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An Examination of the Efficacy of *Ginkgo biloba* Extract EGb 761 on the Neuropsychologic Functioning of Cognitively Intact Older Adults

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ABSTRACT

Objectives: Few investigations have examined the effectiveness of *Ginkgo biloba* extract for enhancing cognitive abilities in individuals with no history of significant neurocognitive dysfunction. The purpose of this research was to examine the relatively short-term (i.e., 6 weeks) efficacy of *Ginkgo biloba* extract EGb 761 on the cognitive functioning of cognitively intact persons over the age of 55 years via a diverse battery of neuropsychologic tests and measures.

Participants: From the 48 cognitively intact participants between the ages of 55 and 86 years who initially enrolled in this study, 21 males and 19 females successfully completed the study's protocol and provided valid data sets.

Design: A 6-week, double-blind, fixed-dose, placebo-controlled, parallel-group experimental design was utilized. Participants were randomly assigned to either a *Ginkgo biloba* extract EGb 761 (180 mg/d) or placebo control group. To evaluate participants' cognitive and behavioral functioning, series of neuropsychological tests were administered to them prior to the initiation of the *Ginkgo biloba* extract/placebo therapy (i.e., pretreatment baseline) and again, just prior to the termination of the treatment regimen (i.e., after 6 weeks).

Results: Participants who received 180 mg of *Ginkgo biloba* extract EGb 761 daily for 6 weeks exhibited significantly more improvement on a task assessing speed of processing abilities (i.e., Stroop Color and Word Test color-naming task) by the end of treatment as compared to participants who received placebo. Trends favoring improved performances in the *Ginkgo biloba* group were also demonstrated in three of the four remaining tasks that involved a timed, speed of processing component, although they did not reach statistical significance. Furthermore, a significant relationship was found between the type of treatment (*Ginkgo biloba* extract or placebo) and participants' ratings of their overall abilities to remember. Specifically, more participants in the *Ginkgo biloba* extract group rated their overall abilities to remember by the end of treatment as "improved," as compared to the placebo group. In contrast, no significant differences were found between the *Ginkgo biloba* and placebo groups by treatment end on any of the four objective memory measures.

Conclusions: Taken together, the findings from standardized neuropsychologic assessment and a subjective, self-report questionnaire suggested that relatively short-term (i.e., 6 weeks) utilization of *Ginkgo biloba* extract EGb 761 may prove efficacious in enhancing certain neurocognitive functions/processes of cognitively intact older adults.

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Ginkgo biloba is a dioecious tree that is indigenous to China, Japan, and Korea (Gruenwald, 1998; LeBars et al., 1997). The species currently grows in many parts of the world and is known and valued for its fan-shaped, bilobed, green leaves. A concentrated extract made from the leaves has been reported to be of therapeutic value in alleviating conditions associated with peripheral vascular diseases such as intermittent claudication, cerebrovascular disease, and cognitive disorders such as dementia (Gruenwald, 1998).

Extraction of the active compounds from the ginkgo leaf is accomplished via a process that involves a solvent composed of acetone and water. The extract is subsequently dried and standardized to contain 24% flavone glycosides and 6% terpene lactones that apparently work synergistically (Gruenwald, 1998; LeBars et al., 1997) to yield the desired therapeutic benefits. Further analysis of the extract reveals that the flavone glycosides are chiefly comprise quercetin, kaempferol, and rutin. The terpene lactones are the other major category of active compounds found in the ginkgo leaf extract and comprise ginkgolides A, B, C, and bilobalide.

In recent years, there has been increased interest in the use of *Ginkgo biloba* extract for the treatment of dementia and "cerebral insufficiency." In fact, the reported neuroprotective properties of the extract (Smith et al., 1995, 1996) and findings from a number of studies that have demonstrated the efficacy of *Ginkgo biloba* extract in cognitively impaired persons has led to its approval as a treatment for dementia in Germany (Itil and Martorano, 1995).

