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ORIGINAL INVESTIGATION

David O. Kennedy · Andrew B. Scholey
Keith A Wesnes

The dose-dependent cognitive effects of acute administration of *Ginkgo biloba* to healthy young volunteers

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Abstract *Rationale:* Chronic administration of extracts from the leaves of the tree *Ginkgo biloba* is known to improve aspects of cognitive performance. However, little is known about the effects of acute doses of Ginkgo on coherent cognitive domains. Recent factor analysis of test measures from subtasks of the Cognitive Drug Research (CDR) computerised assessment battery has revealed that four primary cognitive 'factors' corresponding to speed of attention, accuracy of attention, speed of memory and quality of memory can be useful to describe cognitive function changes. *Objective:* The present study aimed at assessing whether acute administration of *Ginkgo biloba* had any consistent effect on the four CDR factors. *Methods:* The study utilised a placebo-controlled, multi-dose, double-blind, balanced, crossover design. Twenty participants received 120 mg, 240 mg and 360 mg of a standardised extract of Ginkgo (GK501, Pharmaton, SA) or a matching placebo. Cognitive performance was assessed using the CDR computerised test battery immediately prior to dosing and at 1, 2.5, 4 and 6 h thereafter. The primary outcome measures were the four aspects of cognitive performance, which have previously been derived by factor analysis of CDR subtests. *Results:* Compared with the placebo, administration of Ginkgo produced a number of significant changes on the performance measures. The most striking of these was a dose-dependent improvement of the 'speed of attention' factor following both 240 mg and 360 mg of the extract, which was evident at 2.5 h and was still present at 6 h. Additionally, there were a number of time- and dose-specific changes (both positive and negative) in performance of the other factors. *Conclusions:* We conclude that acute administration of *Ginkgo biloba* is capable of producing a sustained improvement in attention in healthy young volunteers.

Key words *Ginkgo biloba* · Cognitive enhancement · Healthy young volunteers

D.O. Kennedy · A.B. Scholey (✉)
Human Cognitive Neuroscience Unit, Division of Psychology, University of Northumbria, Newcastle upon Tyne NE1 8ST, UK
e-mail: a.scholey@unn.ac.uk
Tel.: +44-191-2274468, Fax: +44-191-2273190

K.A. Wesnes
Cognitive Drug Research Ltd, Portman Road, Reading RG30 1EA, UK

Introduction

Extracts and infusions made from the leaves of the *Ginkgo biloba* tree have been used in traditional Chinese medicine for thousands of years (Major 1967). In many western countries, the use of Ginkgo has grown dramatically over the past decades, both as an 'over the counter' herbal supplement and as a prescribed drug (O'Hara et al. 1998). Commercial extracts of Ginkgo are generally standardised with regard to content of the primary active components, the flavone glycosides and terpenoids (comprising 24% and 6% of the total extract, respectively). At the physiological level, Ginkgo extract is both a platelet activating factor antagonist (Braquet and Hosford 1991) and a free radical scavenger (Droy-LeFaix 1997). Ginkgo is known to modulate a number of neurotransmitter systems (Ramassamy et al. 1992; White et al. 1996) as well as to exert effects on cellular metabolism (Oberpichler et al. 1988). These, and possibly other mechanisms, underlie a number of reported positive health effects. These include improvements in haematological parameters, including blood circulation (Jung et al. 1990; Koltringer et al. 1993), and an apparent neuroprotective role after various neuronal insults (Ramassamy et al. 1993).

In humans, the beneficial effects of chronic Ginkgo administration have been shown to ameliorate the symptoms of a number of disorders involving both peripheral and central circulatory disturbances (Kleijnen and Knipschild 1992a). Objectively established improvements in the cognitive decline associated with a number of these disorders have been shown, including demonstrations of benefits in sufferers from intermittent claudication (Draebeck et al. 1996), Alzheimer's disease and

Vascular dementia (Kanowski et al. 1996; Le Bars et al. 1997), and a number of generalised conditions with a cerebro-vascular aetiology often encompassed within the umbrella term 'cerebral insufficiency' (Kleijnen and Knipschild 1992b; Hopfenmüller 1994). Within this latter group, improvements have been demonstrated relative to placebo in short-term memory and rate of learning following 24 weeks administration of Ginkgo (Grässel 1992) and in both reaction times and accuracy throughout a computerised test battery during an 8-week trial (Wesnes et al. 1987a).

