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# Psychophysiological Effects of *Sideritis* and *Bacopa* Extract and Three Combinations Thereof—A Quantitative EEG Study in Subjects Suffering from Mild Cognitive Impairment (MCI)

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## Abstract

**Mild cognitive impairment (MCI) is regarded as a transitional stage during the development of Alzheimer's disease. Diagnosis of MCI can be obtained by the questionnaire "DemTect" in German speaking countries. Quantitative assessment has been successfully performed using psychometric testing concomitantly with quantitative EEG recording. The present investigation aimed at the possible treatment of MCI with two botanicals, namely extracts from *Sideritis scardica* (500 mg) or *Bacopa monnieri* (320 mg) and three combinations thereof using this method in order to find a new treatment. The performance of the d2-test, an arithmetic calculation test (CPT) and a memory-test revealed better performance for the d2-test only in the presence of *Sideritis* extract or the combinations with *Bacopa* extract. Quantitative EEG assessment during the different experimental conditions showed massive differences between both extracts. Whereas *Sideritis* extract and its combination with a low amount of *Bacopa* extract (160 mg) induced increases of spectral power in fronto-temporal brain areas, *Bacopa* and the combination of *Sideritis* with high amounts of *Bacopa* extract produced attenuation of all waves except for delta in fronto-temporal brain areas. These differences were also documented by quantitative EEG maps in comparison to Placebo. A different action of both extracts was confirmed by discriminant analysis, where *Sideritis* extract and its combination with low *Bacopa* grouped together quite at distance to *Bacopa* and the combination of *Sideritis* with high *Bacopa*. A combination of *Sideritis* extract with a low amount of *Bacopa* should be tested with daily repetitive dosing for at least 4 weeks as a consequence.**

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## Keywords

**DemTect, Cognition, Psychometry, EEG, Source density, Mild Cognitive Impairment (MCI), Alzheimer's Disease, CATEEM, *Sideritis*, *Bacopa***

## 1. Introduction

Mild cognitive impairment (MCI) causes a slight but noticeable and measurable decline in cognitive abilities. Long-term studies suggest that 10% to 20% of those aged 65 and older may have MCI. Cognitive changes are not severe enough to interfere with daily life. MCI can be regarded as a first sign of development of severe dementia in a subgroup of patients. Conversion into Alzheimer's disease (AD) can be followed by quantitative electro-encephalography [1]. Region and frequency specific spectral oscillatory characteristics of EEG reflect domain-specific cognitive function in patients with MCI and AD [2]. The question therefore arises if subjects suffering from cognitive impairments should be treated in order to stop a possible progression, which can be followed by quantitative EEG. A systematic review and meta-analysis have shown that for example cholinesterase inhibitors do not show a benefit when compared with a control group [3]. On the other hand, a small cognitive benefit is reported by the same authors using a behavioral therapeutic approach. Other authors state: there is no replicated evidence that any pharmacological intervention is effective [4]. Interestingly, prevention of cognitive decline is reported by treatment with B vitamins in the presence of high omega-3 fatty acid status [5].

Therefore, new approaches were necessary in form of clinical studies. An alternative treatment might be seen in using herbal preparations or botanical extracts. In preclinical and clinical studies, a new candidate was discovered: *Sideritis scardica* extract [6]. A second candidate emerged from the literature: *Bacopa monnieri* extract [7]-[9]. The present investigation was planned as a proof of concept study in order to test the possibility, that one of the two extracts or a combination of them was able to have an acute positive psychophysiological effect in subjects suffering from mild cognitive impairment before entering a clinical study based on repetitive dosing.

## 2. Methods

### 2.1. Subjects

Ten subjects having given informed consent were selected by the questionnaire "DemTect" [10] [11]. DemTect is a simple, quick and objectively to perform screening procedure for the detection of beginning dementia. The questionnaire contains five tasks with respect to memory, word fluency, intellectual flexibility, and attention. Performance is reached within 8 - 10 minutes. Score values cover points between 0 and 18. Numbers below 8 indicate severe dementia, numbers above 13 indicate normal cognitive performance. Subjects having a score between 8 and 13 were included into the study.

Within a crossover design subjects (7 male, 3 female; mean age: 61.88 ± 6.69) were given two herbal extracts and three mixtures thereof as single dosages. Besides Placebo they obtained 500 mg of *Sideritis* extract or 320 mg *Bacopa* extract (provided by Dr. Loges GmbH, Winsen, Germany) or both together in combination during a first series of experiments. During a second series 8 of the 10 subjects were tested with two more combinations: 500 mg *Sideritis* plus 160 mg *Bacopa* or 500 mg *Sideritis* plus 480 mg *Bacopa* extract. For the sake of clarity, data from the administration of *Sideritis* and *Bacopa* extract alone are documented as a first series of experiments, followed by data from all three combinations as a second series. For testing food supplements no ethic vote is recommended in Germany.