The large majority of past studies that have assessed the efficacy of *Ginkgo biloba* extract in the treatment of cognitive dysfunction (e.g., dementia, age-related memory impairment) has been conducted in Europe (Allain et al., 1993; Drabaek et al., 1996; Grassel, 1992; Haase et al., 1996; Hofferberth, 1989, 1994; Hopfermuller, 1994; Kanowski et al., 1996; Rai et al., 1991; Semlitsch et al., 1995; Wesnes et al., 1987). Patients who received the extract in these studies have been noted to exhibit improvements in such cognitive functions as memory (e.g., short-term, verbal [Grassel, 1992; Hofferberth, 1994; Semlitsch et al., 1995]), learning rate (Grassel, 1992), speed of information processing (Allain et al., 1993), speed of responses (Rai et al., 1991), and attention (Hofferberth, 1994), as compared to placebo controls. Drabaek et al. (1996) also reported that patients with "moderate arterial insufficiency" who received *Ginkgo biloba* extract displayed reduced impairment of their concentration abilities and inability to remember. Furthermore, a meta-analysis of 11 controlled trials of *Ginkgo biloba* extract LI 1370 (which has the same standardized formulation as EGb 761) in patients suffering from "cerebral insufficiency" confirmed the effectiveness of the extract (as compared to controls) in seven studies, while in one study, the findings were inconclusive (Hopfermuller, 1994). Three additional studies were excluded from this analysis due to "methodological" or "objective" reasons.

To date, there is only one known, published clinical trial that has examined the effects of *Ginkgo biloba* extract on human cognitive functioning in the United States. Le Bars et al. (1997) assessed the efficacy of *Ginkgo biloba* extract (120 mg/day) in mildly to severely demented outpatients over a 52-week period via a double-blind, placebo-controlled randomized design. Results indicated that the extract group exhibited "modest" improvements on the Alzheimer's Disease Assessment Scale-Cognitive subscale (a relatively brief overview of cognitive functioning) and the Geriatric Evaluation by Relatives Rating Instrument (a measure of daily living and social behaviors) as compared to placebo controls.

There appears to be a relative absence of investigations that have examined the effectiveness of *Ginkgo biloba* extract in individuals with no history of clinically significant neurocognitive dysfunction/impairment. Thus, the purpose of this study was to examine the relatively short-term (i.e., 6 weeks) efficacy of *Ginkgo biloba* extract EGb 761 in cognitively intact (as assessed via the Mini-Mental State Examination; Folstein et al., 1975) persons over the age of 55 years via a diverse battery of neuropsychologic tests and measures. Because a plethora of *Ginkgo* products are presently being widely marketed in the United States that purportedly

improve or enhance the cognitive performances/memory of healthy, nondemented individuals, there appears to be a critical need for such clinical trials that scientifically evaluate these claims. Based on the past studies that have found *Ginkgo biloba* to be efficacious in treating a diversity of cognitive dysfunctions, it was predicted that cognitively intact older adults who received *Ginkgo biloba* extract would also exhibit enhanced neurocognitive abilities, as compared to placebo controls, by treatment end.

METHODS

Participants

Twenty-four males and 24 females between the ages of 55 to 86 years, who reported no history of significant neurocognitive impairment, initially enrolled in this study. To be included in this study and considered as cognitively intact, all participants were required to obtain a total score 24 or more on the Mini-Mental State Examination (MMSE; Folstein et al., 1975). Participants' histories were unremarkable for active, or clinically significant cardiovascular, neurologic, pulmonary, endocrine, renal, hepatic, gastrointestinal, hematologic, or oncologic diseases/disorders, uncontrolled hypertension, learning disabilities, or psychiatric or substance abuse disorders. Individuals who were being treated with anticoagulant or psychotropic medications, or who had histories of bleeding disorders or hemorrhagic stroke were excluded from this study. The utilization of medications for other preexisting conditions was not discontinued, although changes or additions to participants' medication regimens during the study were not permitted. Furthermore, participants' histories were unremarkable for uncorrected vision, hearing, or motor difficulties that could have possibly precluded their participation and/or compliance with all of the neuropsychologic procedures.