Those studies that have examined the potential of Ginkgo as a cognition enhancer in non-pathological populations have tended to concentrate on sufferers from age-associated memory decline. Findings in this domain include increased speed of information processing, as measured by a dual coding task, following a single dose of either 320 mg or 600 mg standardised Ginkgo extract EGB761 (Allain et al. 1993), and improved performance on the digit copying sub-test of the Kendrick battery and shortened reaction times on a computerised classification task following 12 weeks and 24 weeks administration of 120 mg Ginkgo extract per day (Rai et al. 1991). This last study also demonstrated changes in the electroencephalogram (EEG) profile that were interpreted as reflecting an 'alerting' action of the drug, a finding that was broadly supported by the report of Semlitsch et al. (1995) of decreased P300 latency after both acute and chronic Ginkgo administration.

Several studies have also investigated the effects of acute doses of Ginkgo extracts on the cognitive performance of younger, asymptomatic volunteers. Each of these employed a similar multiple dose (of standardised extracts), double-blind, placebo-controlled, balanced crossover design, with a 5- to 7-day wash-out period between trials.

Recently, Rigney et al. (1999) examined the effects of 2-day administration regimens of four doses (120–300 mg) of Ginkgo. Thirty-one participants, ranging in age from 30 years to 59 years, were administered a battery of tests at baseline and then at hourly intervals over 2 days (1000–2100 hours). In comparison with placebo, performance was only significantly improved on reaction times for the Sternberg short-term memory test on day 1 and day 2 for 120 mg and 300 mg Ginkgo extract and on day 2 alone for 240 mg. These improvements were also more marked for the older participants.

These results supported the findings of a previous study by Hindmarch (1986), who utilised three of the eight cognitive tests used in the Rigney study (critical flicker fusion, choice reaction time, Sternberg test). Hindmarch tested eight healthy young participants 1 h after the administration of 120, 240 and 600 mg Ginkgo extract and a placebo. Once again, the reaction times on the Sternberg short-term memory test were the only measure significantly improved, and then only in the 600-mg condition. Warot et al. (1991), in a replication of Hindmarch's study, compared the effects of two 600-mg doses of different Ginkgo preparations against placebo on 12 young participants and included further tasks assessing free and recognition picture recall. They found no difference on the Sternberg test, but a significant improvement for one of the Ginkgo preparations (Tanakan) on the free picture recall task. It should be noted that, in the case of the latter two studies, testing at 1 h post-dose may well have pre-empted peak bioavailability (Nieder et al. 1991; Fourtillan et al. 1995).

Whilst evidence is accumulating for a possible role for *Ginkgo biloba* in the attenuation of cognitive deficits due to disease and old age, the direct evidence of a cognition-enhancing role in younger asymptomatic populations, as outlined above, could be best described as suggestive. It should be noted, however, that previous research has demonstrated improvements in haematological parameters as a consequence of a single dose of Ginkgo extract given to healthy young adults (Jung et al. 1990) and as a consequence of chronic administration to mountaineers at altitude (Roncin et al. 1996). Taken together with evidence of dose-dependent cognitive activation effects of Ginkgo on EEG profiles in healthy young volunteers (Pidoux 1986; Itil et al. 1996), it seems probable that *Ginkgo biloba* may exert a beneficial general effect on cognitive processes in this latter population.

The Cognitive Drug Research (CDR) Ltd. integrated computerised test battery has previously been shown to be sensitive to the cognitive effects of both *Ginkgo biloba* (Wesnes et al. 1987a) and a *Ginkgo biloba–Panax ginseng* combination (Wesnes et al. 1997, 2000) in impaired and middle-aged cohorts. Recent factor analysis has demonstrated relatively discrete loading of individual task outcome measures onto four factors corresponding to 'speed of attention', 'accuracy of attention', 'quality of memory' and 'speed of memory' (Wesnes et al. 1999). Given that the demonstration of enhancement following acute doses of Ginkgo has thus far been restricted to a small subset of tests within much larger test batteries, and has proved difficult to interpret with any reference to coherent cognitive domains, the present study was undertaken to investigate the possibility that ginkgo administration may result in acute cognitive enhancement in healthy young volunteers with reference to the four global factors that can be derived from the complete CDR battery.

