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Effects on cognition and mood in postmenopausal women of 1-week treatment with *Ginkgo biloba*

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Abstract

In a double-blind, placebo-controlled study, postmenopausal women (53–65 years old) were randomly assigned to 7-day treatment with *Ginkgo* (120 mg/day, $n=15$) or matched placebo ($n=16$). They were given a battery of cognitive tests and measurements of mood and menopausal symptoms at baseline (before treatment began) and at the end of 7 days. The group treated with *Ginkgo* was significantly better than the placebo group in a matching-to-sample test of nonverbal memory, but the groups did not differ in immediate or delayed paragraph recall or in delayed recall of pictures. In a test of frontal lobe function (rule shifting) and in the Paced Auditory Serial Addition Test (PASAT) (which measures sustained attention but also involves frontal lobe function), the group treated with *Ginkgo* performed significantly better than the placebo group. However, the groups did not differ in a test of planning. The treatments did not differ in their effects on the volunteers' ratings of menopausal symptoms, sleepiness, bodily symptoms or aggression. The benefits of *Ginkgo* on memory and frontal lobe function found in this study are modest but are unlikely to be secondary to major mood changes.

Keywords: *Ginkgo*; Memory; Frontal function; Attention; Anxiety; Menopause

1. Introduction

Concentrated extracts of *Ginkgo* are prepared from the dried leaves of the *Ginkgo biloba* tree, and the active ingredients are flavonoid glycosides and terpenoids, which include ginkgolides and bilobalide. Standardised extracts, such as EGb 761 and LI 1370 (Ginkyo), contain 25% flavonoid glycosides and 6% terpenoids. It is believed that it is the combined or synergistic action of these constituents that is responsible for the beneficial effects of *Ginkgo* (DeFeudis and Drieu, 2000). These include vasodilation, especially in the cerebral circulation, and antagonism of platelet-activating factor by the ginkgolides (Chung et al., 1987). It is thought that these actions contribute to its cognition-enhancing properties, and it is widely prescribed in Germany for cerebral insufficiency syndrome. This consists of the following 12 symptoms: difficulties in concentration and memory, absent-mindedness, confusion, lack of energy, tiredness, decreased physical performance, depressed mood, anxiety, dizziness, tinnitus and headache. Thus, improvements in this syndrome could result from effects on mood and/or cognition. In addition, the free radical scavenging and antioxidant properties of *Ginkgo* flavonoids (Maitra et al., 1995; Oyama et al., 1994, 1996) may also contribute to cognitive enhancement in the elderly through a neuroprotective mechanism.

Ginkgo has been found to have beneficial effects in Alzheimer's disease, in multi-infarct dementia and in the elderly with mild impairment on the Crichton Geriatric Rating Scale (Le Bars et al., 1997, 2000a; Kanowski et al., 1996; Hofferberth, 1989; Wesnes et al., 1987; for reviews, see Le Bars and Kastelan, 2000b; Curtis-Prior et al., 1999; Oken et al., 1998). However, to date, there have been only a few studies on the effects of repeated *Ginkgo* administration in healthy people. Stough et al. (2001) found that *Ginkgo* (120 mg/day for 30 days) significantly improved working memory and long-term auditory verbal memory in a group of 18–40-year-olds. In a group with a similar wide age range (22–59 years), Polich and Gloria (2001) found that *Ginkgo* (120 mg/day for 14 days) significantly improved working memory capacity but was without effect on immediate and long-term memory. Rigney et al. (1999) found no effects of *Ginkgo* (120–300 mg for 2 days) on immediate or delayed word

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recall, reaction time or attention, but working memory was significantly improved by 120 mg, particularly for the group aged 50–59 years. Wesnes et al. (2000) found an index of quality of memory to be significantly improved in a group of healthy 38–66-year-olds receiving 12 weeks of *Ginkgo* (120 mg/day) plus ginseng (200 mg/day), but there were no effects on attention. Studies of cognitively intact older groups have found relatively few significant effects. In a study of 40 males and females (55–86 years old), Mix and Crews (2000) found that 6 weeks of *Ginkgo* treatment (180 mg/day) improved the colour naming part of the Stroop test but was without effect on the interference component or on immediate or delayed verbal and nonverbal memory or on a test of frontal lobe function. In a large scale study (230 subjects) in a similar age range (60–82 years), *Ginkgo* (120 mg/day for 6 weeks) was without effect on immediate or delayed paragraph recall, long-term visual or verbal memory or digit span (Solomon et al., 2002). However, Mix and Crews (2002) found that 6 weeks of treatment with a higher dose (180 mg/day) did improve delayed recall and recognition in a selective reminding task in subjects older than 60 years (age range not given). There was also an improvement in delayed recognition of faces, but the groups differed in their baseline scores on this task, and the groups also differed significantly in their ages. It is therefore possible that, in healthy older people, the cognitive benefits of *Ginkgo* will be rather slight and perhaps dependent on baseline performance. It is therefore important to define more precisely the groups that may benefit from *Ginkgo* as well as the conditions under which improvements are seen. It is also important to try to determine the nature of any cognitive improvements and whether they are primarily affecting memory. One possibility is that one of the main benefits of *Ginkgo* in healthy middle-aged to elderly people is in working memory, which is mediated by the frontal lobes. Frontal lobe function was not well investigated in the Solomon et al. (2002) study, which could account for their negative findings. The possibility that frontal lobe function will be improved by *Ginkgo* is supported by its activating effects on EEG, particularly in the frontal lobe (see DeFeudis, 1991 for review).

The purpose of the present study was therefore to examine the cognitive effects of 1-week treatment with *Ginkgo* in a well-defined population. Postmenopausal women were selected because this is a population in which difficulties in memory and concentration are a frequent complaint and in which inefficient frontal lobe functioning may contribute to age-related memory impairments (Daum et al., 1996; Persad et al., 2002). In an open-label questionnaire survey study, without placebo control, *Ginkgo* (120 mg/day for 4 months) was reported to reduce self-ratings of anxiety and depression in older (mean age 69 years) volunteers (Cockle et al., 2000), and in a small sample study on sexual dysfunction, *Ginkgo* reduced anxiety and sexual dysfunction (Wheatley, 1999). However, relatively few studies have examined its effects on mood. We therefore also measured self-ratings of anxiety, depression and sleepiness as well as changes in mood and bodily symptoms after the stress of cognitive testing.

2. Materials and methods

2.1. Subjects

Thirty-four postmenopausal women aged 53–65 years were recruited from those responding to articles in the national and local press. Local Ethics Committee approved the study, and all subjects gave written informed consent. All subjects were healthy and defined as postmenopausal if they had not menstruated in the previous 12 months. Only two women (one in each group) had undergone a surgical menopause. Exclusion criteria were use of HRT in the previous 12 months, smoking more than 20 cigarettes per day, current illness or use of psychoactive medication, including soya supplements, *Ginkgo* or ginseng. Only four subjects were smokers, three in the placebo group, smoking a mean of 16 cigarettes per day, and one in the *Ginkgo* group, smoking a mean of 2 cigarettes per day. The subjects were asked whether they were taking any herbal supplements and, if so, to maintain the same regime during the study. Ten subjects in the *Ginkgo* group and nine in the placebo group were taking vitamins and minerals, eight in each group were taking fish oil and four in the *Ginkgo* group and three in the placebo group were taking evening primrose oil.

