table 1).

The use of a healthy control group rather than breast cancer patients not exposed to systemic therapy is justified for a number of reasons. The mean length of time the patient group had been on the ATAC trial was 36 months (S.D. =

Table 1
Patient and control group characteristics

	Patient group ($N = 94$)	Control group ($N = 35$)
Estimated FSIQ		
Mean (S.D.)	112.9 (10.6)	115.3 (8.9)
Median	113	117
95% CI	110.8–115.1	112.2–118.4
Age		
Mean (S.D.)	63.1 (7.2)	60.9 (9.3)
Median	62	60
Range	52–86	50-85
95% CI	61.6–64.6	57.7–64.1
Years of education		
Mean (S.D.)	11.82 (2.66)	12.26 (2.76)
Median	11	12
Range	9–18	9–21
95% CI	11.27–12.36	11.30–13.23
HRT use		
Previous	46 (49%)	9 (26%)
Current	0	12 (34%)
Never	48 (51%)	14 (40%)

11 months; range from 12 to 60 months; median time 36 months). The initial psychological impact of diagnosis and physical impact of surgery are less influential than in a group of patients recently diagnosed. Indeed, the psychological morbidity of this patient group was extremely low for a group of cancer patients (16%). In addition, the majority of early stage breast cancer patients would go on to have some form of systemic therapy. It is, therefore, questionable whether women who were unsuited to or elected against systemic therapy would be a representative control group.

All patients had received surgery for early stage breast cancer; none received adjuvant chemotherapy but 67% (63) were treated with a course of radiotherapy. All participants (patients and controls) were screened for dementia using the information and orientation subtest of the Wechsler Memory Scale-III (WMS-III) [29], a series of autobiographical, historical and current information questions that serve as a general screening device, allowing the detection of significant disorientation. None had a history of stroke, Parkinson's disease, alcohol or drug abuse.

2.2. Assessment

The cognitive test battery assesses several broad areas of cognitive function. The tasks are divided into auditory–verbal memory; visual memory; working memory and attention; processing speed and vigilance and intelligence. All of the tests are fully standardised and validated and are taken from published test batteries with population norms. The battery was evaluated in terms of administration time and acceptability with 10 normal control subjects. A breakdown of the test battery is outlined in Fig. 1. All participants completed the neuropsychological tests and a questionnaire relating to everyday cognitive problems. In addition, *patients* completed questionnaires relating to anxiety and depression. Each assessment lasted 1 h and was conducted when patients attended a routine clinic visit. The study was a cross-sectional design with assessments made at one time point. Cognitive tests were always administered in the same order following the requirements of the WMS-III with assessments of estimated FSIQ and processing speed completed during the period prior to

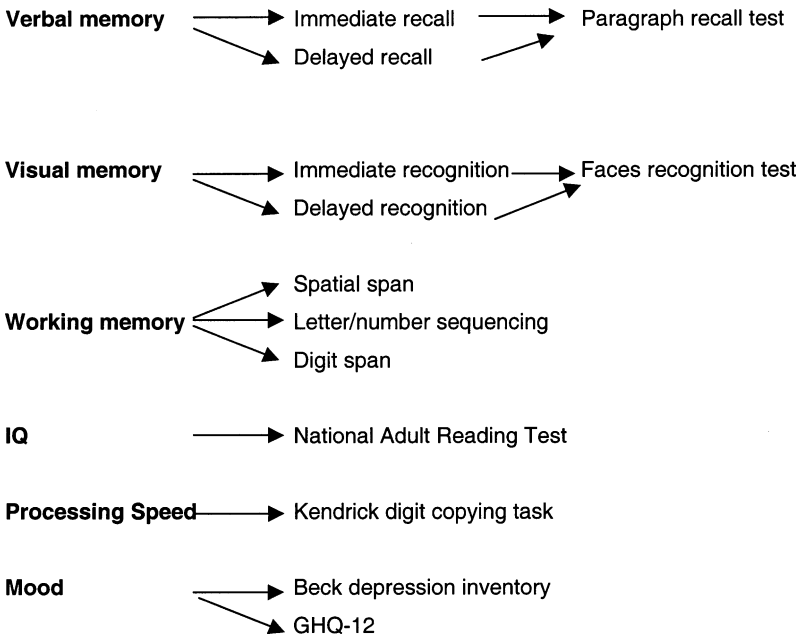

Fig. 1. Cognitive test battery.

delayed recall. The questionnaires were completed at home.