Materials and methods

Participants

Eighteen female and two male undergraduate volunteers (mean age 19.9 years, range 19–24 years) took part in the study which was approved by the Joint Ethics Committee of Newcastle and North Tyneside Health Authority. Prior to participation, each volunteer signed an informed consent form and completed a medical health questionnaire. All participants self reported that they were in good health and were taking no medication with the exception, for some female volunteers, of the contraceptive pill. Heavy smokers (>10 cigarettes/day) were excluded from the study. Of the 20 participants, only two were light social smokers and they agreed to abstain from smoking before and during testing sessions.

All participants abstained from caffeine-containing products and alcohol throughout each study day.

Cognitive measures

The CDR computerised assessment battery (Wesnes et al. 1987b) has been used in well over 500 European and North American drug trials, and has been shown to be sensitive to cognitive improvements (Moss et al. 1998; Scholey et al. 1999) and impairments with a wide variety of substances (O'Neill et al. 1995; Ebert et al. 1998).

A tailored version of the battery, similar to that which has previously been found to be sensitive to improved cognitive function as a consequence of ingestion of both *Ginkgo biloba* (Wesnes et al. 1987a) and a Ginkgo/Ginseng combination (Wesnes et al. 1997), was used. The selection of computer-controlled tasks from the system was administered with parallel forms of the tests being presented at each testing session. Presentation was via VGA colour monitors, and, with the exception of written word recall tests, all responses were recorded via two-button (yes/no) response boxes. The entire selection of tasks took approximately 20 min.

Tests were administered in the following order.

Word presentation

Fifteen words, matched for frequency and concreteness, were presented in sequence on the monitor for the participant to remember. Stimulus duration was 1 s, as was the inter-stimulus interval.

Immediate word recall

The participant was allowed 60 s to write down as many of the words as possible. The task was scored as number correct, errors and intrusions, and the resulting score was converted into a percentage.

Picture presentation

Twenty photographic images were presented sequentially on the monitor at the rate of one every 3 s, with a stimulus duration of 1 s, for the participant to remember.

Simple reaction time

The participant was instructed to press the 'yes' response button as quickly as possible every time the word 'yes' was presented on the monitor. Fifty stimuli were presented with an inter-stimulus interval that varied randomly between 1 s and 3.5 s. Reaction times were recorded in milliseconds.

Digit vigilance task

A target digit was randomly selected and constantly displayed to the right of the monitor screen. A series of digits was presented in the centre of the screen at the rate of 80 per minute, and the participant was required to press the 'yes' button as quickly as possible every time the digit in the series matched the target digit. The task lasted 3 min and there were 45 stimulus–target matches. Task measures were accuracy (%), reaction time (ms) and number of false alarms.

Choice reaction time

Either the word 'no' or the word 'yes' was presented on the monitor, and the participant was required to press the corresponding button as quickly as possible. There were 50 trials, in which the stimulus word was chosen randomly with equal probability, with a randomly varying inter-stimulus interval of between 1 s and 3.5 s. Reaction times (ms) and accuracy (%) were recorded.

Spatial working memory

A pictorial representation of a house was presented on the screen with four of its nine windows lit. The participant was instructed to memorise the position of the illuminated windows. In 36 subsequent presentations of the house, one of the windows was illuminated and the participant decided whether or not this matched one of the lighted windows in the original presentation. The participant made their response by pressing the 'yes' or 'no' response button as quickly as possible. Mean reaction times were measured in milliseconds, and values of accuracy of responses to both original and novel (distractor) stimuli were recorded as percentages.

Numeric working memory

Five digits were presented sequentially for the participant to hold in memory. This was followed by a series of 30 probe digits. The participant decided whether or not the digit had been in the original series and pressed the 'yes' or 'no' response button as appropriate, as quickly as possible. This was repeated two further times with different stimuli and probe digits. Mean reaction times were measured in milliseconds, and values of accuracy of responses to both original and novel (distractor) stimuli were recorded as percentages.

Word recall

The participant was again given 60 s to write down as many of the words as possible. The task was scored as number correct, errors and intrusions, and the resulting score was converted into a percentage.