2.2. Supplement administration

The *G. biloba* supplement administered to the subjects was in the form of Ginkyo One-A-Day tablets (Lichtwer Pharma UK, Mere Park, Marlow, Bucks, UK). Ginkyo One-A-Day tablets contain the standardised special extract LI 1370 obtained from the green leaves of the *G. biloba* tree. This extract contains 25% *Ginkgo* flavonoids and 6% terpenoids. The subjects took a tablet containing 120 mg *G. biloba* extract every morning for 7 days. Those allocated to the placebo group took an identical, colour-matched capsule for 7 days.

2.3. Procedure

The subjects were randomly allocated, 17 each to the *Ginkgo* and placebo groups. Three subjects dropped out of the study. One in the placebo group dropped out because of a brief menstrual period, and two in the *Ginkgo* group dropped out because they found the baseline test day too demanding.

Subjects were required to attend two sessions for cognitive testing. The first test session (baseline) was before the start of supplement treatment and the other session was at the end of 7 days. On the baseline test day, all subjects were given a practice session to familiarise them with the computerised test battery. An estimate of verbal IQ was obtained using the National Adult Reading Test-Revised version (NART-R)

(Nelson and Willison, 1991). Thereafter, the battery of tests was the same on the baseline test day and on the test day after 7 days of supplement intervention. On the test day, all subjects took their tablet at breakfast and were tested 4–5 h later, which coincides with the time at which significant effects have been found following a single dose (Kennedy et al., 2000, 2002). Parallel forms of all tests were used on the two occasions, except for the sustained attention task.

The Hospital Anxiety and Depression Scale (HAD) (Zigmond and Snaith, 1983) was used to determine anxiety and depression. The Greene Climacteric Scale (Greene, 1998) was used to assess menopausal symptoms, yielding four independent symptom measures, psychological, somatic and vasomotor symptoms and sexual dysfunction. Sleepiness was assessed using the Stanford Sleepiness Scale (Hoddes et al., 1973), which was given at the start of testing and then again at the end, and the Epworth Sleepiness Scale (Johns, 1991, 1992), which was given at the end of the test session.

2.4. Episodic memory

There were three tests of episodic memory. Immediate and delayed paragraph recall (from the Weschler Memory Scale-Revised) (Weschler, 1987). In this test, 25 units of information are read at the rate of one unit per second, and the subjects were told to remember as accurately as possible. Recall was tested immediately and after 20 min, and the number of correctly recalled units was scored. The test of short-term nonverbal memory was the Delayed Matching-to-Sample (DMTS) test from the Cambridge Neuropsychological Test Automated Battery (CANTAB CeNeS, Cambridge), which has been shown to activate the temporal cortex (Owen et al., 1995; Monk et al., 2002). In this test, a sample complex pattern is displayed on the computer screen, and the task is to select one of four similar patterns that matches the sample. The four patterns are either displayed simultaneously with the sample or appeared after a delay of 0, 4 or 12 s. The number of correct responses was scored for five patterns at each delay. Long-term episodic memory was also measured by presenting a set of 20 pictures of common objects; each picture was presented for 5 s. Then, 20 min later, the subject was asked to recall as many of these as possible.

2.5. Tests of frontal lobe function

Two tests of frontal lobe function were selected from the CANTAB. A test of rule learning, reversal and shifting (the first six stages of the IDED test) provided a measure of mental flexibility controlled by the frontal cortex (Owen et al., 1991). In this test, a series of pairs of patterns was presented on a computer screen, and the task was to learn the rule that determined which pattern was correct. Once the rule was correctly learned, this rule was reversed or shifted. The time taken to complete each stage (simple discrimination, simple reversal, compound discriminations 1 and 2, compound reversal and intradimensional shift) was recorded. Planning ability was measured using the Stockings of Cambridge (SoC) test, which has also been shown to be a measure of frontal lobe function (Owen et al., 1990). The computer screen displayed two sets of three coloured balls that could be housed in three stockings. The task was to move the balls in the lower part of the screen so that the pattern exactly matched that shown in the upper part. The task varied in difficulty with three levels of difficulty so that the match could be obtained in two, three or four moves. The easy parts of the task were used for training; then, the time to correctly complete the four-move task was recorded.

2.6. Sustained attention

The Paced Auditory Serial Addition Test (PASAT) was used to measure sustained attention (Spreen and Strauss, 1991). This involved adding together successive pairs of digits read from a list of 61 numbers, presented at different speeds from one digit every 2.6 s to one every 1.2 s. This is a difficult test to master, and the first two speeds of presentation (2.6 and 1.9 s between digits) were used as practice. The two fastest speeds, 1.5 and 1.2 s between successive digits, were used to assess performance. The total number of correct responses (maximum of 60 per trial) was recorded for each of these two trials. This task also involves frontal lobe function (Staffen et al., 2002) because of its working memory component and the need to inhibit interfering responses.

2.7. Mood ratings

Self-ratings of mood and bodily symptoms were taken at the start of the test session and then again after completing the cognitive tests. Visual analogue rating scales were used to assess bodily symptoms, aggression and mood (Bond and Lader, 1974, 1986). For the bodily symptoms, the scale went from "no symptoms" to "very severe" and was separated by a 100 mm line. For the aggression and mood scales, each item consisted of a pair of opposite adjectives separated by a 100 mm line. The subject indicated how she felt at the time by placing a perpendicular mark at the appropriate place along each line. Previous studies have found increased ratings of anxiety and aggressive mood after a similar battery of cognitive tests, including the PASAT (File et al., 2001, 2000a; Fluck et al., 2002), suggesting that subjects find completing this test battery to be stressful.

2.8. Statistics

The data from the episodic memory tests were first analysed by a two-way multivariate analysis of variance (MANOVA), which permits analysis of the effects of the supplement whilst controlling for intercorrelations between measures, thus reducing the risk of false positives from a series of univariate tests. The two factors were the between-group factor of experimental group and the repeated-measures factor of test day. Because the first test day was at

baseline, before any treatments were given, the effect of the *Ginkgo* treatment could only be assessed by the Group × Day interaction. Because there was a significant effect of test day, the MANOVA was followed by a series of univariate two-way ANOVAs for each of the individual measures. Similar ANOVAs were used to analyse the data from the other cognitive tests, the Greene Climacteric Scale and the Epworth Sleepiness Scale. The ratings of aggressive mood were analysed by a three-way MANOVA, with treatment as the between-group factor and day (baseline and Day 7) and time (before and after cognitive testing) as the repeated-measures factors. The bodily symptoms were likewise analysed by a three-way MANOVA, and the mood factors and Stanford Sleepiness Scale were analysed by three-way ANOVAs. Where effects reached significance, both F values and probability levels are quoted. Where results did not reach significance, only the F ratios are presented, and nonsignificance is indicated (n.s.). The statistical package used was SPSS version 10.1 for windows.