Verbal memory is assessed using the logical memory I and II (story a) from the WMS-III [29]. In this task, a short story (67 words) is read to the participant who is then immediately asked to repeat the story in as much detail as possible. Recall is tested again after approximately 30 min.

Visual memory is measured using the Faces I and II test from the WMS-III. The participant is shown a series of 24 faces for 2 s each. They are then shown 48 faces and asked to decide whether they have seen that face before. Twenty-four are the original faces, 24 novel faces. The participant is asked to perform the recognition task immediately and after a 30 min delay. They are unaware of the requirements of the task until after they have seen the 24 target stimuli.

Working memory capacity reflects the ability to maintain substantial quantities of information "on-line" whilst sometimes performing manipulations of or calculations involving the data being stored. We assess working memory and attention using three tasks from the Wechsler memory scale-III. In letter–number sequencing the participant is read a string of letters and numbers such as *K 2 C 7 S* and is asked to repeat them out loud giving the numbers first in ascending order then the letters in alphabetical order, e.g. *2 7 C K S*. In the digit span task, the participant is read an increasingly longer string of digits which they must repeat back in the same order (condition a) and in reverse order (condition b). Performance scores are the total correct responses to both conditions. Finally, in the spatial span task, a sequence–pattern is tapped out by the experimenter on a board containing 10 blue blocks arranged in a random fashion. The participant must tap the pattern back in the same order (condition a) and in reverse order (condition b). Performance scores are the total correct responses to both conditions.

Processing speed and vigilance is measured using the KDCT digit-copying task (Kendrick Assessment of Cognitive Ageing battery) [30]. The task requires the participant to copy out 100 digits (0–9) arranged in a 10×10 matrix as quickly as possible. Time to complete the task (s) is used as the performance score.

Intelligence was assessed using the National Adult Reading Test [28]. The test consists of 50 irregular words (e.g. deny, labile) that the subject is asked to read aloud and the number of errors made is recorded. WAIS Verbal, Performance and Full Scale IQs can be predicted from this reading error score.

2.3. Self-report measures of cognitive failures and psychological morbidity

All participants completed the Broadbent Cognitive Failures questionnaire [31]. The 25-item questionnaire comprises a series of questions relating to lapses in attention in everyday life, such as forgetting what the person went into a room to do. Questions are rated on a five-point scale ranging from 0-'never' to 5-'very often'.

2.4. Measures of psychological morbidity (patients only)

In addition to the cognitive measures, each patient completed the GHQ-12 and Beck depression inventory (BDI) [32]. The BDI has 21 items each consisting of four or five alternate statements graded in severity from 0 to 3. The items reflect affective, cognitive, overt behavioural, somatic and interpersonal symptoms of depression. On the BDI a score 5–9 is considered to represent normal ups and downs of life (below 5 may be denial of depression); 10–18 represents mild to moderate depression; 19–29 moderate to severe; 30–63 severe depression. In addition, the GHQ-12 questionnaire was administered to assess psychological morbidity. This instrument has high internal reliability and validity and was designed specifically as a brief screening instrument in large population studies.

2.5. Statistical analysis

Statistical Package for the Social Sciences (SPSS), version 10, was used for all statistical analyses. Raw scores for each of the cognitive measures were converted to *z*-scores using the mean score of the control group as a reference. Equal variance was assumed for all measures (Levines test for equality of variance >0.05) with the exception of delayed face recognition. There were no missing values. Univariate ANOVAs were conducted for each cognitive measure. In the patient group alone, correlational analyses were conducted between scores on the Beck depression inventory and cognitive measures and *t*-tests were conducted comparing patients with GHQ12 scores above threshold (four or above) with those with normal levels (below 4). Correlations were used to analyse the relationship between length of treatment and cognitive performance.

3. Results

3.1. Cognitive measures

3.1.1. Comparisons between patient and the control group

Fig. 2 shows the mean *z*-scores of the patient group compared to the control group on the seven memory measures and on processing speed. The pattern of scores suggests that patients' verbal memory and processing speed are impaired relative to the controls.