### 2.2. EEG Recording

Basically, the method of quantitative EEG recording in combination with performance of psychometric challenges was followed as published [12]. In short, three mental tests were performed concomitantly with the EEG recording for 5 minutes: a d2-concentration test (d2-test), an arithmetic calculation test (CPT) and a memory-test (MEM). Sixteen channels of EEG and one channel EOG (for artifact rejection) were recorded. After frequency analysis (FFT) current source density was calculated as reported earlier [13] [14]. Baseline values ($\mu V^2$) before the administration were set to 100% for further data processing. One, two and three hours after intake of the

herbal extracts or their combinations, the whole procedure was repeated. Results are given in % of this baseline values for each measurement. Brain Imaging was achieved by conversion of numerical values of spectral EEG power into spectral colors and additive color mixture according to RGB as used in TV settings and represented a true result of the measurement [15]. The maps are constructed by nonlinear LaGrange interpolation and mathematically correspond to a 64 channel EEG. In order to differentiate results with respect to effectiveness of the pure extracts or their combinations data were fed into linear discriminant analysis according to Fischer. Results from the first three discriminant functions were depicted in space (x, y and z coordinates). Results from the 4th to 6th discriminant functions were transformed into color according to the RGB mode (like in TV). For statistics the Sign Test was taken due to the crossover design of the study.

### 2.3. Psychometric Testing

The d2-test (d2-concentration test) [16] is a classical test used to describe increased wakefulness and tension with selective orientation of perception, thinking and performance. The presence of focused stimulus selection asks for a high ability to concentrate. It is a so-called paper-pencil test in which the volunteer has to mark for example all "d" spellings with two adds. After 20 seconds he has to jump to the next line. The test is performed for the duration of 5 minutes under the condition of EEG recording. The result is given as average performance per line (out of 14 test lines).

A psychometric test targeting at the performance of arithmetics has been developed under the name of "concentration-performance-test" (CPT) and has been used widely to characterize mental impairments. This test also asks for memorization of the transitory results of the first task to be processed after performance of the second task. In case the first result is larger than the second one, the second one is subtracted from the first one, otherwise both are added. The CPT was carried out as described by Düker and Lienert , 1965 [17]. Number of solved tasks and % correctness gave a performance index.

The third psychometric test used within the study design was the memory test. A combination of numbers and spellings is presented during 4 seconds (for example: Dv8L3oPX). The order of symbols has to be remembered followed by a time period of 10 seconds during which the screen remained dark. After this a four-fold multiple choice including the correct answer was presented for decision. Finally, number of tasks and % correctness were evaluated to give a performance index. Each test was presented for 5 minutes. The row of order was kept constant for the sake of direct comparisons of the result under identical conditions.

### 2.4. Statistics

Since the present investigation followed a crossover design, a non-parametric Wilcoxon Sign Test was used to compare data between verum and Placebo statistically. For comparison, the difference to baseline was calculated with respect to all later recording times after administration. In addition, linear discriminant analysis was used in order to differentiate the psychopharmacological effects of the different preparations from each other. Results from the first three discriminant functions are displayed in space (x, y and z coordinates), results from the $4^{th}$ to the $6^{th}$ function are displayed using the so-called RGB mode (like in TV).

## 3. Results

Two series of experiments were performed with 10 subjects suffering from mild cognitive impairment as selected by the DemTect questionnaire based on score values between 8 and 13. During the first run the *Sideritis* extract (500 mg) was compared to the *Bacopa* extract (320 mg), Placebo and a first combination of both together. During the second run 8 of the 10 subjects were tested under identical conditions in the presence of two more combinations of *Sideritis* and *Bacopa* extract. For the sake of clarity, data from the administration of *Sideritis* and *Bacopa* extract are documented first, followed by data from all three combinations.

### 3.1. Results of Psychometric Tests (Series I)

Success of the psychometric experiments was confined to the d2-concentration test only. Here, *Sideritis* extract induced significantly higher success rates during the $2^{nd}$ and $3^{rd}$ hour after intake. Results are documented in **Table 1**.

