Specific memory effects of Ginkgo biloba extract EGB 761 in middle-aged healthy volunteers

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ABSTRACT

Introduction: Recent reviews showed that Ginkgo biloba extract EGB 7611 is effective to enhance performance in patients with cognitive impairment (e.g., dementia). The aim of this study was to investigate the effects of EGB 761 on memory and the specificity of such effects on distinct memory functions in middle-aged healthy volunteers.

Methods: A total of 188 healthy subjects aged 45–56 years were randomised to receive EGB 761 (240 mg once daily) or placebo for 6 weeks. Outcome measures were the change in memory performance in a demanding standardised free recall paradigm (list of appointments) and a less demanding standardised recognition test (driving-route). Based on previous findings we predicted superiority of EGB 761 in recall testing. Specificity in effects was assessed by separating immediate vs. delayed and quantitative vs. qualitative free recall measures.

Results: After 6 weeks, EGB 761-treated subjects improved significantly in quantity of recall, i.e., the number of correctly recalled appointments (drug-placebo differences: p = 0.038 for immediate and p = 0.008 for delayed recall). Effects on qualitative recall performance (ratio of false to correct items) were similar (drug-placebo differences: p = 0.092 for immediate and p = 0.010 for delayed recall). No superiority of Ginkgo was evident in another everyday memory test which asked for recognition of a driving route (drug-placebo differences: p > 0.10). The incidence of adverse events was low and not significantly different between treatment groups.

Discussion: EGB 761 (240 mg once daily) improves free recall of appointments in middle-aged healthy volunteers, which requires high demands on self-initiated retrieval of learned material. This function is known to be sensitive to normal aging, i.e., reduced in healthy middle-aged subjects. No effects are seen in a less demanding everyday memory task which does not tap this critical function. This ties in with previous studies which found specific patterns of benefit from EGB 761 in demanding cognitive tasks.

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Introduction

Ginkgo biloba extracts are widely used for the enhancement of cognition in aging-related conditions such as mild cognitive impairment and dementia. The efficacy of the standardised extract EGB 761 has been demonstrated by a number of randomised controlled trials and meta-analyses (IQWIG 2008; Weinmann et al. 2010; Wang et al. 2010) and this extract has been registered for the treatment of dementia syndromes in Germany and elsewhere. However, effects of EGB 7611 in healthy younger subjects are less clear, as only a few randomised controlled trials (RCT) do exist. Mix and Crews (2000) conducted a 6-weeks RCT in 40 cognitively intact elderly (mean age: 67.5 years). 180 mg EGB 761 per day improved performance in the colour-naming trial of the Stroop test but did not alter other cognitive tests. Furthermore, more subjects in the Ginkgo group rated their ability to remember as better than did in the placebo-group. Mix and Crews (2002) replicated their finding of better self-rated memory performance after 180 mg of EGB 761 per day in a larger RCT (n = 262; mean age: 67.0 years in the Ginkgo and 68.6 years in the placebo group). Subjects with evident cognitive decline (MMSE < 26) were excluded. They also reported significant enhancement for delayed recall and recognition sub-tests in the active treatment group after 6 weeks and this was consistent for auditory-verbal (selective reminding test) as well as for visual-nonverbal material (faces-test of Wechsler Memory Scale III). Thus, results from both objective psychometric tests and subjective self-report questionnaires provided complementary evidence for improved delayed long-term memory. By contrast, Solomon et al. (2002) reported no effects in a 6-weeks RCT using 120 mg per day of a Ginkgo extract in 130 subjects of a mean age of 69.3 years, but there have been serious concerns regarding the way of double-blinding in this particular trial. Snitz et al. (2009)

1 Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany.
reported no difference in change of cognitive function over 6 years between placebo and 240 mg per day of EGb 761 in a secondary analysis of a dementia prevention trial. However, appropriate tests of cognitive functioning were not performed consistently during the first half of the trial, attrition rates were high and compliance was as low as 60% at the end of the trial. Both positive and negative findings have been reported from trials using other Ginkgo biloba leaf extracts in healthy young as well as in elderly persons (Canter and Ernst 2007).

A number of reasons may account for these divergent findings: In cognitively intact individuals running an RCT asks for specific methodological pre-requisites, psychometric assumptions and a refined consideration of methodological demands. They have to take into account specific characteristics of cognitively intact individuals still seeking to improve their cognitive everyday-performance. If these methodological features are neglected, studies in healthy individuals tend to provoke beta-errors, i.e., they falsely suggest a lack of effectiveness without considering poor methodology. Therefore, Ginkgo may not even have had a fair chance to demonstrate its efficacy in healthy individuals (Kaschel 2009).