Delayed word recognition

The original words plus 15 distractor words were presented one at a time in a randomised order. For each word, the participant indicated whether or not he recognised it as being included in the original list of words by pressing the 'yes' or 'no' button as appropriate and as quickly as possible. Mean reaction times were measured in milliseconds, and values of accuracy of responses to both original and novel (distractor) stimuli were recorded as percentages.

Delayed picture recognition

The original pictures plus 20 distractor pictures were presented one at a time in a randomised order. For each picture, participants indicated whether or not it was recognised as being from the original series by pressing the 'yes' or 'no' button as appropriate and as quickly as possible. Mean reaction times were measured in milliseconds, and accuracy of responses to both original and novel (distractor) stimuli were recorded as percentages.

These measures were collapsed into four global outcome factors derived from the battery by factor analysis (Wesnes et al. 1999), as previously utilised by Wesnes et al. (1997) and Wesnes et al. (2000). The contribution of individual task measures to each of these factors is illustrated schematically in Fig. 1.

Speed of attention Speed of attention was derived by combining the reaction times of the three attentional tasks – simple reaction time, choice reaction time and digit vigilance (units are summed milliseconds for the three tasks).

Accuracy of attention Accuracy of attention was derived by calculating the combined percentage accuracy across the choice reac-

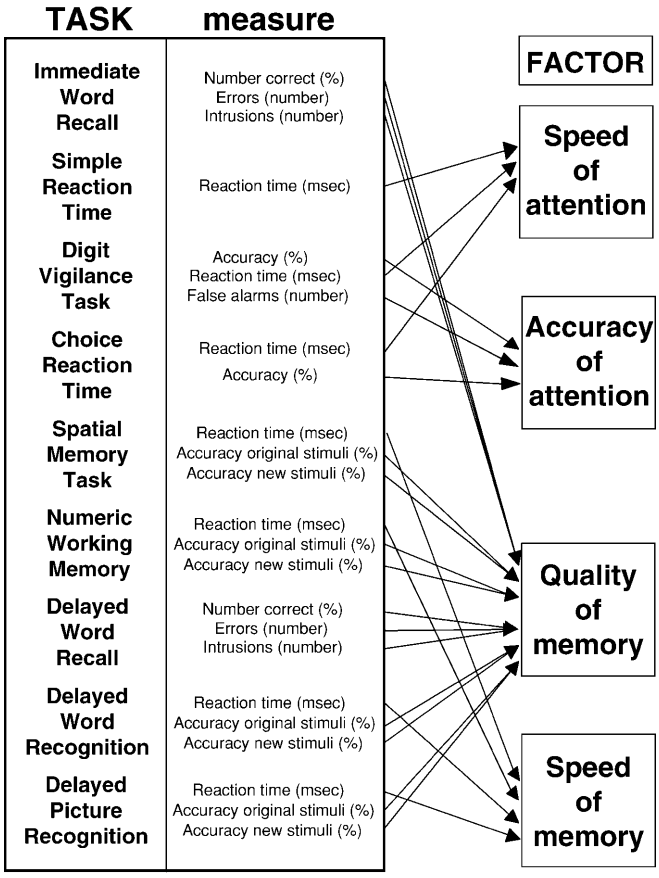


Fig. 1 Schematic representation of the Cognitive Drug Research (CDR) battery showing (from *left* to *right*) running order of tasks, individual task outcome measures and the four factors derived by factor analysis – speed of attention, accuracy of attention, quality of memory and speed of memory. *Arrows* indicate that a task outcome measure contributes to the given factor

tion time and digit vigilance tasks with adjustment for false alarms from the latter test. One hundred percent accuracy across the two tasks would generate a maximum score of 100.

Quality of memory Quality of memory was derived by combining the percentage accuracy scores (adjusted for proportions of novel and new stimuli where appropriate) from all of the working and secondary memory tests – spatial working memory, numeric working memory, word recognition, picture recognition, immediate word recall and delayed word recall (with adjustments to the total percentage correct for errors and intrusions on the latter two tasks). One hundred percent accuracy across the six tasks would generate a maximum score of 600 on this index.

Speed of memory Speed of memory was derived by combining the reaction times of the four computerised memory tasks – numeric working memory, spatial memory, delayed word recognition and delayed picture recognition (units are summed milliseconds for the four tasks).

Subjective mood measure

The Bond-Lader visual analogue scales

The 16 visual analogue scales of Bond-Lader (Bond and Lader 1974) were combined as recommended by the authors to form three mood factors: alertness, calmness and contentedness.