Univariate ANOVAs were conducted with *z*-scores on the eight cognitive measures as dependent variables, and group (patient versus control) as the independent variable. A significant group difference was found on the immediate verbal recall task ($F = 4.578$, $P = 0.034$) and processing speed ($F = 3.966$, $P = 0.049$). However, previous research suggests that HRT use may affect cognitive performance, particularly verbal memory [33]. It is conceivable that HRT

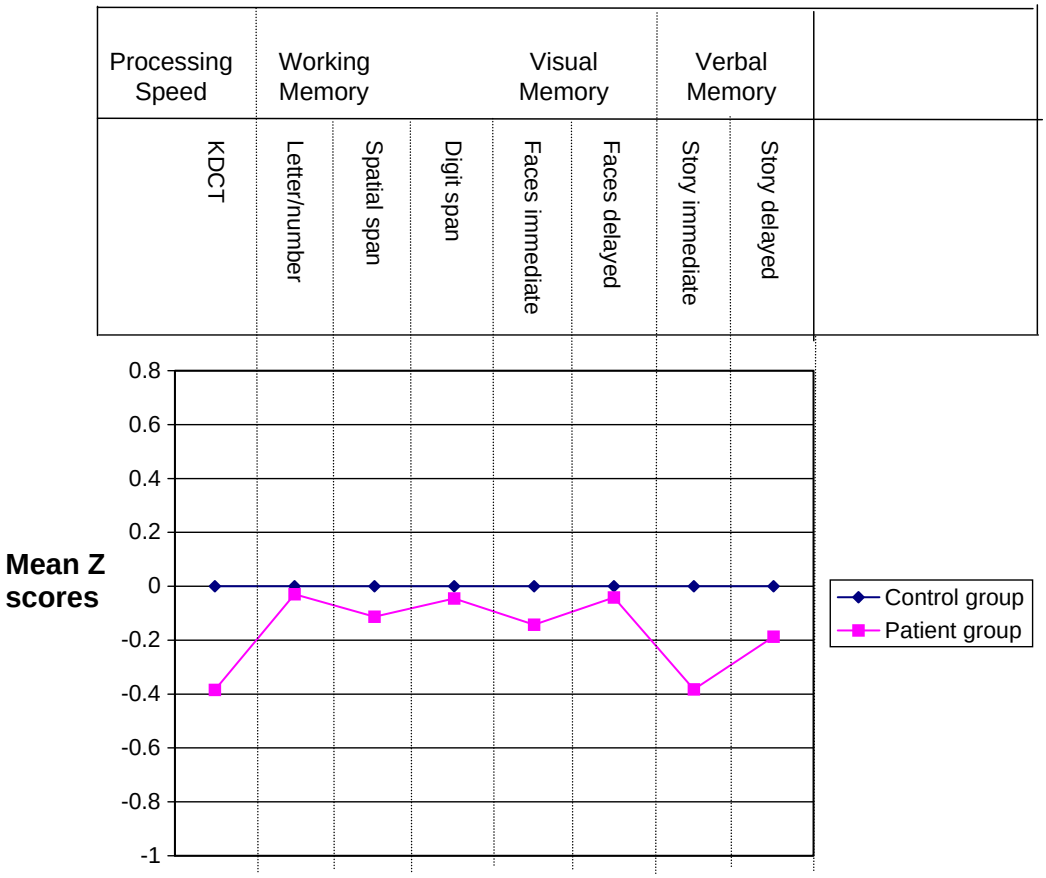

Fig. 2. Plot showing mean control group and patient *z*-scores.

use in the past may have a long-term benefit for cognition. We conducted Univariate ANCOVAs for processing speed and immediate verbal memory with HRT use as a covariate. In the patient group, HRT was classified as never used or used prior to diagnosis in the control group it was classified as never used, current use or used in the past. Both effects remain significant; the processing speed task ($F = 4.72$, $P = 0.032$) and the immediate verbal recall task ($F = 5.10$, $P = 0.026$). Length of time on trial, and hence on hormone therapy, did not correlate significantly with any cognitive measure.