This project was approved by the Institutional Review Board and Human Subjects Committee at Liberty University. Prior to the initiation of this study's procedures the nature and purpose of this research were explained to each participant and written, informed consent obtained.

Experimental design and procedures

The experimental design consisted of a 6-week, double-blind, fixed-dose, placebo-controlled parallel-group design. Participants meeting inclusionary criteria were randomly assigned to either the *Ginkgo biloba* extract EGb 761 (180 mg/d) or placebo group. Randomization and pharmaceutical preparation procedures (e.g., bottling) for the *Ginkgo biloba* extract and placebo groups were completed by an impartial licensed pharmacy that remained independent from the study. Specifically, a random numbers table was utilized to randomly assign numbers to bottles containing either *Ginkgo biloba* extract EGb 761 or placebo (i.e., methylcellulose). These bottles (and their corresponding numbers) were then allocated to participants in an ascending/sequential order as they entered the study (i.e., at the time of their pretreatment baseline neuropsychological assessments). The *Ginkgo biloba* extract EGb 761 (60 mg/dose) or placebo was taken orally by participants three times daily in the form of opaque capsules that did not differ as regards appearance (e.g., color, size), taste, or smell. It should also be noted that all of the *Ginkgo biloba* extract EGb 761 (Ginkgold; manufactured by Schwabe Pharmaceuticals, Gmbh, Karlsruhe, Germany) that was utilized in this project originated from the same batch/lot number of *Ginkgo* extract that had been purchased from a regional distributor.

To evaluate participants' cognitive-behavioral functioning, series of neuropsychologic tests were administered to them just prior to the initiation of *Ginkgo biloba* extract/placebo therapy (i.e., pretreatment baseline evaluation) and again, after 6 weeks of treatment and just prior to the termination of this regimen. All neuropsychologic testing sessions were conducted by trained research assistants under the supervision of a licensed clinical neuropsychologist.

On arrival for the pretreatment baseline assessment, a brief, rapport-building session was conducted with each participant during which

time the purpose of the study was explained, questions answered, and written informed consent obtained. This was followed by administration of a medical history questionnaire and an assessment of each participant's vital signs (i.e., blood pressure, pulse and respiratory rates, oral body temperature). Participants with abnormal vital signs and those not meeting inclusionary medical criteria were debriefed and excused.

Neuropsychologic testing was then initiated. All participants were administered the following neuropsychologic tests while adhering to each measure's standardized administration and scoring procedures: the MMSE (Folstein, et. al., 1975), Stroop Color and Word Test (SCWT; Stroop, 1935; see Golden, 1978), Trail Making Test (TMT; Parts A and B; Reitan, 1979; Reitan and Wolfson, 1993), and the Wechsler Memory Scale—Revised (WMS-R) Logical Memory I and II (LM I and II) and Visual Reproduction I and II subtests (VR I and II; Wechsler, 1987). After testing, participants were then assigned the next ascending participant number and provided with a supply of randomly assigned capsules containing either *Ginkgo biloba* extract or placebo.

After 6 weeks of *Ginkgo biloba* extract or placebo treatment and just prior to the termination of the regimen, identical neuropsychologic procedures were conducted with each participant with two exceptions. Because the MMSE was utilized as an inclusionary/exclusionary criterion measure, this examination was administered only during the pretreatment baseline assessment. Secondly, a self-report questionnaire was administered during the second neuropsychologic assessment to subjectively assess participants' perceptions of changes in the following variables from pretreatment baseline to the end of the treatment phase (i.e., after 6 weeks): overall recall ability, mood changes, energy level, sexual responsiveness, and overall health.