Treatments

On each study day, participants received six capsules of identical appearance, each containing either an inert placebo or 60 mg *Ginkgo biloba* extract (GK 501, Pharmaton SA, Lugano, Switzerland) standardised to a content of 24% Ginkgo flavone glycosides and 6% terpene lactones. Depending on the condition to which they were allocated on that particular day, the combination corresponded to a dose of either 0 (placebo), 120 mg, 240 mg or 360 mg *Ginkgo biloba* extract.

Procedure

Each participant was required to attend a total of five study days that were conducted 7 days apart, to ensure a sufficient wash-out between conditions. Testing took place in a suite of laboratories with participants visually isolated from each other.

On arrival at their first session on the first day, participants were randomly allocated to a treatment regime using a Latin-square design that counterbalanced the order of treatments across the four active days of the study.

The first day was identical to the following four, except that no treatment (active or placebo) was offered, to allow familiarisation with the test battery and procedure. Data from the five sessions of this practice day were not included in any analysis.

Each study day comprised five identical testing sessions. The first was a pre-dose testing session, which established baseline performance for that day and was immediately followed by the day's treatment on visits 2–5. Further testing sessions began at 1, 2.5, 4 and 6 h following consumption of the day's treatment. Each testing session comprised completion of the Bond-Lader visual analogue scales, followed by completion of the CDR test battery.

Statistics

Scores from individual task measures were combined to form the four global outcome scores and were analysed as 'change from baseline' using the SAS statistical package. Comparisons between doses and time points were made using the general linear models procedure (PROC GLM), with planned comparisons being made between the placebo and the three Ginkgo conditions (120, 240 and 360 mg) utilising *t*-tests with the mean squares for dose × time × subjects as an error term. To ensure the overall protection level, only probabilities associated with pre-planned comparisons were used.

The three mood outcomes derived from the Bond-Lader scales were analysed using within-subjects analyses of variance.

Results

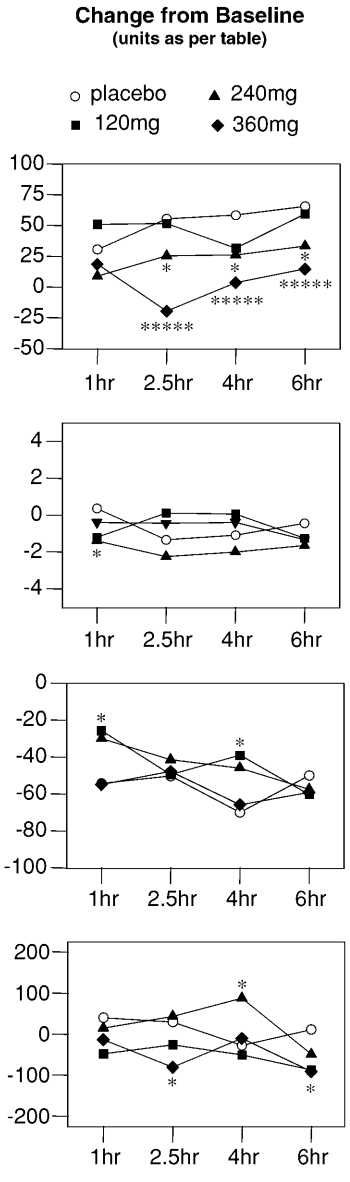
Global outcome measures

Speed of attention factor

Speed was significantly enhanced on the attention tasks for 240 mg at 2.5 h (t_{171}=2.11; P=0.036), 4 h (t_{171}=2.28; P=0.024) and 6 h post-dose (t_{171}=2.25; P=0.026). The same pattern was evident for the 360-mg dose, with enhancement at 2.5 h (t_{171}=5.28; P=0.0001), 4 h (t_{171}=3.87; P=0.0002) and 6 h post-dose (t_{171}=3.58; P=0.0004). Whilst there were no significant improvements on this factor for the lowest dose (120 mg), it should be noted that there was a trend towards improvement at 4 h (t_{171}=1.88; P=0.06).