3. Results

It can be seen from Table 1 that at baseline the groups did not differ in their age, IQ, years of secondary education, time since the menopause, height, weight, weekly intake of tea, coffee or alcohol [$F(1,29) < 1.2$, n.s. in all cases]. At baseline, the groups did not differ in their levels of anxiety or depression as measured on the HAD scale [$F(1,29) < 1.6$, n.s. in both cases] (see Tables 1 and 2). There were no group differences in their menopausal symptoms [$F(1,31) < 2.1$, n.s. in all cases] (see Table 2) or in their ratings of sleepiness on either the Epworth or the Stanford scales [$F(1,29) < 1.0$, n.s. in both cases] (see Tables 2 and 4).

3.1. Episodic memory

There was a significant effect of test day on the factor measuring episodic memory [MANOVA, Day, $F(4,26) = 5.9$, $P < .002$], reflecting the fact that both groups showed a significant practice effect. However, the Group × Day interaction did not reach significance [$F(4,26) = 1.8$, n.s.]. Examining the results for the individual tests, there was a marked practice effect on both paragraph and picture recall [$F(1,29) = 12.6$, $P < .001$ for paragraph; $F(1,29) = 11.6$, $P < .002$ for picture] but no effects of treatment [$F(1,29) < 1.2$, n.s. in both cases] (see Table 3). However, there was a significant effect of *Ginkgo* treatment in the DMTS test [Group × Day interaction, $F(1,29) = 4.2$, $P < .05$]. This was because the *Ginkgo* group showed improvement in this task after 1 week of treatment, whereas the placebo group got slightly worse (see top left panel of Fig. 1). To illustrate this interaction term, Fig. 1 shows these effects as the change in

Table 1
Mean ± S.E.M. age, estimated IQ (based on the NART), years in secondary education, time since the menopause (months), height (cm), weight (kg), daily tea and coffee consumption (cups) and weekly alcohol intake (units) and HAD_A anxiety scores of subjects allocated to the placebo or *Ginkgo* treatment

	Placebo ($n = 16$)	*Ginkgo* ($n = 15$)
Age (years)	58.6 ± 1.0	58.3 ± 1.0
IQ	111.6 ± 2.4	114.7 ± 1.5
Years of secondary education	5.4 ± 0.3	5.2 ± 0.5
Time since the menopause	100.9 ± 18.9	105.6 ± 17.4
Height (cm)	161.6 ± 2.7	164.1 ± 1.5
Weight (kg)	67.0 ± 3.4	65.7 ± 2.1
Daily tea intake (cups)	3.2 ± 0.7	2.3 ± 0.6
Daily coffee intake (cups)	1.8 ± 0.4	2.1 ± 0.7
Weekly alcohol intake (units)	3.1 ± 1.1	4.3 ± 1.2
HAD_A	8.0 ± 1.2	6.1 ± 0.8

Table 2
Mean ± S.E.M. scores for psychological, somatic and vasomotor symptoms and sexual dysfunction on the Greene Climacteric Scale, depression (HAD_D) and sleepiness on the Epworth Sleepiness Scale at baseline and after 1 week of placebo or *Ginkgo* treatment

	Placebo ($n = 16$)		*Ginkgo* ($n = 15$)	
	Baseline	1 week	Baseline	1 week
Greene Climacteric Scale				
Psychological symptoms	9.6 ± 1.6	6.7 ± 1.4	6.9 ± 1.0	5.1 ± 1.2
Somatic symptoms	3.8 ± 0.9	2.9 ± 0.8	3.1 ± 0.6	2.5 ± 0.7
Vasomotor symptoms	1.9 ± 0.5	1.6 ± 0.5	1.8 ± 0.5	1.2 ± 0.4
Sexual dysfunction	1.0 ± 0.3	0.7 ± 0.3	1.4 ± 0.2	1.2 ± 0.2
HAD_D	4.4 ± 0.8	3.1 ± 0.7	3.1 ± 0.7	3.1 ± 0.7
Epworth Sleepiness Scale	7.8 ± 1.3	7.6 ± 1.2	7.4 ± 1.2	7.2 ± 1.4

Table 3
Mean ± S.E.M. of number correct in the picture and paragraph recall tasks, times (ms) to learn simple and complex discriminations and to reverse the simple and complex discrimination rules in the IDED task and number of moves and times (ms) to complete the four-move planning task at baseline and after 1 week of placebo or *Ginkgo* treatment

	Placebo		*Ginkgo*	
	Baseline	1 week	Baseline	1 week
Picture recall (number correct)	8.9 ± 0.7	10.5 ± 0.7	8.2 ± 0.6	9.7 ± 0.7
Paragraph immediate recall (items recalled)	11.7 ± 0.9	14.9 ± 1.0	11.8 ± 1.0	14.1 ± 0.9
Paragraph delayed recall (items recalled)	10.7 ± 1.0	13.5 ± 1.0	11.7 ± 1.0	12.6 ± 1.0
IDED				
Simple discrimination (ms)	1620 ± 205	2058 ± 349	1954 ± 259	2633 ± 565
Simple reversal (ms)	1371 ± 163	1052 ± 84	1474 ± 178	1383 ± 158
Compound discrimination 1 (ms)	2128 ± 300	1464 ± 130	2692 ± 318	1810 ± 154
Compound discrimination 2 (ms)	1590 ± 211	1171 ± 89	2084 ± 236	1419 ± 158
Compound reversal (ms)	1270 ± 153	1328 ± 178	1505 ± 144	1365 ± 102
Stockings of Cambridge				
Number of moves to complete task	5.7 ± 0.3	5.6 ± 0.3	5.9 ± 0.2	6.1 ± 0.3
Thinking time (ms)	7443 ± 863	8268 ± 1257	7957 ± 1429	8562 ± 926
Subsequent thinking time (ms)	2098 ± 366	1458 ± 225	1795 ± 313	1548 ± 260

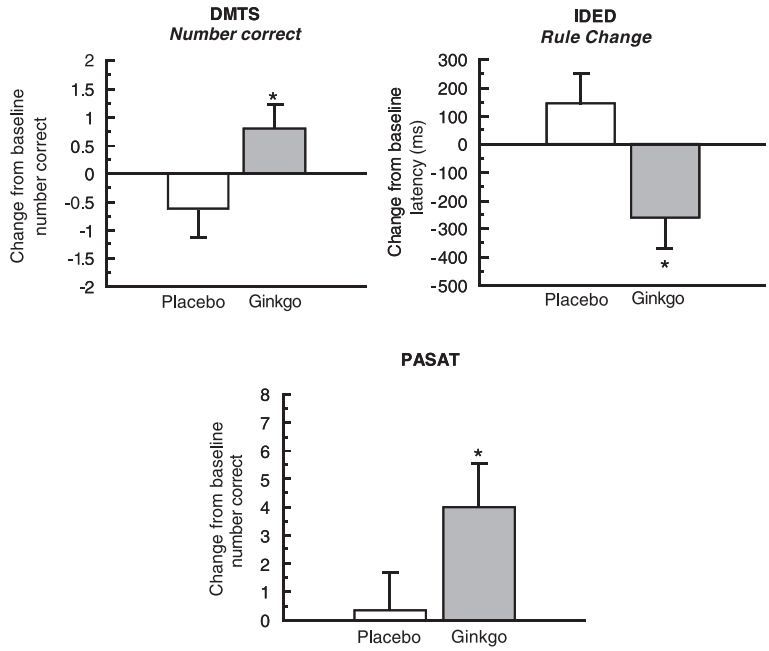

Fig. 1. Mean ± S.E.M. change in performance from baseline day to test day after 1 week of treatment with placebo (clear bars) or *Ginkgo* (filled bars). Top left panel shows the difference in the number of correct responses in the DMTS task between the two test days. Top right panel shows the difference in the time (ms) taken to learn a new rule in the test of mental flexibility (IDED) between the two test days. Bottom panel shows the difference between the two test days in the number of correct responses at 1.6 s speed of presentation minus the number correct at 1.2 s speed of presentation in PASAT. * $P < .05$, compared with placebo.

