Neuropsychological changes after 30-day *Ginkgo biloba* administration in healthy participants

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Abstract

Ginkgo biloba extract (EGb) from the world's oldest living tree has been reputed to ameliorate cognitive decline in the elderly and slow cognitive deterioration in patients with dementia of the Alzheimer's type. EGb remains as one of the most popular plant extracts to alleviate symptoms associated with a range of cognitive disorders such as Alzheimer's disease, vascular dementia and age-related amnesic conditions. EGb is known to contain a range of chemically active components that have antagonistic effects on platelet-activating factor, free-radical scavenging activity and direct effects on the cholinergic neurotransmitter system. Recently there has been much speculation, that EGb may act as a 'smart drug' or nootropic agent in the healthy young to improve intelligence. We conducted a 30-d randomized, double-blind, placebo-controlled clinical trial in which 61 participants were administered a battery of validated neuropsychological tests before and after treatment. Statistical analysis indicated significant improvements in speed of information processing working memory and executive processing attributable to the EGb.

Introduction

Ginkgo biloba extract (EGb) from the world's oldest living tree has been reputed to ameliorate cognitive decline in the elderly and slow cognitive deterioration in patients with dementia of the Alzheimer's type (Oken et al., 1998). It remains as one of the most popular plant extracts to alleviate symptoms associated with a range of cognitive disorders such as Alzheimer's disease, vascular dementia and age-related amnesic conditions (Warburton, 1986). EGb has also been the subject of much speculation that it may be used as a nootropic agent to enhance intelligence or cognition in healthy non-clinical individuals. In a dose–response study comparing placebo, 120, 140 and 600 mg doses of EGb in healthy young subjects Subhan and Hindmarch (1984), reported a significant improvement in short-term memory scanning speed and in reaction time (RT) to visual stimuli with the 600 mg dose 1 h following administration. In healthy older subjects (mean age = 69.3 yr), doses of 320 and 600 mg EGb were found to decrease the time necessary to encode

verbal and visual material compared to placebo administered 1 h prior to testing (Allain et al., 1993). However these studies have examined acute doses of EGb and it is likely that the chronic effects of EGb may be different than acute effects on cognitive performance. There is clearly a need to conduct studies on the effects of chronic administration of EGb on a well validated battery of psychological tests.

Pharmacological action of EGb

Animal studies have suggested that the cognitive-enhancing effects of EGb may arise because of its action on the central cholinergic system. These studies have generally found that EGb potentiates muscarinic receptors (Taylor, 1986). However significant increases in the synthesis of catecholamines have also been found in rats following treatment with EGb (Brunello et al., 1985). More recent studies suggest that the antioxidant effects of EGb may operate to increase cell membrane fluidity, thereby improving cognitive function (Stoll et al., 1996), or to protect against oxidative stress induced by per-oxidation (Maitra et al., 1995; Oyama et al., 1994). In this context, the free radical scavenger properties of EGb, at a

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neuronal level, may improve cognitive function following CNS damage or protect CNS neurons from pre-programmed or accidental death.

Aims

The main aim was to determine whether administration of EGb enhances performance on a wide battery of neuropsychological tests. Specifically we wish to examine whether EGb administration enhances performance on tests assessing memory, abstract reasoning, spatial, perception and information processing in young healthy adults ranging in age from 18 to 40 yr. An additional aim was to examine whether there were differential effects of EGb on participants differing in cognitive ability. To assess cognitive ability at baseline we administered the Vocabulary sub-scale of the Wechsler Adult Intelligence Scale III. However participants were not selected on the basis of premorbid level of cognitive ability.

Method

Participants

Sixty-one young healthy volunteers were recruited from the general community from advertisements placed in Melbourne newspapers and by word of mouth. Exclusion criteria included: past history of head injury requiring hospitalization, intellectual developmental disability, past or current neurological or psychiatric illness, inability to speak or understand English, past or current history of substance abuse, current pregnancy, currently taking other putative cognitive enhancers (lecithin, melatonin and guarana), and current use of any other medication. All participants provided written informed consent. The research was approved by the Swinburne University Human Research Ethics Committee.

Procedure

We employed a randomized double-blind methodology in which participants were randomly allocated to either a placebo or a 120 mg *Ginkgo biloba* for 30 d. The placebo and ginkgo tablets were identical in shape, colour and weight. At visit 1 subjects were screened against the exclusion criteria and if suitable were enrolled and randomized into the EGb or placebo arm of the study. Participants were then assessed on the neuropsychological tests (baseline assessment). Each participant was then given EGb or placebo tablets in a bottle containing 30 d supply. In addition to the trial regime (3 tablets for 30 d) additional tablets ranging in number from 1–10 (randomly
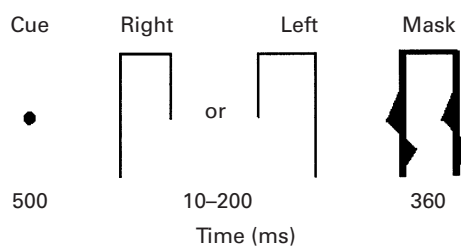

Figure 1. Inspection time procedure. A cue is presented for 500 ms (far left) followed by either one of two stimulus alternatives (centre) followed by a mask (right).

allocated) were also placed in the bottles so that compliance could be accurately examined. At the completion of the 30 d, participants were asked to bring in their bottles of EGb or placebo and the remaining capsules were counted. The number of capsules remaining was also compared to the participant's personal diaries recording the consumption of the EGb or placebo. Participants were excluded if greater than 10% of the total number of capsules required were not consumed by day 30. Eleven participants were omitted from the analyses on this basis. Therefore 50 participants completed the trial comprising 26 females and 24 males (Mean age = 30.4 yr, s.d. = 5.7 yr, range 18–40 yr). Following the 30-d treatment all participants were reassessed on the same battery of neuropsychological tests. Research nurses contacted each participant by telephone every second day of the trial to check for adverse events and to maximize compliance. Subjective effects were recorded and subsequently analysed.