Compliance with the treatment regimen was assessed via pill counts conducted at the mid- (i.e., after 3 weeks) and end (i.e., after 6 weeks) points of the project with a deviation of more than 20% from the optimum study regimen being operationally defined as noncompliant. In an effort to ensure compliance, participants were telephoned weekly to remind them of the importance of adhering to their treatment regimens. Safety evaluations to assess participants' vital signs were conducted at 0, 3, and 6 weeks while adverse reactions were monitored at 3 and 6 weeks and on an as needed basis.

Neuropsychologic tests/efficacy measures

Follow-up self-report questionnaire. This was an author-generated, self-report questionnaire designed to subjectively assess participants' perceptions of changes in the following variables from pretreatment baseline to the end of the treatment phase (i.e., after 6 weeks): overall recall ability, mood changes, energy level, sexual responsiveness, and overall health. The specific questions that were posed to participants included the following: (1) Based on what your memory was like before the study, how would you rate your overall ability to remember things now?; (2) Based on what your overall mood was like before the study, how would you rate your mood now?; (3) Based on what your energy level was before the study, how would you rate it now?; (4) Some studies from Europe have indicated that ginkgo may increase sexual responsiveness. As compared to before the study, have you noticed any change in this area?; (5) Based on your overall health before the study, how would you rate your general health now? Participants were requested to circle the one category from the following that most accurately reflected their perceptions with regard to each question: much worse, somewhat worse, no change, somewhat improved, much improved. Participants were also asked to report in a narrative any unusual symptoms or side effects that they had experienced during this treatment regimen.

MMSE (Folstein et al., 1975). This measure provides a brief screen of the following cognitive domains: orientation, registration, attention and calculation, recall, and language. Scores can range from 0 to 30 (maximum/perfect score). Scores of 23 or less have been suggested to denote cognitive impairment in individuals with greater than eight years of education (Cockrell and Folstein, 1988). The MMSE was utilized as an inclusionary/exclu-

sionary criterion measure in this study where all participants were required to score between 24 and 30 to be considered cognitively intact and included in this project.

SCWT (Stroop, 1935; Golden, 1978). This standardized test (Golden, 1978) has been suggested to assess response inhibition (Kolb and Whishaw, 1990), the effects of perceptual interference (the Stroop interference effect; Lezak, 1995; Golden, 1978), concentration, and speed of processing abilities. It is composed of three separate tasks. The first task, consisting of 100 items, requires individual to read correctly, as quickly as possible, the names of colors (red, green, and blue) that are printed in black ink and randomly arranged in five columns. Task two items consist of 100 groupings of Xs (i.e., XXXX) that are printed in either red, green, or blue ink. Participants are required to name the colors as quickly as possible. In task three, participants are presented a list of 100 color words (red, green, and blue) where each word is printed in a color ink (either red, green, or blue) that is different from the color's printed name. Individuals are required to ignore the printed word and provide only the name of the colored ink in which the word is printed as quickly as possible. For each task, there is a 45-second time limit.

Trail Making Test, Parts A and B (Reitan, 1992; Reitan and Wolfson, 1993). These tasks are standardized measures that are included in the Halstead-Reitan Neuropsychological Battery (Reitan and Wolfson, 1993). The test comprises two parts, Parts A and B (Reitan and Wolfson, 1993; Jarvis and Barth, 1994). Part A comprises 25 numbers that are randomly arranged on a sheet of white paper. Participants are required to sequentially connect the numbers via drawn lines as quickly as possible until they reach the number 25. Part B consists of 13 numbers (i.e., 1–13) and 12 letters (i.e., A–L) that are randomly arranged on a sheet of white paper. Individuals are required to start with the number 1 and sequentially alternate between numbers and letters of the alphabet via drawn lines as quickly as possible until they reach the last number (i.e., 13). This test has been suggested to assess the abilities to sequence and shift perceptual sets, as well as concentration/vigilance and visuomotor scanning/tracking speed (Lezak, 1995). Such abilities have been suggested to reflect executive control functioning (Kolb and Whishaw, 1990; Luria, 1973; Stuss and Benson, 1984). According to Reitan (1992), this test appears to be one of the best measures of general brain functioning.