performance from the baseline test day to the test at 1 week. However, the groups did not differ in their baseline scores in this task (number of correct responses, mean ± S.E.M., *Ginkgo* = 16.7 ± 0.5, placebo = 17.2 ± 0.4).

3.2. Tests of frontal lobe function

Only 25 of the women were able to complete this task as far as the first six stages. The data were therefore analysed only for those who were able to do the task ($n = 13$ in the placebo group, $n = 12$ in the *Ginkgo* group). The scores for the first five stages of the IDED task are shown in Table 3, and the groups did not differ in their baseline scores for these stages. In Stage 1, learning the rules for simple discrimination, there were no significant effects [Day, $F(1,23) = 2.7$, n.s.; Group × Day interaction, $F(1,23) < 1.0$, n.s.]. In Stage 2, learning the reversal of the simple discrimination rule, there was a practice effect [Day, $F(1,23) = 4.5$, $P < .05$], but there was no effect of the *Ginkgo* treatment [Group × Day interaction, $F(1,23) = 1.4$, n.s.]. There was also a significant practice effect in learning the first and second compound discriminations [Day, $F(1,23) = 14.9$ and 12.6, $P < .001$], but there was no effect of the *Ginkgo* treatment in learning these compound discrimination rules [Group × Day interaction, $F(1,23) < 1.0$ in both cases, n.s.]. There was no significant practice effect in learning the reversal of the compound discrimination or any effect of *Ginkgo* [$F(1,23) < 1.0$, n.s. in both cases]. There was no practice effect in learning the intra-dimensional rule shift [$F(1,23) < 1.0$, n.s.], but there was a significant effect of *Ginkgo* [Group × Day interaction, $F(1,23) = 6.8$, $P < .02$]. This was because the *Ginkgo* group got better (shown by a faster time to complete the task), whereas the placebo group got worse (see top right panel of Fig. 1). Once again, the figure illustrates the change from baseline, but the groups differed in their baseline scores of time (ms) to complete the task (mean ± S.E.M., *Ginkgo* = 1883.4 ± 157.9, placebo = 1356.6 ± 98.5, $P < .05$). Analysis of covariance was therefore conducted in the change in scores from baseline to Week 1, with the baseline score as a covariate. This showed that the effect of *Ginkgo* was dependent on the baseline score.

In the test of planning, there was no practice effect in the initial thinking time nor was there any effect of treatment [$F(1,29) < 1.0$, n.s. in both cases]. In the time taken to complete the task, there was no significant practice effect [Day, $F(1,29) = 3.1$, n.s.] and no effect of *Ginkgo* [Group × Day interaction $F(1,29) < 0.1$, n.s.] (see Table 3).

3.3. Sustained attention

In the PASAT test of sustained attention, there was a significant Treatment × Day × Speed interaction [$F(1,29) = 7.1$, $P = .01$], because although the groups did not differ at the fastest presentation speed (1.2 s), at the 1.6 s speed, the *Ginkgo* group showed improvement after 1 week of treatment, whereas the placebo group showed little change (see

Table 4
Mean ± S.E.M. scores on the Stanford Sleepiness Scale and scores for the factors of anxiety, sedation and well-being derived from the Bond and Lader Mood Scale in subjects before (PRE) and after (POST) cognitive testing at baseline and after 1 week of treatment with placebo or *Ginkgo*

	Placebo ($n=16$)				*Ginkgo* ($n=15$)			
	Baseline		1 week		Baseline		1 week	
	PRE	POST	PRE	POST	PRE	POST	PRE	POST
Stanford Sleepiness Scale***	2.3 ± 0.3	3.2 ± 0.4	2.4 ± 0.3	3.3 ± 0.4	2.1 ± 0.2	3.1 ± 0.2	2.3 ± 0.2	2.8 ± 0.2
Anxiety***	50.7 ± 4.0	69.7 ± 4.4	43.0 ± 4.3	58.7 ± 5.3	45.8 ± 3.3	72.6 ± 3.7	50.2 ± 4.5	64.1 ± 3.7
Sedation**	49.3 ± 3.0	61.4 ± 3.1	47.3 ± 2.8	56.0 ± 3.6	53.8 ± 1.9	67.8 ± 2.1	51.8 ± 3.3	61.6 ± 3.1
Well-being*	54.7 ± 3.7	41.8 ± 3.8	57.0 ± 3.5	48.3 ± 3.5	49.7 ± 2.0	41.1 ± 3.3	50.1 ± 3.7	48.4 ± 3.3

* $P<.05$, PRE–POST testing difference for both groups, ANOVA.
** $P<.01$, PRE–POST testing difference for both groups, ANOVA.
*** $P<.001$, PRE–POST testing difference for both groups, ANOVA.

bottom panel of Fig. 1). This figure shows the difference in scores between these presentation speeds between baseline and Week 1. Post hoc tests showed that the groups did not differ in their scores at baseline (difference between number correct at 1.2 and 1.6 s speeds, placebo = 5.6 ± 1.8, *Ginkgo* = 2.9 ± 1.1; number correct at 1.6 s speed, placebo = 21.1 ± 3.3, *Ginkgo* = 19.9 ± 3.1).

3.4. Menopausal symptoms

There were no significant effects of treatment on any of the menopausal symptoms assessed by the Greene Climacteric Scale (Group × Day, $F<1.0$, n.s. in all cases) (see Table 2). However, there was a significant effect of day for all symptoms [$F(1,29)=13.7$, $P<.001$ for psychological; $F(1,29)=6.8$, $P=.01$ for vasomotor; $F(1,29)=9.0$, $P<.01$ for somatic], except for sexual dysfunction [$F(1,29)=3.8$, $P=.06$]. This means that simply taking part in the trial had the effect of significantly reducing menopausal symptoms over a period of a week (see Table 2).