Fig. 2 Table presenting both raw scores and change from baseline scores for each dose of *Ginkgo Biloba* (mean±SEM). *Graphs* represent the change from baseline scores for the four primary outcome measures (*P<0.05; *****P<0.0005 compared with the corresponding placebo score)

Global Outcome Measure		Time of testing post-dose									
		Baseline (Pre-dose)		1 hour		2.5 hours		4 hours		6 hours	
Speed of Attention Msecs (summed)	Placebo	Score	**1035.13**	*19.17*	**1065.56**	*21.46*	**1090.44**	*21.72*	**1092.19**	*20.86*	**1100.49**	*22.72*
		Change from baseline			**30.44**	*12.48*	**55.32**	*12.38*	**58.32**	*12.87*	**65.36**	*14.08*
	120 mg	Score	**1048.29**	*18.17*	**1099.29**	*25.04*	**1099.98**	*24.01*	**1079.85**	*19.42*	**1107.58**	*24.01*
		Change from baseline			**51.00**	*22.4*	**51.69**	*16.83*	**31.56**	*16.43*	**59.29**	*16.89*
	240 mg	Score	**1053.86**	*19.36*	**1062.55**	*18.24*	**1079.29**	*17.89*	**1079.93**	*20.90*	**1087.31**	*17.01*
		Change from baseline			**8.68**	*14.15*	**25.43**	*17.84*	**26.07**	*19.38*	**33.44**	*15.41*
	360 mg	Score	**1070.88**	*20.01*	**1089.25**	*25.44*	**1053.10**	*18.68*	**1074.36**	*23.71*	**1085.48**	*20.62*
		Change from baseline			**18.37**	*15.44*	**-19.58**	*14.16*	**3.48**	*16.06*	**14.60**	*14.92*
Accuracy Of Attention Combined % (max 100)	Placebo	Score	**90.85**	*0.73*	**91.20**	*0.71*	**89.50**	*1.02*	**89.63**	*1.63*	**90.40**	*0.88*
		Change from baseline			**0.35**	*0.94*	**-1.35**	*0.86*	**-1.10**	*1.32*	**-0.45**	*0.82*
	120 mg	Score	**90.40**	*0.86*	**89.20**	*1.45*	**90.50**	*1.10*	**90.45**	*0.84*	**89.15**	*0.89*
		Change from baseline			**-1.20**	*1.23*	**0.10**	*1*	**0.05**	*0.7*	**-1.25**	*0.85*
	240 mg	Score	**92.15**	*0.60*	**90.75**	*0.71*	**89.90**	*0.84*	**90.15**	*0.96*	**90.50**	*0.81*
		Change from baseline			**-1.40**	*0.89*	**-2.25**	*0.84*	**-2.00**	*0.93*	**-1.65**	*0.88*
	360 mg	Score	**91.40**	*0.58*	**91.00**	*0.75*	**91.00**	*0.67*	**91.00**	*1.14*	**90.05**	*1.04*
		Change from baseline			**-0.40**	*0.69*	**-0.45**	*0.55*	**-0.40**	*0.88*	**-1.35**	*0.75*
Quality of Memory Summed % (Max 600)	Placebo	Score	**415.02**	*14.71*	**360.67**	*17.16*	**364.63**	*19.14*	**347.60**	*21.71*	**364.90**	*14.35*
		Change from baseline			**-54.35**	*12.85*	**-50.40**	*13.76*	**-70.06**	*16.59*	**-60.12**	*11.59*
	120 mg	Score	**396.52**	*15.57*	**370.72**	*12.81*	**346.96**	*17.68*	**357.42**	*17.43*	**336.20**	*17.63*
		Change from baseline			**-25.81**	*10.07*	**-49.56**	*11.07*	**-39.10**	*10.4*	**-60.32**	*9.84*
	240 mg	Score	**416.98**	*13.27*	**386.93**	*15.93*	**375.51**	*15.06*	**371.05**	*13.71*	**359.52**	*16.76*
		Change from baseline			**-30.05**	*10.57*	**-41.47**	*10.13*	**-45.93**	*12.25*	**-57.46**	*12.23*
	360 mg	Score	**422.37**	*13.21*	**367.43**	*18.01*	**377.83**	*16.99*	**356.55**	*15.26*	**363.26**	*17.46*
		Change from baseline			**-54.94**	*10.21*	**-47.86**	*10.93*	**-65.82**	*11.77*	**-59.11**	*13.83*
Speed Of Memory Msecs (summed)	Placebo	Score	**2431.50**	*73.89*	**2471.21**	*91.62*	**2460.27**	*86.69*	**2406.47**	*68.45*	**2441.88**	*106.77*
		Change from baseline			**39.71**	*43.42*	**28.77**	*31.03*	**-28.13**	*31.22*	**10.38**	*67.08*
	120 mg	Score	**2480.58**	*79.71*	**2432.37**	*70.09*	**2453.91**	*81.81*	**2429.63**	*73.59*	**2393.29**	*79.62*
		Change from baseline			**-48.21**	*39.74*	**-26.67**	*50.92*	**-50.94**	*50.47*	**-87.29**	*46.42*
	240 mg	Score	**2424.44**	*69.75*	**2438.41**	*67.77*	**2467.63**	*72.40*	**2511.77**	*95.71*	**2374.90**	*74.47*
		Change from baseline			**13.97**	*39.3*	**43.20**	*45.7*	**87.33**	*60.34*	**-49.54**	*38.3*
	360 mg	Score	**2444.50**	*70.31*	**2430.45**	*73.20*	**2383.72**	*62.41*	**2433.44**	*83.52*	**2352.75**	*67.02*
		Change from baseline			**-14.05**	*65.53*	**-81.50**	*63.81*	**-11.06**	*53.79*	**-91.74**	*45.05*