WMS-R; LM I and II (Wechsler, 1987). These tasks are standardized subtests that are parts of the WMS-R. Logical Memory I consists of two stories that are individually read to participants. Immediately after each story is read, participants are requested to recall all of the details of the story that they can remember. After 30 minutes, Logical Memory II is administered. During this task, participants are asked to recall from memory all of the details that they can remember about each story that had initially been read to them. The WMS-R Logical Memory I and II subtests have been suggested to assess immediate and delayed auditory-verbal memory for material occurring in a context/story format, respectively (Lezak, 1995).

WMS-R, VR I and II (Wechsler, 1987). These tasks are standardized subtests that are parts of the WMS-R. Visual Reproduction I comprises four items/cards, three that contain a single geometric figure/design and a fourth card on which there are printed two designs (Lezak, 1995). Each card is presented to participants individually for 10 seconds. After each presentation, participants are requested to draw from memory each figure they recall being on the card. After 30 minutes, the Visual Reproduction II subtest is administered. During this subtest, participants are requested to draw from memory all of the designs that had initially been presented to them. The WMS-R Visual Reproduction I and II have been suggested to assess immediate and delayed nonverbal/visual memory, respectively (Lezak, 1995).

RESULTS

From the 48 participants who initially enrolled in this project, 21 males and 19 females

successfully completed the study's protocol and provided valid data sets. Two female participants in the *Ginkgo biloba* extract group withdrew prematurely from the study for the following reasons: self-reported "chest pain" that the participant later acknowledged she had experienced, periodically, for some time prior to enrolling in the study; involvement in a motor vehicle accident and the subsequent development of abdominal pain. A third female participant in the *Ginkgo biloba* extract group acknowledged at the end of the second neuropsychologic assessment (after 6 weeks) that she was suffering from an "isolated" headache that she believed negatively impacted her neurocognitive test performance. She was subsequently excluded from the final analyses due to the questionable validity of her end of treatment test results. Similarly, one male participant in the *Ginkgo biloba* extract group was excluded from the final analyses as he called the day after the second neuropsychologic assessment and acknowledged that he did not perform to the best of his abilities as he had been under a significant amount of work-related stress. Overall, the *Ginkgo biloba* extract appeared to be well tolerated over the duration of the study as no notable adverse reactions were reported by participants who received the extract.

Two female participants in the placebo group withdrew prematurely from the study for the following reasons: unconfirmed (by medical personnel) "high blood pressure"; unconfirmed "high blood sugar." Two male participants in the placebo group also did not complete this study for the following reasons: noncompliance with the treatment regimen; pericarditis.

Separate *t* tests were conducted on the following descriptive and criterion measures: age in years, educational level in years. MMSE total scores, and the actual treatment regimen compliance (based on the participants who successfully completed the study) denoted as a percentage of the maximum compliance. There were no significant differences between the *Ginkgo biloba* extract and placebo groups on any of these variables. Table 1 provides an overview of the groups' means and standard deviations for each variable.

To examine any significant changes in performance over time between the *Ginkgo biloba* extract and placebo control groups on the neuropsychological test variables, separate t-tests were performed using participants' change in performance scores from the pretreatment baseline to those obtained just prior to the termination of treatment (i.e., pretreatment baseline scores minus those obtained after 6 weeks of therapy). Based on the study's directional, *a priori* hypothesis, one-tailed tests were utilized to determine significance. Table 2 provides a summary of the groups' change in performance score means and standard deviations for each neuropsychologic test variable.