This study was not designed or powered to investigate differences between treatment arms of the ATAC trial. Given the differences between the mechanisms of action of tamoxifen and anastrozole, however, it is possible that different hormonal therapies will have different effects on cognitive function. To this end we further analysed the two tasks that showed a significant difference between patient and control groups. We compared each treatment group with the healthy control group. The experimenters are blinded to the nature of the treatment received by each group, which are referred to as treatment arms A–C. Fig. 3 shows the mean *z*-scores of the three patient groups compared to the control group on the processing speed task and the immediate verbal recall task. On both tasks it can be seen that the mean *z*-scores for the three groups are below the *x*-axis that represents the control group score. On the processing speed task this difference is significant only for Group A ($F = 5.785$, $P = 0.019$) a difference which remains significant after controlling for HRT use ($F = 9.50$, $P = 0.003$). On the immediate verbal recall task the difference is significant only for Group B ($F = 6.047$, $P = 0.017$) a difference that remains significant after HRT use is controlled for ($F = 4.35$, $P = 0.041$). This difference is not significant if a correction for multiple comparisons is applied.

3.2. Measures of psychological morbidity (patient group only)

Higher scores on the BDI were not significantly associated with lower scores on any cognitive measure. Patients with above threshold scores on the GHQ_{12} did not score significantly lower on any cognitive measure than patients with below threshold scores. High BDI scores were significantly associated with self-reported everyday cognitive failures (Cognitive failures questionnaire) ($r = 0.425$, $P < 0.0001$). Similarly, those patients with above threshold GHQ_{12} scores reported a greater number of cognitive failures ($t = 2.05$, $P = 0.044$). However, these self-reported failures were not born out in the objective measures.

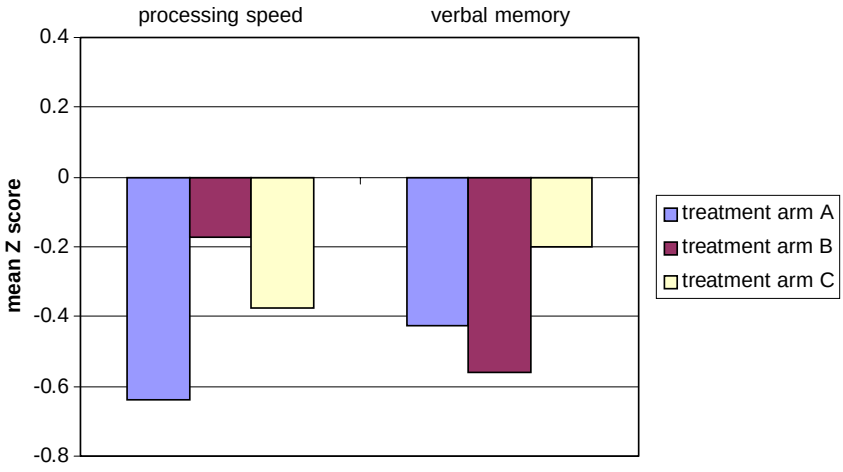

Fig. 3. Mean *z*-scores for the three treatment arms on the processing speed and immediate verbal memory tasks.

4. Discussion

The results from this exploratory pilot study suggest that hormone therapy for the treatment of breast cancer does not affect overall cognitive performance. Instead the anti-oestrogenic effects of the treatments appear to produce a specific impairment on one test of verbal memory—immediate paragraph recall. Verbal memory has been shown to be positively associated with higher serum oestradiol levels [3] and a number of studies have reported higher verbal memory in women taking hormone replacement therapy [10] or soya supplements [34]. The paragraph recall test may be particularly sensitive to the effects of oestrogen on cognition [35] and one implication of our findings is that the anti-oestrogenic effects of tamoxifen and/or anastrozole have a measurable effect on verbal memory, which is the reverse pattern to that seen in healthy women taking HRT. Differences were found between the patient and control groups on the measure of immediate verbal recall but not delayed verbal recall. This pattern has been reported previously in the literature. File et al. [34] report a similar effect in a study of soya and memory. After a 10-week high soya diet, participants showed greater improvement on immediate verbal recall than a control group (soya acts as an oestrogen agonist or partial agonist). Phillips and Sherwin [36] similarly found improved immediate recall rather than delayed in surgically post-menopausal women treated for 6 months with oestrogen compared to a placebo group. The failure to find group differences at delayed recall in this study may also be due to the small number of participants.