Whereas respective scales for clinical conditions such as Alzheimer’s disease are well established, in non-demented subjects the selection of tests is often arbitrary and there is a lack of operationalization of distinct cognitive functions by a corresponding test, thus leading to a confusing, redundant and unstructured array of cognitive outcome measures (cf. Crews et al. 2005; pp. 57–58).

A corresponding methodological prerequisite is the claim for not just demonstrating objective effects in the structured situation of a memory test, but also to improve subjective well-being in terms of everyday memory failures. This is usually assessed by meta-memory questionnaires and there is sound evidence from healthy and abnormal aging that objective memory tests and subjective memory questionnaires yield qualitatively different information. For example, subjective memory complaints, even in the absence of objective memory impairment, appear to be a strong predictor of future cognitive decline and dementia (Schmand et al. 1997; Schofield et al., 1997a,b; Geerlings et al. 1999). The notion that memory-questions tap aspects of well-being is shown by its close relationship to dysphoric mood and depressive disorder. For example, in a cross-sectional perspective, subjective memory complaints were associated with depression rather than with objective cognitive impairment, but this did not affect their predictive value for cognitive decline in the longitudinal perspective (Schmand et al. 1997).

Following these methodological considerations, we report here on a trial assessing the clinical efficacy and tolerability of EGb 761 in cognitively intact, middle-aged, well-educated individuals. Apart from adequate power of selected samples and adequate intensity and duration of treatment, we selected ecologically valid everyday memory tests and questionnaires which were shown to be able to monitor change in neuropsychological rehabilitation (Kaschel 1993; Kaschel et al. 2002; Wagner et al. 2008).

The study aimed:

- to assess effects on long-term memory using delayed recall tasks
- to replicate evidence suggesting that objective improvement is paralleled by changes in subjective memory ratings and
- to link changes in objective psychometric test performance with everyday life in terms of ecological validity (memory tests relevant to daily living).

Given hints from the existing literature we postulated effects of medication in complex recall but not in simple recognition tests.

Methods

Selection of subjects

Male and female subjects were eligible for inclusion in this study, if they were mentally healthy, aged 45–85 (both inclusive), had higher-level secondary education (at least middle or high school), sufficient language skills to understand and respond to all interview questions and undergo neuropsychological testing without difficulties and without assistance, and who had provided written informed consent.

Criteria for exclusion were: participation in another experimental drug trial within the past 4-weeks before enrolment, prior participation in a clinical trial with Ginkgo biloba, hospitalization, ischaemic stroke within the last three months, cognitive impairment due to any neurological origin or psychiatric disorder, history of recurrent major depression or recurrent anxiety disorder. Those patients with a history of a single episode were accepted if the episode was finished at least one year before enrolment. Further exclusion criteria were: Use of antidementia drugs or cognition enhancers, anticholinergic drugs, haemorheological drugs, anti-epileptics, anti-Parkinson drugs, continued use of psychoactive (including sedating) drugs. At least 8-weeks washout was required if any prohibited drug had been used before. Occasional use (up to 3 times a week) of tranquilizers for sleep disturbances was permissible, but not within 48 h prior to test sessions. Substance addiction or abuse within the last 5 years, severe, uncontrolled cardiovascular disease, severe renal or hepatic dysfunction, insufficiently controlled insulin-dependent diabetes mellitus or any other severe illness were reasons for exclusion. Subjects with any condition that could compromise the absorption of orally applied drugs were excluded, as were those with severe and insufficiently corrected loss of vision or hearing, severe language difficulties or any other disability that could have compromised the subject’s ability to cooperate adequately. Female patients of childbearing potential were not enrolled either.

Randomization procedure

A randomised, double-blind, placebo-controlled, mono-centre trial design was chosen. The trial was approved by the Independent Ethics Committee of the Ruhr University Bochum and run in Germany between December 2005 and March 2006. It was conducted in accordance with the Declaration of Helsinki and the Guideline for Good Clinical Practice (GCP) issued by the International Conference on Harmonisation (ICH). Informed consent was obtained from all patients before enrolment.