Accuracy of attention factor

There was a single significant decrement in accuracy on the attention tasks, which was restricted to the 240-mg dose at 1 h post-dose (t_{171}=2.02; P=0.045).

Mean raw and change from baseline global outcome measure scores for each condition across each session are displayed in Fig. 2.

Quality of memory factor

Planned comparisons revealed significant improvements, compared with placebo, for 120 mg Ginkgo at both 1 h (t_{171}=2.14; P=0.033) and 4 h (t_{171}=2.32; P=0.02) post-dose. A similar pattern was evinced for 240 mg Ginkgo, with trends towards an improvement in comparison with placebo at the same time points – 1 h post (t_{171}=1.82; P=0.069), 4 h post (t_{171}=1.81; P=0.071). There were no significant improvements associated with the 360-mg dose of Ginkgo.

Speed of memory factor

Speed was significantly enhanced on the memory tasks for 360 mg Ginkgo at 2.5 h post-dose (t_{171}=2.07; P=0.04), with trends towards enhancement for both 120 mg and 360 mg at 6 h post-dose – 120 mg (t_{171}=1.83; P=0.068), 360 mg (t_{171}=1.91; P=0.057). The 240-mg dose of Ginkgo, however, under-performed the other doses at all time points and evinced a significant reduction in speed in comparison with placebo at 4 h post-dose (t_{171}=2.16; P=0.03).

Subjective mood measures

None of the three factors derived from the Bond-Lader visual analogue scales (Bond and Lader 1974) showed a significant difference as a consequence of administration of *Ginkgo biloba* (alertness $F_{3,57}$=0.44; contentedness $F_{3,57}$=0.66; calmness $F_{3,57}$=0.82, all values NS).

Discussion

These results show that acute *Ginkgo biloba* administration enhances cognitive performance in healthy young adults. This cognition enhancement following the administration of the GK 501 extract was manifested most notably in increased speed of performance on tasks assessing attention. This effect was both dose and time dependent, with significant improvements seen only for the two highest doses (240 mg and 360 mg) at the later time points, with increased speed of attention at 2.5, 4 and 6 h following ingestion. The only other factor that evinced a convincing pattern of effects was quality of memory, on which performance was significantly enhanced for the lowest dose (120 mg) at 1 h and 4 h, with trends towards significant enhancement for the 240-mg dose at the same time points. These differing patterns of results on the two factors are particularly interesting as, although they appear to be both time and dose dependent, the memory enhancement is manifested for the lowest dose at the earliest time, whereas the speed of performance of attention tasks is increased for the highest doses at the later times post-dose. Whether these results represent the working of two distinct pharmacological mechanisms, rather than the separate time- and dose-dependent effects of one mechanism, remains to be elucidated.

Several other significant changes noted across the speed of memory and accuracy of attention measures, contradictory significant results in the case of the former, and a solitary decrement in accuracy in the case of the latter, all restricted to single time/dose points, are not readily interpretable.