3.5. Sleepiness

There were no significant effects of treatment or of test day on the rating of sleepiness as assessed by the Epworth Sleepiness Scale [$F(1,29)<0.2$, n.s. in both cases] (see Table 2). On the Stanford Sleepiness Scale, the subjects rated themselves as more tired after completing the test battery than before starting it [Time, $F(1,29)=20.1$, $P<.0001$] (see Table 4). However, there was no effect of treatment in the change in sleepiness ratings [Group × Day × Time, $F(1,29)<1.0$, n.s.] (see Table 4).

3.6. Mood ratings

Three mood factors (anxiety, sedation and well-being) can be extracted from the Bond and Lader Mood Scale (Bond

Table 5
Mean ± S.E.M. individual scores comprising the aggression factor in subjects before (PRE) and after (POST) cognitive testing at baseline and after 1 week of treatment with placebo or *Ginkgo*

	Placebo ($n=16$)				*Ginkgo* ($n=15$)			
	Baseline		1 week		Baseline		1 week	
	PRE	POST	PRE	POST	PRE	POST	PRE	POST
Angry***	82.9 ± 3.4	64.3 ± 5.3	81.3 ± 5.2	65.9 ± 7.3	87.1 ± 2.9	68.7 ± 5.5	85.4 ± 3.5	72.4 ± 5.5
Quarrelsome*	80.8 ± 5.6	71.9 ± 5.5	83.3 ± 4.8	76.9 ± 4.9	81.4 ± 6.1	82.7 ± 3.8	88.1 ± 3.7	82.4 ± 3.8
Furious***	83.7 ± 3.2	64.9 ± 5.9	83.9 ± 3.2	74.1 ± 5.8	85.8 ± 2.9	61.1 ± 6.3	82.6 ± 3.8	66.5 ± 3.5
Unsociable	84.7 ± 3.1	76.8 ± 5.6	86.0 ± 3.7	80.8 ± 5.7	87.5 ± 3.0	83.0 ± 3.8	87.4 ± 2.9	87.5 ± 2.9
Aggressive***	78.6 ± 3.7	64.5 ± 5.3	77.4 ± 4.3	72.4 ± 4.3	85.1 ± 2.9	70.8 ± 5.9	83.6 ± 3.3	72.9 ± 5.2
Belligerent*	71.9 ± 5.8	61.6 ± 6.9	64.6 ± 6.1	65.7 ± 6.4	80.5 ± 4.2	71.6 ± 5.0	79.4 ± 5.0	77.1 ± 4.3
Resentful	79.4 ± 4.7	71.8 ± 5.8	80.7 ± 4.8	73.1 ± 6.2	78.5 ± 5.9	80.6 ± 3.4	86.9 ± 2.4	82.1 ± 3.2
Impatient*	77.3 ± 6.8	65.9 ± 7.0	75.4 ± 8.0	74.6 ± 5.4	85.5 ± 4.4	63.9 ± 7.1	84.8 ± 4.9	74.7 ± 6.0
Hostile	88.1 ± 2.9	78.9 ± 4.4	90.4 ± 1.5	85.3 ± 4.2	84.2 ± 5.2	85.0 ± 3.1	85.7 ± 3.5	82.8 ± 4.7
Spiteful	81.0 ± 4.1	82.3 ± 3.9	84.7 ± 2.8	82.3 ± 3.2	86.3 ± 3.4	85.3 ± 2.6	84.9 ± 4.0	82.5 ± 3.6
Annoyed***	84.7 ± 2.6	64.1 ± 7.3	81.1 ± 4.4	69.6 ± 5.5	85.3 ± 3.5	51.3 ± 7.7	85.1 ± 3.3	58.1 ± 7.5
Disgusted***	90.3 ± 3.0	62.3 ± 5.8	87.9 ± 3.4	69.4 ± 7.1	84.3 ± 4.8	47.1 ± 7.5	78.9 ± 4.6	64.5 ± 6.7
Rebellious*	80.4 ± 3.8	72.3 ± 7.0	83.4 ± 3.9	73.3 ± 6.2	85.4 ± 3.4	78.9 ± 4.0	82.4 ± 4.6	81.9 ± 3.3

* $P<.05$, PRE–POST testing difference for both groups, ANOVA.
*** $P<.001$, PRE–POST testing difference for both groups, ANOVA.

Table 6
Mean ± S.E.M. individual scores comprising the bodily symptoms factor in subjects before (PRE) and after (POST) cognitive testing at baseline and after 1 week of treatment with placebo or *Ginkgo*

	Placebo ($n=16$)				*Ginkgo* ($n=15$)			
	Baseline		1 week		Baseline		1 week	
	PRE	POST	PRE	POST	PRE	POST	PRE	POST
Anxiety***	23.9 ± 5.0	39.1 ± 7.0	27.3 ± 7.2	36.9 ± 7.3	16.7 ± 2.7	47.7 ± 7.5	17.4 ± 3.5	41.5 ± 5.7
Sweating	13.3 ± 4.4	22.1 ± 6.5	17.4 ± 5.6	19.8 ± 5.3	20.2 ± 6.2	22.4 ± 6.2	15.7 ± 4.0	22.2 ± 5.0
Shaking**	13.4 ± 3.8	21.4 ± 6.2	11.3 ± 4.0	11.9 ± 2.8	12.6 ± 3.3	27.5 ± 5.7	10.8 ± 1.8	20.4 ± 4.7
Palpitations***	13.3 ± 3.7	30.3 ± 6.7	16.4 ± 5.2	16.0 ± 4.0	14.4 ± 3.1	29.7 ± 5.9	18.1 ± 4.8	26.7 ± 5.6
Nausea	5.4 ± 1.3	12.4 ± 0.5	8.4 ± 1.9	7.5 ± 1.6	8.3 ± 2.2	9.6 ± 2.6	8.7 ± 1.6	13.5 ± 4.7
Loss of appetite	3.8 ± 0.9	13.8 ± 5.5	7.8 ± 1.5	8.1 ± 1.5	6.7 ± 1.6	8.4 ± 2.1	7.1 ± 1.4	7.3 ± 1.3
Restlessness***	16.8 ± 5.8	36.9 ± 7.9	21.8 ± 6.1	22.6 ± 6.2	16.4 ± 3.6	33.4 ± 7.3	13.6 ± 3.2	22.1 ± 4.7
Dryness of mouth***	9.5 ± 1.9	24.4 ± 6.6	18.3 ± 5.7	17.1 ± 5.7	12.9 ± 3.6	38.3 ± 7.0	20.1 ± 7.2	27.9 ± 6.7
Muscular tension***	12.4 ± 4.1	30.7 ± 7.4	16.6 ± 5.0	21.0 ± 6.2	18.9 ± 4.0	34.1 ± 6.7	19.5 ± 4.3	25.1 ± 5.8
Irritability***	14.9 ± 3.8	34.6 ± 7.5	15.6 ± 5.1	22.6 ± 5.6	16.7 ± 3.4	29.2 ± 7.2	14.3 ± 3.4	18.9 ± 3.9
Physical tiredness**	17.1 ± 6.0	44.3 ± 8.2	29.1 ± 6.8	33.2 ± 6.5	27.3 ± 5.6	25.3 ± 4.8	20.7 ± 5.3	28.3 ± 6.6
Headache	7.5 ± 3.3	21.9 ± 7.4	14.4 ± 5.3	19.9 ± 7.2	11.1 ± 3.3	13.9 ± 4.9	15.1 ± 5.2	7.8 ± 1.6
Dizziness	7.7 ± 3.3	21.6 ± 7.0	12.8 ± 4.1	17.3 ± 5.9	9.3 ± 2.4	11.2 ± 3.1	13.1 ± 4.6	11.7 ± 2.4
Stomach trouble	4.6 ± 0.9	12.4 ± 5.2	5.3 ± 1.1	5.9 ± 1.3	10.4 ± 3.5	9.4 ± 2.7	14.4 ± 5.5	11.8 ± 3.5