For the Stroop Color and Word Test color-naming task, a significant difference ($t(37) = 1.92$, $p < 0.03$) was found between the Ginkgo biloba extract and placebo groups' change in performance scores. Specifically, the *Ginkgo biloba* extract group exhibited significantly more improvement on the color-naming task from pretreatment baseline to after 6 weeks of treatment as compared to the placebo control group. No significant differences were found between the two groups' change in performance scores on any of the other neuropsy-

TABLE 1. GROUP MEANS AND STANDARD DEVIATIONS FOR THE DESCRIPTIVE AND CRITERION MEASURES

	Ginkgo		*Placebo*	
Variable	*Mean*	*SD*	*Mean*	*SD*
Age (in years)	67.50	9.23	68.65	6.95
Education level (in years)	14.15	3.41	14.15	2.90
Mini-Mental State Examination (total scores)	29.00	1.56	28.75	1.07
Treatment regimen compliance (in percentages)	93.15	5.71	92.80	5.99

Note: No significant differences found between groups on any of the above variables.

TABLE 2. NEUROPSYCHOLOGICAL TEST CHANGE IN PERFORMANCE SCORES[a]: MEANS AND STANDARD DEVIATIONS

	Ginkgo		*Placebo*	
Test/Variable	*Mean*	*SD*	*Mean*	*SD*
Stroop Color and Word Test (items read/named)				
Word-naming Task	6.50	13.36	2.75	12.62
Color-naming Task	5.30[b]	9.83	0.05	7.34
Color-Word Task	0.70	3.51	1.72	4.08
Trail-Making Test (in seconds)				
Part A	−5.00	7.93	−1.50	12.49
Part B	−12.60	27.58	−5.11	30.62
Wechsler Memory Scale-Revised (details recalled)				
Logical Memory I	3.20	5.25	3.15	5.73
Logical Memory II	4.80	4.25	5.26	4.91
Visual Reproduction I	2.15	4.88	0.30	3.61
Visual Reproduction II	2.15	7.24	4.25	6.77

[a]Pretreatment baseline scores minus those obtained after 6 weeks of therapy.
[b]Significant difference (one-tailed test).

chologic test variables. It should also be noted that there were no significant differences between the two groups' pretreatment baseline scores for any neuropsychologic test variable.

Separate χ^2 tests were performed on the categorical data obtained from participants on each of the five questions that were included on the Follow-up Self-report Questionnaire. For analysis purposes, frequency data from the categories, "much worse" and "somewhat worse" were combined together into one category entitled, "worse," and the categories, "somewhat improved" and "much improved" were likewise combined to form an "improved" category. Data from the "no change" category remained in a separate category. This resulted in the frequency data for each question being classified into three categories, namely, "worse, no change," or "improved." Of the five questions, only a significant relationship, $\chi^2(2) = 6.75$, $p < 0.03$, was found between the type of treatment received (i.e., *Ginkgo biloba* extract or placebo) and participants' ratings of their "overall abilities to remember things." Specifically, more participants in the *Ginkgo* group rated their overall ability to remember things by the end of treatment as either "somewhat improved" or "much improved" as compared to the placebo group. Figure 1 provides an overview of these results.

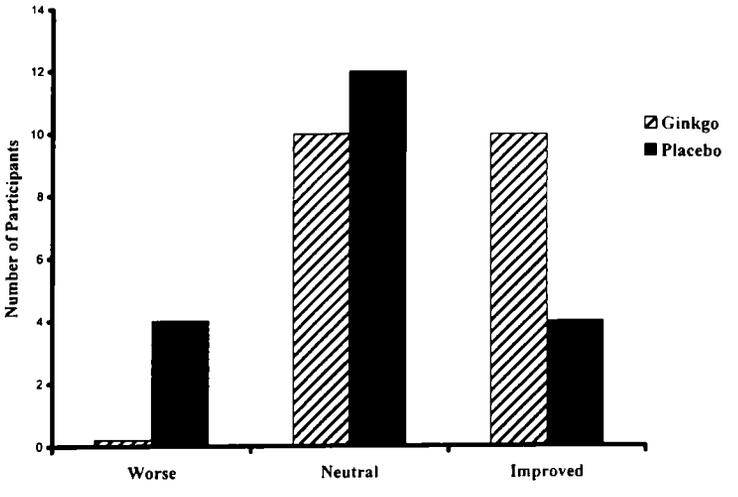

FIG. 1. Participants' ratings of their overall abilities to remember.