Eligible subjects were randomly allocated to receive 240 mg (once daily in the morning) EGb 761 or placebo. For a period of 6-weeks, they underwent the investigational treatment without undertaking further memory-enhancing activities. EGb 761 is a dry extract from Ginkgo biloba leaves (drug-extract ratio 35–67:1), adjusted to 22–27% Ginkgo flavonoids and 5–7% terpene lactones, consisting of 2.8–3.4% ginkgolides A, B, C and 2.6–3.2% bilobalide, with a content of ginkgolic acids below 5 ppm. Active drug and placebo were of identical appearance.

Randomisation in a 1:1 ratio was performed by a validated computer program. The length of the balanced blocks was fixed in a separated document that was withheld from the study sites. The investigators received sealed emergency-envelopes for individual patients, all of which were returned unopened after completion of the trial.

2 EGb 761 is a registered trade mark of Dr. Willmar Schwabe GmbH & Co. KG Pharmaceuticals, Karlsruhe, Germany.
Sample size calculation and statistical analysis

As this was the first clinical trial of EGB 761 using these outcome measures, a sample size calculation based on former experience was not possible. Hypothesis testing was exploratory rather than confirmatory. Therefore, a significance level of \( p = 0.05 \) and two-sided tests were applied to all outcome variables without adjustment of the type-one error rate.

Outcome measures

Main outcome measures were two memory tests relevant to daily living and one subjective memory questionnaire. An assessment scale for well-being and mood disturbances was employed as an additional outcome measure. Whereas the first mentioned measures were used to assess effects of Ginkgo on memory, the rating scale for well-being and mood was used as a control measure to account for changes in mood which might mediate changes in primary outcome measures.

Cognitive outcome measures were objective memory tests – one test of free recall (appointments test) and one test of recognition (driving route film). Additionally, a questionnaire was administered by which elderly subjects were asked to rate their own memory for similar verbal and non-verbal materials. All outcome measures are standardised psychometric tests proven to show high objectivity, reliability and validity. They were developed especially to assess changes in daily living-related memory in the field of neuropsychological rehabilitation (high ecological validity; cf. Kaschel 1994) and were shown to be sensitive enough to evaluate changes in objective performance and corresponding subjective memory ratings (e.g., Kaschel et al. 1993, 2002).

Given the specific hypothesis derived from the literature, a target measure of particular interest was free recall of different lists of appointments (Kaschel 1993). This test measures the retention of the (verbal) contents of actions to be performed in the future which is one element for successful prospective memory performance (Kazen et al. 2008). This test was shown to be sensitive in the same age range as in our study in psychosomatic (Wagner et al. 2006) as well as in psychiatric (Kaschel et al. 2009) patients. There are 6 parallel forms for repeated measurements, and norms are available for different age groups. The test is designed in a way that even cognitively intact persons do not achieve the maximum possible score, thus excluding ceiling effects. Each parallel form of this test comprises 8 complex appointments to be learnt by heart within 2 min, followed by an un-aided short-term free recall and another free recall test after 45 min filled delay (long-term free recall), which is expected as it is stated after the first recall that a second test will be done without having the opportunity to look at the list again. Each appointment consists of 4 parts (e.g., “Tuesday between 11 a.m. and 12 a.m. ring Tom in Manchester”). Dependent measures are the number of correctly recalled parts of these appointments out of 8 items, thus the range of this quantitative recall measure ranges from 0 to 32 points (for short- and long-term recall respectively). For reasons of clarity, this variable will be labelled “Quantity of Recall”. A second variable will be referred to as “Quality of Recall”. This is defined by the ratio of incorrect answers to the number of items correctly reproduced. For example, if the answer is partly correct saying “between 11 a.m. and 12 a.m. ring Tom in Manchester” but “Monday” is added to this instead of “Tuesday”, then 1 error is made and 3 out of 4 quarters are correct. The ratio of errors to correct would be 1:3; i.e., 0.33.

The second memory test involved less complex learning and remembering operations: Subjects watched a 15 min film of a driving route on a computer screen and were asked to keep in mind at each of the 18 crossings whether to turn right, left or straight ahead. Following this learning period they saw the same driving route once again and the film stopped at each of the crossings – subjects marked the respective direction on a response sheet. Given 18 crossings the raw score in this recognition test ranged from 0 to 18 points. Similar to the recall test, this recognition test provided 2 parallel forms of comparable difficulty which were administered in counterbalanced order.

A standardised memory self-rating questionnaire (Inventory of Memory Experiences, IME; Herrmann and Neisser 1978; German version by Kaschel 1994) asked for the ability of memory performance (e.g., to remember a toy one had when one was a child) and occurrence of memory failures (forgetting to call a friend on the phone). Well-being and mood were assessed by the BFI-questionnaire which asks for psychosomatic symptoms (such as feelings of tension); higher total scores indicate worse well-being and mood (von Zerssen 1976).