** $P<.01$, PRE–POST testing difference for both groups, ANOVA.
*** $P<.001$, PRE–POST testing difference for both groups, ANOVA.

and Lader, 1974). There were no significant effects of treatment on any of these factors (Group × Day, $F<2.0$, n.s. in all cases). Furthermore, the two groups did not differ in their response to the stress of testing (Group × Day × Time, $F<1.0$, n.s. in all cases) (see Table 4). There were significant time effects on the three mood factors showing that both groups became more anxious [$F(1,29)=45.0$, $P<.0001$], more sedated [$F(1,29)=12.5$, $P<.001$] and more discontented [$F(1,29)=6.2$, $P<.02$] as a result of testing (Table 4).

There was no effect of treatment on the factor measuring aggressive mood [MANOVA, Group × Day, $F(13,17)<1.0$, n.s.] and no effect of treatment in response to the stress of cognitive testing [MANOVA, Group × Day × Time, $F(13,17)<1.0$, n.s.]. However, there was a significant effect of time, with both groups feeling more aggressive at the end of testing [MANOVA, $F(13,17)=4.1$, $P<.005$]. Table 5 shows the scores for the individual items that make up the aggression factor.

The bodily symptoms provide measures of somatic anxiety, and on this factor, there was no significant effect of treatment [MANOVA, Group × Day, $F(14,16)<1.0$, n.s.] and no difference between the groups in response to cognitive testing [MANOVA, Group × Day × Time, $F(14,16)=1.7$, n.s.]. However, the increase in symptoms after the stress of cognitive testing nearly reached significance [MANOVA, Time, $F(14,16)=2.2$, $P<.06$] (see Table 6 for the individual symptoms that comprised this factor).

4. Discussion

The present study was a relatively small size one, but the volunteers were randomly assigned to the treatment groups and did not differ significantly on any measures at baseline. As the groups were matched in age, IQ and years in secondary education, it is unlikely that differences in demographic characteristics could account for the effects that we found after 1 week of *Ginkgo* treatment. Because the design of the experiment was double blind, we can also exclude the possible contribution of attitudes and expectancies. The group size for this study was calculated on the basis of the group sizes that showed significant effects of conventional HRT in postmenopausal women (Fluck et al., 2002; File et al., 2002a). It is not likely that a larger group size would have resulted in more significant effects, because there were few *Ginkgo* effects at marginal levels of significance. Because there were no differences between the groups in menopausal symptoms, mood or sleepiness, the improvements that resulted from the *Ginkgo* treatment cannot be secondary to any of these effects. *Ginkgo* had no effect on the menopausal symptoms as measured on the Greene Climacteric Scale. This may have been partly because our subjects had quite low levels of symptoms (maximum score on psychological symptoms could have been 33, on somatic 21, on vasomotor 6 and on sexual dysfunction 3). However, the symptoms were amenable to amelioration, and both groups reported significant reductions over the 7 days of the trial. This suggests that there was a nonspecific placebo effect of taking part in the trial. This is perhaps because of the nature of our subject population who were very health conscious and concerned enough about their memory to volunteer for a trial.

The improvement in the DMTS task must be interpreted with caution, because the overall MANOVA for the episodic memory factor did not reach significance. However, one factor that may have masked *Ginkgo* effects on memory was the very marked practice effect that we obtained on the

paragraph and picture recall tests. These tests were very new for our volunteers, and it seems that the two test days, only 1 week apart, resulted in a more marked practice effect than was found in a previous study when the two test sessions were separated by several weeks (File et al., 2002b). In a larger scale study with longer treatment (6 weeks) with a higher dose (180 mg/day), Mix and Crews (2002) found improved delayed recall and recognition in a selective reminding task. However, these two measures are highly correlated and there was no treatment effect on the other seven measures from this task. A significantly better performance by the *Ginkgo* group was found in one of the two face recognition tests, but this may have been due to baseline differences between the groups. Thus, at the present stage, although *Ginkgo* might improve some aspects of episodic memory in the cognitively intact older population, it is clear that the tests used at present do not always detect this effect. However, significantly more people treated with *Ginkgo* than with placebo rated their memory overall to be improved after 6 weeks of treatment (Mix and Crews, 2002).

Our results provide some evidence that *Ginkgo* also improves frontal lobe function. The improvement in the rule shifting task indicates a positive effect, but this was dependent on the poorer baseline performance of the *Ginkgo* group. This may reflect *Ginkgo* improving performance on measures where performance was poor, or it may reflect a regression to the mean. On the second compound discrimination, the *Ginkgo* group had lower baseline scores than the placebo group (that nearly reached significance), but there was no effect of *Ginkgo* treatment. Thus, the effect of baseline performance does not seem to be a sufficient explanation for the results in the IDED task. Because the PASAT involves working memory and response inhibition, it is a test involving frontal function (Staffen et al., 2002) as well as sustained attention, and in this task, there were positive effects of *Ginkgo* that were not dependent on baseline levels. However, not all frontal functions were affected, as there was no effect of *Ginkgo* on ability to plan. On the contrary, in a factor analysis of these different frontal tasks, Robbins et al. (1994) and Robbins (1996) found that ability to plan loaded on a different factor from the other tests. Thus, it is possible that *Ginkgo* can improve only some of the factors underlying frontal lobe function. Mix and Crews (2002) found no effects of *Ginkgo* on the Trails B Task or the Stroop Interference Test, which are two tests considered at least partly to involve frontal lobe function. However, our results, together with the previous findings of *Ginkgo* improving working memory, do suggest that the frontal cortex might be one important site for *Ginkgo*'s actions as has been shown from previous EEG studies (DeFeudis, 1991). It would be of benefit if future studies were designed to examine this possibility in more detail.

Our results showed that 1 week of *Ginkgo* treatment improved performance in three of the cognitive tasks—the tests of short-term nonverbal recognition memory, mental flexibility and sustained attention. Task difficulty does not seem to be a unifying explanation for the pattern of improvements that we found. The DMTS task was the easiest of the memory tasks, as judged by performance (the maximum score was 20), and recognition is easier than recall. In contrast, the improvement in the IDED task was shown only at the hardest stage, involving a rule shift. The PASAT is a very hard task, but the improvements were found at the second hardest stage. It is possible that the final stage is just too hard for improvements to be seen. In a study on the effects of 3 months of soya supplements to postmenopausal women, significant improvements were also found in the second hardest stage of PASAT (File et al., 2002b; Duffy et al., 2003). Differences in baseline performance were found only in the rule shifting task; thus, this is unlikely to account for the treatment effects found in the DMTS and PASAT.