DISCUSSION

To our knowledge, this study is among the first to examine the short-term (i.e., 6 weeks) efficacy of *Ginkgo biloba* extract EGb 761 in a sample of cognitively intact (as assessed via the MMSE) older adults across a diversity of neuropsychological tests and measures. The primary neuropsychologic finding of this research provided at least partial support for our *a priori* hypothesis that older, cognitively intact adults who received *Ginkgo biloba* extract EGb 761 would exhibit enhanced neurocognitive abilities, as compared to placebo controls, by the end of treatment.

Specifically, participants who received 180 mg of *Ginkgo biloba* extract EGb 761 daily for 6 weeks exhibited significantly more improvement on the Stroop Color and Word Test's color-naming task by the end of treatment as compared to participants who received placebo. This finding was suggestive of improved speed of processing abilities in the *Ginkgo* versus placebo group, and appeared consistent with previous studies that have found improved speed of information processing (Allain et al., 1993) and speed of response (Rai et al., 1991) abilities in cognitively impaired individuals receiving *Ginkgo biloba* extract.

It should also be noted that while not statistically significant, participants receiving *Ginkgo biloba* extract EGb 761, as compared to the placebo group, also tended to exhibit more improvement after 6 weeks on tasks assessing relatively simple speed of processing abilities (i.e., Stroop Color and Word Test word-naming task, $t(38) = 0.91$, $p < 0.18$) and cognitive processing speed and visuomotor scanning (i.e., Trail Making Test, Part A, $t(38) = -1.06$, $p < 0.15$) abilities. A similar trend $t(37) = -0.80$, $p < 0.21$, for improved performances in the *Ginkgo* versus the placebo group was also noted on the Trail Making Test, Part B, a test assessing complex cognitive processing speed and cognitive flexibility. Overall, of the five neuropsychologic measures included in the study that involved a timed, speed of processing component, the *Ginkgo* group demonstrated more improvement on four of these tasks by the end of treatment as compared to placebo controls.

Although no significant differences were found between the *Ginkgo* and placebo groups' change in performance scores on any of the verbal or nonverbal/visual memory measures, the difference between the two groups approached significance ($t(38) = 1.36$, $p < 0.09$) on the Wechsler Memory Scale-Revised Visual Reproduction I subtest. Specifically, participants in the Ginkgo group tended to exhibit more improvement by the end of treatment on this measure of immediate free recall of nonverbal/visual material as compared to participants in the placebo group. Overall, however, the memory test results (i.e., WMS-R subtests) of this study provided only limited support to past studies involving cognitively impaired individuals that have found improvements in memory functions (e.g., Grassel, 1992; Hofferberth, 1994; Semlitsch et al., 1995).

There are several possible reasons why more significant differences were not found between the two groups' neuropsychologic change in performance scores. For one, the relatively small sample size that was utilized in this study likely decreased the power of the statistical measures to find statistically significant differences. Second, because all participants appeared to be cognitively intact at the onset of this study, the majority of the neuropsychologic measures may not have been of sufficient sensitivity to identify relatively subtle differences that may have actually existed, and been statistically significant, had larger samples of intact participants been utilized. Relatedly, it is possible that some of the neurocognitive measures (e.g., contextual verbal memory tests) failed to assess the specific types of abilities that are most sensitive to the effects of *Ginkgo biloba* extract. Finally, it remains possible that *Ginkgo biloba* extract EGb 761 has only limited efficacy on the neurocognitive functions/processes of cognitively intact older adults.