Results

Out of a total of 188 subjects randomised, the full analysis set (FAS) comprised 177 (n = 89 placebo, n = 88 EGB 761). In the per protocol set (PPS) 159 subjects without major protocol violations (n = 79 placebo and n = 80 EGB 761) were analysed (Table 1). As the results for the FAS and the PPS are nearly identical, we report here only on the FAS.

The proportion of females was significantly lower in the active treatment group (59.1%) than in the placebo-group (76.4%; two-sided \( \chi^2 \)-test \( p = 0.014 \). However, since there are no gender differences for the evaluated tasks of the memory tests (appointments test, driving route test) or the Inventory of Memory Experiences (Kaschel 1993, 1994; Kaschel et al. 1993), there was no need to account for this in the statistical analysis. Age was not significantly different between the groups with an average of 54.8 years (SD = 6.4) in the placebo group and 54.2 years (SD = 6.0) in the EGB 761 group (two-sided Wilcoxon-test \( p = 0.670 \).

Results for the two everyday-memory tests are depicted in Table 2 and Fig. 1. In the quantitative measure of correctly recalled items, EGB 761 is superior in the immediate and in the delayed recall. A larger drug–placebo difference was found under delayed (\( p = 0.008 \)) as compared to immediate recall conditions (\( p = 0.038 \)). This pattern is replicated using the qualitative measure of ratio

| Table 1 |
| Patient sample, absolute numbers (number of volunteers). |
| EGB 761 | Placebo |
| Planned for randomisation | n = 94 | n = 94 |
| Randomised | n = 94 | n = 94 |
| Safety set | n = 94 | n = 94 |
| Full analysis set (FAS) | n = 88 | n = 89 |
| Per protocol set (PPS) | n = 80 | n = 79 |

Fig. 1. Appointments Test – delayed recall; changes from baseline to week 6 in correctly recalled pieces of information (means, 95%-confidence intervals); \( * p < 0.01 \) (two-sided Wilcoxon test).
Table 2
Objective memory tests: baseline values and changes from baseline (means (SD)) for total patient sample (FAS), two-sided p-values for between-group comparisons of changes (Wilcoxon-test); of note, positive values for quantity and negative values for quality of recall indicate improvement.

<table>
<thead>
<tr>
<th>Objective performance test</th>
<th>Baseline EGB 761® (n = 89)</th>
<th>Placebo (n = 89)</th>
<th>Changes from baseline to week 6 EGB 761® (n = 89)</th>
<th>Placebo (n = 89)</th>
<th>p-Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appointments test – immediate recall quantity of recall</td>
<td>16.67 (4.89)</td>
<td>18.56 (5.48)</td>
<td>2.20 (4.39)</td>
<td>1.03 (4.98)</td>
<td>0.038</td>
</tr>
<tr>
<td>Appointments test – delayed recall quantity of recall</td>
<td>12.90 (3.36)</td>
<td>15.79 (6.13)</td>
<td>2.26 (5.05)</td>
<td>0.35 (5.26)</td>
<td>0.008</td>
</tr>
<tr>
<td>Appointments test – immediate recall quality of recall</td>
<td>0.24 (0.20)</td>
<td>0.17 (0.18)</td>
<td>-0.08 (0.23)</td>
<td>-0.02 (0.25)</td>
<td>0.092</td>
</tr>
<tr>
<td>Appointments test – delayed recall quality of recall</td>
<td>0.35 (0.29)</td>
<td>0.25 (0.21)</td>
<td>-0.09 (0.24)</td>
<td>0.01 (0.29)</td>
<td>0.010</td>
</tr>
<tr>
<td>Driving route test items correct</td>
<td>14.51 (2.37)</td>
<td>14.22 (2.34)</td>
<td>-0.92 (2.60)</td>
<td>-0.74 (2.56)</td>
<td>0.439</td>
</tr>
</tbody>
</table>

of errors to correctly reproduced items: Whereas EGB 761 is only slightly better than placebo as indicated by a trend in immediate recall (p = 0.092) it is significantly superior (p = 0.01) in long-term delayed recall.