### 3.2. Baseline Characteristics of the EEG (Series I)

In order to relay on the results firstly the absolute spectral power was documented for each electrode position and each frequency range as shown in **Table 2**. As one can see from these baseline values, data are quite com-

**Table 1.** Overview on psychometric results with respect to the three preparations used: PL = Placebo. Bac. = 320 mg of *Bacopa* extract. Sid. = 500 mg of *Sideritis* extract. Data are given for the baseline (0 h) as well as 1, 2 and 3 hours after intake. Data obtained during the tests are compared to Placebo at each time of measurement. Statistical significance is indicated by stars: $^{**}p < 0.05$; $^{***}p < 0.01$. Data represent an average of 10 subjects. SD = Standard Deviation, SEM = Standard Error of the Mean.

| Performance of d2-concentration test (d2) | | | | | Performance of Arithmetic Calculation test (CPT) | | | | | Performance of Memory-test (MEM) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | PL | Bac. | Sid. | | | PL | Bac. | Sid. | | | PL | Bac. | Sid. |
| | **Mean** | **11.23** | **11.85** | **12.17** | | **Mean** | **2.74** | **3.38** | **3.40** | | **Mean** | **8.00** | **9.80** | **9.19** |
| **0 h** | SD | 1.91 | 2.56 | 2.36 | **0 h** | SD | 2.84 | 3.10 | 2.72 | **0 h** | SD | 3.30 | 3.56 | 3.11 |
| | SEM | 0.60 | 0.81 | 0.75 | | SEM | 0.90 | 0.98 | 0.86 | | SEM | 1.04 | 1.13 | 0.98 |
| | **Mean** | **11.82** | **12.56** | **12.85** | | **Mean** | **3.31** | **4.20** | **4.05** | | **Mean** | **9.74** | **9.93** | **9.60** |
| **1 h** | SD | 1.99 | 2.67 | 2.83 | **1 h** | SD | 2.73 | 3.22 | 3.64 | **1 h** | SD | 2.65 | 3.88 | 3.62 |
| | SEM | 0.63 | 0.84 | 0.89 | | SEM | 0.86 | 1.02 | 1.15 | | SEM | 0.84 | 1.23 | 1.15 |
| | **Mean** | **12.36** | **12.63** | **13.61**$^{**}$ | | **Mean** | **3.22** | **2.30** | **3.42** | | **Mean** | **8.73** | **10.56** | **10.22** |
| **2 h** | SD | 1.99 | 2.91 | 2.96 | **2 h** | SD | 2.45 | 2.44 | 3.64 | **2 h** | SD | 2.75 | 3.05 | 3.65 |
| | SEM | 0.63 | 0.92 | 0.94 | | SEM | 0.78 | 0.77 | 1.15 | | SEM | 0.87 | 0.97 | 1.13 |
| | **Mean** | **12.60** | **12.58** | **13.64**$^{***}$ | | **Mean** | **3.68** | **3.94** | **3.62** | | **Mean** | **10.34** | **10.71** | **10.30** |
| **3 h** | SD | 2.71 | 2.57 | 2.90 | **3 h** | SD | 3.19 | 4.81 | 2.52 | **3 h** | SD | 3.73 | 3.67 | 3.31 |
| | SEM | 0.86 | 0.81 | 0.92 | | SEM | 1.01 | 1.52 | 0.80 | | SEM | 1.18 | 1.16 | 1.05 |

**Table 2.** Starting values of absolute EEG spectral power in relaxed condition with eyes open. Data are given in $\mu V^2$ for each electrode position and each frequency range. PL = Placebo. Bac. = 320 mg of *Bacopa* extract. Sid. = 500 mg of *Sideritis* extract. E = electrode position, Med = median over all electrode positions.