The cognitive improvements found in this study are of interest, because they have been demonstrated in a group in which deteriorating memory is a major concern and in which there is evidence that inefficient frontal lobe functioning might contribute to age-related memory impairments (Daum et al., 1996; Persad et al., 2002). Improvements in verbal episodic memory in postmenopausal women treated with conventional HRT have been shown in several well-controlled studies (Phillips and Sherwin, 1992; Jacobs et al., 1998, Duka et al., 2000; Hogervorst et al., 2000). Fewer studies have investigated the effects of conventional HRT on frontal lobe function, but two have found positive effects (Keenan et al., 2001; Duff and Hampson, 2000) and positive effects have been found after 12-week treatment with a soya phytoestrogen supplement (File et al., 2002b; Duffy et al., 2003). It will be of major importance to determine whether a longer period of *Ginkgo* treatment will result in cognitive benefits and whether these are more or less marked than those we have observed after 1 week. With conventional HRT, there is evidence that very long-term treatment (10 years) may impair frontal functions (Fluck et al., 2002; File et al., 2002a).

Ginkgo has been found to produce similar EEG changes to tacrine (a cholinesterase inhibitor), in that it decreases slow wave theta activity and increases alpha wave activity, having the profile of an EEG activator (Itil et al., 1996). These effects could be one of the factors underlying cognitive improvement, but other actions, such as increased cerebral blood flow, protection against hypoxia, cerebral oedema, free radical-scavenging activity or antagonism of platelet-activating factor, may play additive or synergistic roles (DeFeudis and Drieu, 2000). An overall increase in alertness would not seem to be an explanation for *Ginkgo*'s effects on cognition. *Ginkgo* did not affect subjective ratings of sedation or sleepiness, a finding that is in agreement with a previous report after 2 days of *Ginkgo* treatment (Rigney et al., 1999), although after 4 months reduced ratings of sedation and improved ratings in sleep quality were found (Cockle et al., 2000). In general, it seems that improved alertness is found after several weeks of treatment (see Soholm, 1998 for review).

In conclusion, the present study has shown that 1-week treatment with *Ginkgo* can have some beneficial cognitive effects. The beneficial effects have been shown in a well-defined population of healthy postmenopausal women aged 53–65 years. We cannot say whether the effects that we have observed after 1 week would also be found after a single dose. Nathan et al. (2002) found no effects of *Ginkgo* in healthy older volunteers 90 min after a single dose. However, the pharmacokinetics may differ in the elderly; therefore, it is possible that this was not the optimal time point. The cognitive benefits of *Ginkgo* may include improved frontal lobe function, and it would be important to explore this possibility further in future studies. It will also be important to determine whether similar effects will be found after a longer period of treatment and whether they will be found in an older age group.

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References

Bond AJ, Lader M. The use of analogue scales in rating subjective feelings. Br J Med Psychol 1974;47:211–8.

Bond AJ, Lader M. A method to elicit aggressive feelings and behaviour via provocation. Biol Physcol 1986;22:69–79.

Chung KF, Dent G, McCusker M, Guinot P, Page CP, Barnes PJ. Effect of a ginkgolide mixture (BN 52063) in antagonising skin and platelet responses to platelet activating factor in man. Lancet 1987;1:248–51.

Cockle SM, Kimber S, Hindmarch I. The effects of *Ginkgo biloba* extract (LI 1370) supplementation on activities of daily living in free living older volunteers: a questionnaire survey. Hum Psychopharmacol 2000; 15:227–35.

Curtis-Prior P, Vere D, Fray P. Therapeutic value of *Ginkgo biloba* in reducing symptoms of decline in mental function. J Pharm Pharmacol 1999;51:535–41.

Daum I, Graber S, Schugens MM, Mayes AR. Memory dysfunction of the frontal type in normal ageing. NeuroReport 1996;7:2625–8.

DeFeudis FV. *Ginkgo biloba* extract (EGb 761): pharmacological activities and clinical applications. Amsterdam: Elsevier; 1991.

DeFeudis FV, Drieu K. *Ginkgo biloba* extract (EGb 761) and CNS functions: basic studies and clinical applications. Curr Drug Targets 2000;1: 25–58.

Duff SJ, Hampson E. A beneficial effect of estrogen on working memory in post-menopausal women taking hormone replacement therapy. Horm Behav 2000;38:262–76.

Duffy R, Wiseman H, File SE. Improved cognitive function in post-menopausal women after 12 weeks of consumption of a soya extract containing isoflavones. Pharmacol Biochem Behav 2003;75:721–9, this issue.

Duka T, Tasker R, McGowan JF. The effects of 3-week estrogen hormone replacement on cognition in elderly healthy females. Psychopharmacology 2000;149:129–39.

File SE, Fluck E, Leahy A. Nicotine has calming effects on stress-induced mood changes in females, but enhances aggressive mood in males. Int J Neuropsychopharmacol 2001;4:371–6.

File SE, Heard JE, Rymer J. Trough oestradiol levels associated with cognitive impairment in post-menopausal women after 10 years of oestradiol implants. Psychopharmacology 2002a;161:107–12.

File SE, Duffy R, Wiseman H. Improved memory and frontal lobe function in post-menopausal women after 3 months' treatment with soya supplements. Eur J Neuropsychopharmacol Abstr 2002b;12:S406.

Fluck E, File SE, Rymer J. Cognitive effects of ten years of hormone-replacement therapy with tibolone. J Clin Psychopharmacol 2002;22:62–7.

Greene JC. Constructing a standard climacteric scale. Maturitas 1998;29: 25–31.

Hoddes E, Zarcone V, Smythe H, Phillips R, Dement WC. Quantification of sleepiness: a new approach. Psychophysiology 1973;10:431–6.

Hofferberth B. The effect of *Ginkgo biloba* extract on neurophysiological and psychometric measurement results in patients with psychotic organic brain syndrome. A double-blind study against placebo. Arzneim-Forsch 1989;39:918–22.

Hogervorst E, Williams J, Budge M, Riedel W, Jolles J. The nature of the effect of female gonadal hormone replacement therapy on cognitive function in post-menopausal women: a meta-analysis. Neuroscience 2000;101:485–512.

Itil TM, Eralp E, Tsambis E, Itil KZ, Stein U. Central nervous system effects of *Ginkgo biloba*, a plant extract. Am J Ther 1996;3(1):63–73.

Jacobs DM, Tang MX, Stern Y, Sano M, Marder K, Bell KL, et al. Cognitive function in nondemented older women who took estrogen after menopause. Neurology 1998;50:368–73.

Johns MW. A new method for measuring daytime sleepiness—the Epworth sleepiness. Sleep 1991;14:540–5.

Johns MW. Reliability and factor-analysis of the Epworth sleepiness scale. Sleep 1992;15:376–81.

Kanowski S, Herrmann WM, Stephan K, Wierich W, Horr R. Proof of efficacy of the *Ginkgo biloba* special extract EGb 761 in outpatients suffering from mild to moderate primary degenerative dementia of the Alzheimer type or multi-infarct dementia. Pharmacopsychiatry 1996;29: 47–56.