In the driving-route recognition task, both groups show a similar degree of change from baseline with no significant difference between drug and placebo groups (p = 0.439). Lack of effect in the driving-route task is not a consequence of a ceiling effect: as the number of crossings was 18 and each of them asked for a decision which direction to drive, this corresponds to a range of 0–18 points in the total score and scores around 9 reflect recognition performance at chance level, because only two types of response, correct or wrong, were possible. The baseline scores at week 0 were 14.51 (SD = 2.37) and 14.22 (SD = 2.34) points for the EGB 761 and placebo group, respectively – thus leaving room for improvement as this is far from top performance (18 correct decisions).

Regarding the subjective memory questionnaire, both treatment groups reported a slight improvement from baseline to week 6, but there was no between-group difference, i.e., the sum score was not sensitive to medication. On the other hand, the specific factor score in which all items asking for topographical (places) or prospective (intentions) everyday memory is taken together, showed a strong trend in favour of EGB 761 (p = 0.058). This is reflected by different direction of changes: whereas the number of occasions of memory failures dropped in the EGB 761 group (−0.41) it remained stable in the placebo-group (+0.08). There were no differential effects in the questionnaire of well-being and mood (p = 0.974). Changes by 0.88 (active treatment) and 1.30 (placebo) over time indicate a slightly negative trend which is evident to a comparable degree in both groups. On the other hand, these changes are very subtle as covering only about 2% of the total range (0–56) of this scale. Thus, mood was stable over the course of 6-weeks. Furthermore, high standard deviations of changes in both groups indicate a heterogenous pattern of pre-post-differences (Table 3).

Safety

Overall, during the active treatment period, a total of 35 adverse events were reported for 31 subjects. In the active treatment group, 20 adverse events occurred in 19 subjects: in the placebo group, 15 adverse events were reported for 12 subjects. For 7 adverse events in the EGB 761 group (headache, n = 4; gastric complaints, n = 3) and 5 events in the placebo group (gastric complaints, n = 3; conjunctivitis, nettle rash) a causal relationship with treatment could not be ruled out. No serious adverse event occurred during the study. The incidence of adverse events was similar in both treatment groups.

Discussion

Three topics seem to be worth discussing: firstly, all of the specific aims of this study, which were outlined in the introduction, could be achieved. Secondly, this yields to a specific neuropsychological pattern of benefit from EGB 761 which fits well to other studies dealing with healthy individuals. Thirdly, the most important message may be that previous notions that Ginkgo improves performance only in elderly but not in younger healthy individuals do not reflect an age-effect but were due to a methodological artefact.

Turning to the first topic, our study showed effects on long-term memory using a delayed recall (appointment) task and it also replicates evidence (Mix and Crews 2002) suggesting that objective improvement is paralleled by changes in subjective memory ratings. Thus we achieved the goal to link changes in objective psychometric test performance with everyday life in terms of ecological validity as everyday relevant memory tests (appointments) and questionnaires showed similar changes (factor score ‘topographical and prospective memory’ of the IME). The safety and tolerability of EGB 761 was excellent. There were only few and minor adverse events that were balanced between active drug and placebo. This safety profile is in line with findings from former clinical trials and long-standing clinical experience.

Concerning the second topic of specificity of change, long-term and – to a somewhat lesser degree – also short-term free recall, were improved in the appointments test. Effects were prominent in the quantitative parameter of the number of appointments which were recalled correctly, but also in the qualitative measure of ratio of errors to correct answers. Thus there were long-term memory improvements in complex demands but there were no effects in a more simple test of immediate recognition, even though this task was also everyday-orientated (driving route film). These effects on quantitative and qualitative complex free recall performance were not mediated by general feelings of better mood (BfS®) nor did they show any covariation with general ratings of memory in the subjective questionnaire (IME). Global scores of memory self-rating are closely related to depression and dysphoric mood in the literature, thus adding corroborative evidence for the statement that improvements in the appointments test were not mediated by changes in mood. As mood remained stable over the course of the trial and we found effects only in complex parameters of the highly demanding appointments but not in the easier driving route recognition task, changes induced by Ginkgo showed a specific pattern. This pattern is in line with the finding of a recent neuropsychological review of Ginkgo effects in non-demented subjects (Kaschel 2009) and to previous studies (Mix and Crews 2000, 2002; Stough et al. 2001; Burns et al. 2006). They also found either effects on complex attentional (e.g., Stroop test) or memory (long-term memory) parameters.