The daily dosage was three 2000 mg tablets of Blackmore's Ginkgo Biloba Forte containing 120 mg of active ingredient. The active compounds of the extract are mainly flavonal glycosides (24%) and the terpene substances such as ginkgolides and bilobalide (6%) with smaller amounts of proathocyanidines and some organic acids (Drieu, 1986).

Neuropsychological tests

A battery of well-validated neuropsychological tests were employed to assess a wide range of cognitive variables including attention, working and short-term memory, verbal learning, memory consolidation, executive processes, planning and problem solving, information processing speed, motor responsiveness and decision making. This battery comprised; Digit Symbol Substitution Test (DSST); Speed of Comprehension Test (SCT); Symbol Digit Modalities Test (SDMT); Digit Span; Trail Making Test (TMT); Rey Auditory Verbal Learning Test (AVLT); Inspection Time (IT, see Figure 1); Two tests from the

Cognometer Battery of Tests, measuring simple RT and working memory.

Results

A series of one-way repeated-measure analysis of variance (ANOVA) employing time (pre- and post-assessments of each test) by group (EGb and placebo) interactions indicated that there were significant changes in Digit Span Backwards ($F = 3.6$, $p < 0.05$), Working Memory Speed ($F = 5.3$, $p < 0.05$), the AVLT (delay list) ($F = 6.1$, $p < 0.01$). Inspection Time approached significance ($F = 3.2$, $p = 0.05$). These significant changes indicate significant EGb related improvements specifically in memory processes. Digit Span Backwards and working memory speed specifically measure the efficiency and quality of working memory processes. The AVLT (delay list) indicates a significant improvement in memory consolidation over the 30 min delay between list presentations. Given the number of comparisons, the IT result may not be considered as a reliable result and should be the focus of future research employing larger samples.

Both positive and negative subjective effects were also monitored throughout the trial and recorded and subjected to ANOVA. Interestingly there was no significant differences between the EGb and placebo groups for negative side effects (e.g. headaches and nausea) but there was a significant number of positive subjective reported effects due to the EGb treatment than the placebo treatment ($F = 14.7$, $p < 0.001$). Positive subjective reported effects include subjective feelings of cognitive clarity, and self-reported improvements in memory and attention.

To examine whether changes in cognitive performance due to EGb treatment were related to differences in cognitive ability, the participants were allocated to a high and low vocabulary group on the basis of a split half method. A significant time × group × vocabulary was observed for Trail Making A indicating that the low cognitive ability group significantly improved Trail Making A due to the EGb treatment ($F = 4.6$, $p < 0.01$). This result indicates that for at least some aspect of executive functioning, lower cognitive ability participants may benefit significantly more than lower cognitive ability participants. This effect was not observed on any of the other tests.

Discussion

The results of the present study are indicative of two broad findings. First that EGb treatment improves memory processes, particularly working memory and memory consolidation. This finding is consistent with previous animal research in which chronic administration of EGb has been shown to restore muscarinic receptors in the hippocampus and research indicating increased EEG power frontally, particularly in areas in the frontal lobe (e.g. dorsolateral prefrontal cortex) that are involved in generating working memory (see DeFeudis, 1991 for a review). Second, this improvement in functioning was clearly evident to participants throughout the trial indicating that the changes were not only statistically significant but of a magnitude that could be subjectively noticed by the participants despite the double blinding of the study. The latter finding is consistent with more recent anecdotal reports and historical use of the extract to improve cognition. However, the reports of positive subjective effects should not be considered to be equivalent or commensurate to the actual changes in cognitive processing after EGb treatment. Although subjective changes in well-being may be reported by many participants these changes may not necessarily translate into improvements in memory, information processing and so on. In fact, the selectivity of the effect of EGb on specific cognitive processes suggests that the positive subjective improvements in well-being and mental clarity do not cause the changes in cognition because we would expect all cognitions to be improved. There is obviously an important distinction to be made between subjective and objective assessment of change after EGb treatment. Whilst the results of this study are consistent with studies administering EGb to patients and elderly populations in which some amelioration in cognitive functioning has been demonstrated, this is the first randomized trial that we are aware of that has examined cognitive performance after chronic administration of the extract. Further research is required to substantiate these findings in healthy participants. Of particular interest for future studies may be the specificity of EGb action on cognitive performance (i.e. is the effect specific to certain types of cognitive and motor processes or does it act more generally?), potential dose–response relationships, and the cognitive effects of shorter and longer administration durations. Because the exact mechanism of action of *Ginkgo biloba* is still uncertain, further pharmacological and biochemical work should also be undertaken.

It was important to note that in the present trial although there were few side-effects, the sample size was not adequate to determine whether relatively rare adverse reactions may occur in healthy populations. The present research was also not able to address whether the cognitive enhancing effects of 30-d administration of EGb would continue after discontinuation of EGb administration or whether the magnitude of enhancement could be increased with prolonged chronic administration or with increased dosage of EGb. As there are no published

studies examining the neuropsychological sequelae of EGb administration in relatively young healthy participants, further research is urgently required.

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