Keenan PA, Ezzat WH, Ginsburg K, Moore GJ. Prefrontal cortex as the site of estrogen's effect on cognition. Psychoneuroendocrinology 2001;26: 577–90.

Kennedy DO, Scholey AB, Wesnes KA. The dose-dependent cognitive effects of acute administration of *Ginkgo biloba* to healthy young volunteers. Psychopharmacology (Berlin) 2000;151(4):416–23.

Kennedy DO, Scholey AB, Wesnes KA. Modulation of cognition and mood following administration of single doses of *Ginkgo biloba*, ginseng, and a *Ginkgo*/ginseng combination to healthy young adults. Physiol Behav 2002;75(5):739–51.

Le Bars PL, Katz MM, Berman N, Itil TM, Freedman AM, Schatzberg AF. A placebo-controlled, double-blind, randomized trial of an extract of *Ginkgo biloba* for dementia. North American EGb study group. JAMA 1997;278:1327–32.

Le Bars PL, Kieser M, Itil KZ. A 26-week analysis of a double-blind, placebo-controlled trial of the *Ginkgo biloba* extract EGb 761 in dementia. Dement Geriatr Cogn Disord 2000a;11:230–7.

Le Bars PL, Kastelan J. Efficacy and safety of a *Ginkgo biloba* extract. Public Health Nutr 2000b;3:495–9.

Maitra I, Marcocci L, Droy-Lefaix MT, Packer L. Peroxyl radical scavenging activity of *Ginkgo biloba* extract EGb 761. Biochem Pharmacol 1995;49:1649–55.

Mix JA, Crews Jr WD. An examination of the efficacy of *Ginkgo biloba* extract EGb761 on the neuropsychologic functioning of cognitively intact older adults. J Altern Complement Med 2000;6(3):219–29.

Mix JA, Crews Jr WD. A double-blind, placebo-controlled, randomized trial of *Ginkgo biloba* extract EGb 761(R) in a sample of cognitively intact older adults: neuropsychological findings. Hum Psychopharmacol 2002;17(6):267–77.

Monk CS, Zhuang J, Curtis WJ, Ofenloch IT, Tottenham N, Nelson CA, et al. Human hippocampal activation in the delayed matching- and nonmatching-to-sample memory tasks: an event-related functional MRI approach. Behav Neurosci 2002;116(4):716–21.

Nathan PJ, Ricketts E, Wesnes K, Mrazek L, Greville W, Stough C. The acute nootropic effects of *Ginkgo biloba* in healthy older human subjects: a preliminary investigation. Hum Psychopharmacol 2002;17(1):45–9.

Nelson HE, Willison JR. Restandardisation of the NART against the WAIS-R. Windsor: NFER-Nelson; 1991.

Oken BS, Storzbach DM, Kaye JA. The efficacy of *Ginkgo biloba* on cognitive function in Alzheimer disease. Arch Neurol 1998;55:1409–15.

Owen AM, Downes JJ, Sahakian BJ, Polkey CE, Robbins TW. Planning and spatial working memory following frontal lobe lesions in man. Neuropsychologia 1990;28:1021–34.

Owen AM, Roberts AC, Polkey CE, Robbins TW. Extra-dimensional versus intra-dimensional set shifting performance following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. Neuropsychologia 1991;29:993–1006.

Owen AM, Sahakian BJ, Semple J, Polkey CE, Robbins TW. Visuospatial short-term recognition memory and learning after temporal lobe excisions, frontal lobe excisions or amygdalo-hippocampectomy in man. Neuropsychologia 1995;33:1–24.

Oyama Y, Fuchs PA, Katayama N, Noda K. Myricetin and quercetin, the flavonoid constituents of *Ginkgo biloba* extract, greatly reduce oxidative metabolism in both resting and Ca(2+)-loaded brain neurons. Brain Res 1994;635:125–9.

Oyama Y, Chikahisa L, Ueha T, Kanemaru K, Noda K. *Ginkgo biloba* extract protects brain neurons against oxidative stress induced by hydrogen peroxide. Brain Res 1996;712:349–52.

Persad CC, Abeles N, Zacks RT, Denburg NL. Inhibitory changes after age 60 and their relationship to measures of attention and memory. J Gerontol Ser B Psychol Sci Soc Sci 2002;57:223–32.

Phillips SM, Sherwin BB. Effects of estrogen on memory function in surgically menopausal women. Psychoneuroendocrinology 1992;17:485–95.

Polich J, Gloria R. Cognitive effects of a *Ginkgo biloba*/vinpocetine compound in normal adults: systematic assessment of perception, attention and memory. Hum Psychopharmacol 2001;16:409–16.

Rigney U, Kimber S, Hindmarch I. The effects of acute doses of standardized *Ginkgo biloba* extract on memory and psychomotor performance in volunteers. Phytother Res 1999;13:408–15.

Robbins TW. Dissociating executive functions of the prefrontal cortex. Philos Trans R Soc Lond B Biol Sci 1996;351:1463–70.

Robbins TW, James M, Owen A, Sahakian BJ, McInnes L, Rabbitt PM. Cambridge Neuropsychological Test Automated Battery (CANTAB): a factor analytic study of a large sample of normal elderly volunteers. Dementia 1994;5:266–81.

Soholm B. Clinical improvement of memory and other cognitive functions by *Ginkgo biloba*: review of relevant literature. Adv Ther 1998;15(1):54–65.

Solomon PR, Adams F, Silver A, Zimmer J, DeVeaux R. *Ginkgo* for memory enhancement: a randomized controlled trial. JAMA 2002;288:835–40.

Spreen O, Strauss E. A compendium of neuropsychological tests: administration norms and commentary. Oxford: Oxford Univ. Press; 1991.

Staffen W, Mair A, Zauner H, Unterrainer J, Niederhofer H, Kutzelnigg A, et al. Cognitive function and fMRI in patients with multiple sclerosis: evidence for compensatory cortical activation during an attention task. Brain 2002;125(Pt 6):1275–82.

Stough C, Clarke J, Lloyd J, Nathan PJ. Neuropsychological changes after 30-day *Ginkgo biloba* administration in healthy participants. Int J Neuropsychopharmacol 2001;4:131–4.

Weschler D. Weschler Memory Scale-Revised. San Antonio: Harcourt Brace Jovanovich; 1987.

Wesnes K, Simmons D, Rook M, Simpson P. A double blind placebo-controlled trial of tanakan in the treatment of idiopathic cognitive impairment on the elderly. Hum Psychopharmacol 1987;2:159–69.

Wesnes KA, Ward T, McGinty A, Petrini O. The memory enhancing effects of a *Ginkgo biloba*/*Panax ginseng* combination in healthy middle-aged volunteers. Psychopharmacology (Berlin) 2000;152:353–61.

Wheatley D. *Ginkgo biloba* relieves sexual dysfunction due to antidepressant drugs. Eur Neuropsychopharmacol 1999;9(S5):253–4.

Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983;67:361–70.