Turning to the third topic for discussion we were able to show long-term memory effects although our subjects were considerably younger (mean age: 54.5 years) than the corresponding samples in the literature where similar effects could be demonstrated (mean age: 67.5 years, Mix and Crews 2000; mean age: 67.8 years, Mix and Crews 2002; mean age: 61.7 years, Burns et al. 2006). With the exception of Stough et al. (2001) (range 18–40 years) no previous study reported such long-term memory effects in tests and questionnaires. This demonstration of effects even in younger subjects casts doubts on the notion that in individuals younger than 60 years effects of Ginkgo are lacking (Cantor and Ernst 2007). We want to
postulate that the lack of effects in younger as opposed to older healthy individuals is not an effect of age but of methodological artefacts.

In younger healthy subjects a number of variables makes it really difficult to demonstrate efficacy of any cognition enhancing drug. Main sources of corresponding beta-errors in Ginkgo research comprise the arbitrary and problematic use of psychometric principles, lack of power in small samples, practice and ceiling effects of tests and other aspects indicating low sensitivity of measures (cf Kaschel 2009). Apart from the quest for a theoretically and empirically based selection of modern and psychometrically grounded tests, trivial practice effects confounded with pre-post-differences should be taken into account. Given large retest-effects, superiority of any drug over placebo is difficult to demonstrate in non-impaired subjects. Large retest-effects were reported even after months in normal but not in cognitively impaired individuals (Zehnder et al. 2007). Additionally, specific remembering effects may occur if no parallel-forms of memory tests are used.

Furthermore, sensitivity to assess the normal range of cognitive functioning and sensitivity to change are further methodological prerequisites: Whereas most RCTs in clinical populations used measures of cognitive impairment, the selection of dependent variables in studies using cognitively intact subjects requires objective measures of cognitive performance (Burns et al. 2006). Global cognitive measures used in dementia are not adequate in assessing healthy volunteers. Instead, sensitive objective measures which discriminate amongst normal performance were rarelly used so far (cf Kaschel 2009).

Additionally, sensitivity for change is also a crucial prerequisite: Testing cognitively intact individuals over time bears a narrow therapeutic window for demonstrating change as many of these persons are already performing at ceiling. In addition, demand characteristics of the test situation may motivate them for top-performance. Another problem linked to ceiling-effects is the question whether a specific psychometric test is able to monitor change. For example, a neuropsychological memory test might be excellent regarding objectivity, reliability, validity for measurement of the current status quo, but not able to capture change (sensitivity for change). Therefore, memory tests for clinical trials assessing cognitive enhancement in healthy subjects should demonstrate objectivity, reliability and validity, provide equivalent parallel forms but additionally show small retest-effects and sensitivity to change. Furthermore, they should prove to correlate with everyday cognitive functioning. This ecological validity is one aspect of external validity: If you show beneficial effects on cognition in an RCT (internal validity), you want to know whether this result generalises from a specific test to everyday life (ecological validity).

This study adds to the evidence and understanding of effects of Ginkgo biloba extract EGB 761® in healthy subjects. The methodological prerequisites outlined above should be kept in mind, if further studies are done in this type of population.

**Disclosure**

The clinical trial was funded by Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany.

**References**


Table 3

<table>
<thead>
<tr>
<th>Subjective questionnaire (self-rating)</th>
<th>Baseline EGB 761® (n=88)</th>
<th>Baseline Placebo (n=89)</th>
<th>Changes from baseline to week 6 EGB 761® (n=88)</th>
<th>Changes from baseline to week 6 Placebo (n=89)</th>
<th>p-Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inventory of memory experiences</td>
<td>EGB 761® (n=88)</td>
<td>Placebo (n=89)</td>
<td>EGB 761® (n=88)</td>
<td>Placebo (n=89)</td>
<td></td>
</tr>
<tr>
<td>global score</td>
<td>63.53 (7.75)</td>
<td>62.52 (9.66)</td>
<td>–2.39 (6.99)</td>
<td>–2.10 (6.76)</td>
<td>0.665</td>
</tr>
<tr>
<td>Inventory of memory experiences – factor score: “Memory for Places and Intentions”</td>
<td>11.40 (2.01)</td>
<td>11.25 (2.54)</td>
<td>–0.41 (2.00)</td>
<td>0.08 (1.86)</td>
<td>0.058</td>
</tr>
<tr>
<td>BIS mental balance scale</td>
<td>10.98 (8.94)</td>
<td>10.26 (7.98)</td>
<td>0.88 (8.53)</td>
<td>1.30 (8.26)</td>
<td>0.974</td>
</tr>
</tbody>
</table>