The findings of the current study offer some support to those of Hindmarch (1986) and Rigney et al. (1999), who both demonstrated significant improvements relative to placebo, which were restricted to reaction times on the Sternberg short-term memory scanning task. These results, however, would seem to suggest that the enhancement evinced in the former studies may be attributable to improved speed of performance on the task per se. The above authors' suggestions that the cognition-enhancing effect of *Ginkgo biloba* is more pronounced for memory processes receives little support from the current study's finding of limited improvements on the quality of memory factor utilised here. It must, however, be noted that this factor was found to be composed of accuracy data from all of the memory tasks, which may have submerged a specific working memory effect. Given the specific aims of this study, it was felt that it would be inappropriate to examine the effects of Ginkgo on specific task outcomes in an ad hoc fashion.

The results are also in line with those from studies investigating the effects of *Ginkgo biloba* in pathological cohorts that have included measures of reaction times. Examples include an improvement in the combined reaction times derived from a selection of tasks from the CDR battery throughout a 3-month trial involving elderly sufferers from 'idiopathic cognitive impairment' (Wesnes et al. 1987a), improvements in simple reaction times (Gessner et al. 1985), reaction times on a computerised classification task (Rai et al. 1991) and shorter stimulus evaluation times as evinced by decreases in P300 event related potentials following both acute and chronic administration of Ginkgo in sufferers from age-related memory impairment (Semlitsch et al. 1995). It is interesting to note that evidence of the other cognitive improvements demonstrated in pathological populations was limited in the current study to relatively mild enhancement of mnemonic function for the lowest doses of Ginkgo. It seems plausible to suggest that such improvements may reflect an attenuation of age- or disease-related deficits, and would be unlikely to be manifested to any great extent in a young, healthy cohort.

Whilst the results of the current study could not be said to constitute an adequate platform for a discussion of possible mechanisms, it is interesting to note similarities with other research findings. Animal experimentation has demonstrated a partial re-establishment of glucose consumption and an increase in glucose transfer rate during hypoxia (Rapin et al. 1986). Similarly, prolonged survival time under lethal hypoxia in mice and retardation of the breakdown of brain energy metabolism and increased local cerebral blood flow in rats following administration of Ginkgo extract have been demonstrated (Oberpichler et al. 1988). In healthy young volunteers, Schaffler and Reeh (1985) demonstrated improvements, in comparison with placebo, in complex choice reaction times during hypoxia, following 14 days treatment with Ginkgo. Conversely, utilising the same battery as the current study in an investigation of the cognitive effects of oxygen administration, Moss et al. (1998) demonstrated dose-dependent improvements on each of the three components of the speed of attention factor (simple, choice, and digit vigilance reaction times), with more restricted improvements observed on the components of the quality of memory factor. It seems plausible to suggest that Ginkgo owes its cognition-enhancing effect either to modulation of cerebral cellular metabolism or, alternatively, to improved haemorrheological parameters (Jung et al. 1990; Roncin et al. 1996), leading to simple augmentation of the levels of metabolic substrates reaching the brain. In light of research indicating a relationship between the efficiency of glucose delivery and utilisation, and performance on 'demanding' non-memory tasks (Kennedy and Scholey 2000), it would be of interest to investigate *Ginkgo biloba*'s possible role during cognitive demand.

It should also be noted that whilst the current study demonstrated improved performance on both the speed of attention and quality of memory factors, two previous

studies on the cognitive effects of a *Ginkgo biloba*/*Panax ginseng* combination (Gincosan, Pharmaton SA), which utilised the same four factors from the same battery, reported improved performance for sufferers from 'neurasthenic' complaints and the healthy middle aged. Statistically significant improvements were, however, restricted to the quality of memory factor (Wesnes et al. 1997, 2000). It is also noteworthy that, in the case of the former study, these improvements became apparent 1 h following the first dose of a 90-day regimen. This does suggest the possibility of opposing, additive or synergistic properties for the two compounds.

The findings of the current study are of particular interest as they demonstrate specific pharmacological actions as a consequence of single doses of *Ginkgo biloba*, with this effect being apparent in a population of healthy young participants who could be conceived of as performing near the zenith of their cognitive capabilities. As the general consensus is, particularly with regard to its use as a treatment in pathological populations, that Ginkgo's effects increase during a prolonged period of administration, it would be of interest to establish whether the effects demonstrated here would be augmented by a chronic regimen.

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