In contrast to the nonsignificant memory tests findings, a significant relationship was found at the end of treatment assessment between the type of treatment that was received (i.e., *Ginkgo biloba* extract or placebo) and participants' ratings of their "overall abilities to remember things" as assessed via the Follow-up Self-report Questionnaire. Specifically, more participants in the *Ginkgo biloba* extract group

rated their overall ability to remember things by the end of treatment as either "somewhat improved" or "much improved" as compared to participants in the placebo group. This subjective finding suggests that the *Ginkgo biloba* extract may have actually enhanced aspects of some participants' overall memories that were perceptible to them, but that were not identified by the specific standardized memory measures that were included in this study. As noted previously, it is possible that the generally negative findings from the "objective" memory measures (i.e., WMS-R subtests) were due to the relatively small sample size that was utilized in the study, the possibility that these measures were not of sufficient sensitivity to identify relatively subtle differences in small samples of cognitively intact individuals, and/or that the memory tests selected for the study failed to assess the specific components of memory that were most sensitive to *Ginkgo biloba* extract.

Taken together, the findings from the standardized, neuropsychologic tests and subjective, self-report questionnaire suggest that relatively short-term utilization (i.e., 6 weeks of therapy) of *Ginkgo biloba* extract EGb 761 may prove efficacious in enhancing certain neurocognitive functions/processes of cognitively intact older adults. Specifically, by treatment end, the *Ginkgo* versus the placebo group exhibited significantly more improvement in their speed of processing abilities on a color-naming task. Although nonsignificant, the *Ginkgo* group (as compared to placebo controls) also exhibited trends for more improvement after 6 weeks of treatment on three additional tests involving a timed, speed of processing component. A similar nonsignificant trend was noted on an immediate recall task involving nonverbal/visual material. Results of the subjective, Follow-up Self-report Questionnaire revealed a significant relationship between treatment type and participants' "overall abilities to remember things" where more participants in the *Ginkgo* group rated their abilities to remember things by the end of treatment as "somewhat improved" or "much improved" as compared to placebo controls.

Although a detailed discussion of the possible mechanisms/factors that may have contributed to this study's positive findings is beyond the scope of this article, a diversity of mechanisms have been proposed to explain the beneficial effects of *Ginkgo biloba* extract that have been observed in past studies. These mechanisms include: the prevention of ultrastructural ischemic brain damage via a reduction of capillary fragility and decreased blood loss from capillary vessels, inhibition of peroxidation of cell membranes via *Ginkgo biloba*'s broad spectrum of antioxidant properties/activities, inhibition/suppression of the platelet-activating factor, improved hypoxic tolerance, increased circulation, maintenance of arterial and venous vascular tone, enhancement of muscarinergic receptor systems and norepinephrine turnover, and normalization of neuronal/cerebral metabolism (Gruenwald, 1998; Itil and Martorano, 1995; Maitra et al., 1995; Pietri et al., 1997; Semlitsch et al., 1995; Smith et al., 1996; Tyler 1994). It should be noted, however, that because the true mechanisms that are responsible for *Ginkgo biloba* extract's effectiveness continue to not be fully understood, the precise mechanisms that were responsible for this study's results also cannot be determined at present. It seems reasonable, however, that two or more of these factors possibly interacted synergistically to produce the positive results observed in this study.

Future research is required to replicate this study's findings utilizing larger samples of cognitively intact older adults and possibly more diverse neuropsychologic batteries to examine the potential differential impact of the extract on various neurocognitive functions. Relatedly, based on this study's positive subjective finding concerning "overall abilities to remember," future investigations should examine additional components/aspects of memory (e.g., memory for faces, complex figures, etc.) in cognitively intact participants. Studies should also be conducted that use different daily dosages of *Ginkgo biloba* extract to examine possible dose-related effects in cognitively intact individuals. Finally, similar studies are needed that examine the efficacy of *Ginkgo biloba* extract EGb 761 in younger (less than 55 years of age) cognitively intact groups.

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