We also found a significant difference between the patient and control group on a measure of processing speed. This finding is supported by anecdotal evidence that women experience sluggishness of thought and a general slowing of mental function after treatment for breast cancer. Furthermore, studies of women who have received chemotherapy for breast cancer have shown processing speed deficits [37]. Similarly, links between processing speed and oestrogen have previously been found in girls with Turner's syndrome, who do not produce ovarian oestrogen [38]. Processing speed was impaired in these girls relative to controls, a deficit that was significantly reduced with oestrogen therapy. One factor to consider is that many patients with breast cancer undergo axillary surgery (either node clearance or node sampling) leading to arm morbidity [39]. If the dominant arm is affected this could produce confounding results on many processing speed type tasks where manual dexterity is required. In this study, we found no significant differences on the processing speed task between those women whose surgery affected their dominant arm and those that did not, however, this may be a more pertinent issue when assessments are made a shorter time after surgery.

The results from this exploratory pilot study appear to support a relationship between hormone therapy for the treatment of breast cancer and verbal memory and that this finding requires further investigation. The remit of this pilot study was primarily to assess the suitability of the cognitive measures and the acceptability of the assessment to patients rather than to compare functioning between treatment arms. Nevertheless it is possible that cognitive function is differentially affected as selective oestrogen receptor modulators such as tamoxifen work in a different way to the aromatase inhibitors such as anastrozole. The study was not designed or powered to investigate differences between the treatments arms and the experimenters are blinded to the treatment received by each group but we looked specifically at the two tasks that showed an overall deficit comparing each treatment arm with controls. There were no significant differences for Group C, Group A was significantly slower on the processing speed task and Group B recalled significantly less on the immediate verbal memory task. It is possible though speculative that the differences reflect the different action of tamoxifen and anastrozole. Although the evidence from existing studies is far from conclusive, raloxifene and tamoxifen have not yet been shown to have a negative effect on cognitive performance (e.g. [23,26])

indeed recent imaging studies suggest that raloxifene [40] and tamoxifen [27] have a similar effect to oestrogen in the brain. Performance deficits were found in our patient sample however; two-thirds of whom (presumably) were taking anastrozole either alone or in combination with tamoxifen. No study has yet examined the effects of anastrozole on cognition but it is known that circulating oestradiol levels in these women are greatly suppressed.

The potential cognitive effects of anastrozole will be investigated in the forthcoming international trial of chemoprevention comparing placebo and anastrozole (IBIS II). The IBIS II trial is a multicentre, randomised placebo-controlled clinical trial of 6000 post-menopausal women between the ages of 40 and 70. The trial will recruit women whose risk of breast cancer is at least twice that of the general population. Women will be randomised to receive either anastrozole or placebo daily for 5 years. The cognitive sub-protocol will draw 350 participants from each arm of the main IBIS II trial who will be tested at baseline and followed up at 6 months, 2 and 5 years using a modified assessment battery selected from the tests used in this pilot study. The longitudinal assessment of cognitive function in the IBIS II trial will provide invaluable, reliable data on the effects of anastrozole on cognition in a group of women, who, although at high risk of breast cancer, are otherwise healthy. This allows us to avoid the possible confounding influences of illness, surgery, chemotherapy and depression.

This pilot study has captured a specific cognitive impairment using a cross-sectional design at a single time point. Thorough investigation of the cognitive effects of hormone therapy for breast cancer requires longitudinal assessment of the risk of cognitive decline. Yaffe et al. [6] reported that women with high serum concentrations of non-protein bound and hence bioavailable oestradiol were less likely to develop cognitive impairment than women with low concentrations. The same group [24] found a slight reduction in the risk of cognitive decline for women over 70 receiving raloxifene. The IBIS II trial will provide the same information for women taking anastrozole, where oestrogen levels will be significantly reduced.

The investigation of cognitive impairment also has practical implications for trialists. If lowering oestrogen levels leads to significant cognitive impairment, medication compliance could be compromised. Patients may actively chose to become non-compliant because they feel the cognitive deficits associated with compliance are severe, or compliance may be indirectly compromised because drug-induced memory deficits lead to patients missing appointments or forgetting to take their medication. In addition, women recruited to the study will be at an age where normal age-related cognitive decline begins to be apparent and, therefore, they may be particularly vulnerable to the effects of anti-oestrogens.

Adjuvant hormonal therapy for the treatment of breast cancer confers obvious benefit to a significant majority of women [41] but its value in prevention remains equivocal. It is very important that the side effect profiles are clear to assist clinicians and their patients when discussing therapeutic options. Potential cognitive effects should play an important role in such considerations.

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