| Absolute Values of "Eyes Open" Baseline | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Delta | | | Theta | | | Alpha1 | | | Alpha2 | | | Beta1 | | | Beta2 | | |
| **E** | **PL** | **Bac.** | **Sid.** | **PL** | **Bac.** | **Sid.** | **PL** | **Bac.** | **Sid.** | **PL** | **Bac.** | **Sid.** | **PL** | **Bac.** | **Sid.** | **PL** | **Bac.** | **Sid.** |
| **Cz** | 2.35 | 1.79 | 1.78 | 0.49 | 0.43 | 0.49 | 0.57 | 0.31 | 0.52 | 0.42 | 0.37 | 0.39 | 0.79 | 0.67 | 0.63 | 0.89 | 1.15 | 1.08 |
| **Fz** | 2.69 | 3.07 | 3.42 | 0.70 | 0.61 | 0.57 | 0.62 | 0.74 | 0.53 | 0.53 | 0.53 | 0.39 | 0.84 | 0.84 | 0.73 | 0.89 | 1.04 | 0.79 |
| **F3** | 4.95 | 2.82 | 3.84 | 0.61 | 0.70 | 0.63 | 0.66 | 0.71 | 0.58 | 0.48 | 0.64 | 0.48 | 1.11 | 0.98 | 1.03 | 2.03 | 1.85 | 2.30 |
| **C3** | 1.95 | 1.82 | 1.53 | 0.44 | 0.37 | 0.38 | 0.50 | 0.49 | 0.33 | 0.76 | 0.77 | 0.47 | 1.18 | 1.45 | 1.23 | 1.00 | 1.76 | 1.64 |
| **P3** | 1.64 | 1.24 | 0.99 | 0.35 | 0.39 | 0.33 | 0.52 | 0.59 | 0.32 | 0.47 | 0.65 | 0.37 | 0.76 | 0.65 | 0.66 | 0.68 | 0.62 | 0.70 |
| **Pz** | 1.46 | 1.60 | 1.22 | 0.60 | 0.37 | 0.47 | 0.63 | 0.36 | 0.43 | 0.40 | 0.36 | 0.36 | 0.70 | 0.50 | 0.50 | 0.67 | 0.49 | 0.35 |
| **P4** | 1.52 | 1.45 | 1.29 | 0.38 | 0.36 | 0.30 | 0.53 | 0.44 | 0.43 | 0.43 | 0.47 | 0.39 | 0.86 | 0.87 | 0.58 | 0.62 | 0.62 | 0.72 |
| **C4** | 1.96 | 2.60 | 1.43 | 0.40 | 0.56 | 0.36 | 0.48 | 0.75 | 0.31 | 1.20 | 0.93 | 0.61 | 1.83 | 1.83 | 1.24 | 1.10 | 2.24 | 1.75 |
| **F4** | 2.35 | 3.19 | 2.71 | 0.83 | 0.56 | 0.61 | 0.92 | 0.84 | 0.65 | 0.61 | 0.67 | 0.48 | 1.25 | 1.88 | 1.41 | 1.95 | 2.31 | 2.39 |
| **F7** | 10.67 | 9.50 | 16.02 | 1.49 | 1.64 | 1.81 | 1.26 | 1.17 | 1.56 | 1.05 | 1.17 | 1.13 | 1.70 | 1.91 | 2.00 | 4.47 | 4.02 | 3.48 |
| **T3** | 3.39 | 3.22 | 3.76 | 0.68 | 0.87 | 0.73 | 1.02 | 1.16 | 0.89 | 1.03 | 1.11 | 1.02 | 1.43 | 1.81 | 1.66 | 2.34 | 2.97 | 2.15 |
| **T5** | 3.57 | 3.49 | 2.31 | 1.39 | 1.36 | 0.88 | 2.12 | 2.09 | 0.99 | 1.41 | 1.39 | 0.94 | 1.94 | 2.68 | 1.60 | 1.45 | 1.23 | 2.02 |
| **O1** | 3.42 | 3.69 | 3.09 | 0.70 | 0.78 | 0.62 | 0.67 | 0.73 | 0.52 | 1.11 | 0.89 | 0.74 | 2.03 | 1.60 | 1.65 | 1.71 | 2.84 | 1.55 |
| **O2** | 3.61 | 3.97 | 3.10 | 0.55 | 0.67 | 0.54 | 0.53 | 0.99 | 0.60 | 1.22 | 1.02 | 0.89 | 2.17 | 1.84 | 1.80 | 1.38 | 2.65 | 1.94 |
| **T6** | 2.60 | 2.23 | 2.54 | 0.99 | 0.72 | 0.84 | 1.39 | 1.47 | 1.09 | 1.41 | 0.86 | 0.93 | 1.68 | 2.07 | 1.32 | 1.42 | 1.60 | 1.50 |
| **T4** | 3.51 | 4.08 | 3.01 | 0.90 | 0.81 | 0.85 | 1.28 | 1.28 | 1.00 | 1.26 | 1.49 | 0.97 | 2.54 | 2.24 | 1.90 | 2.96 | 2.83 | 1.75 |
| **F8** | 6.82 | 6.79 | 8.19 | 1.71 | 1.68 | 1.65 | 1.73 | 1.27 | 1.28 | 1.29 | 1.39 | 1.20 | 1.95 | 2.89 | 1.66 | 3.43 | 4.64 | 2.74 |
| **Med** | **2.86** | **2.85** | **2.66** | **0.66** | **0.60** | **0.51** | **0.80** | **0.73** | **0.52** | **1.00** | **0.96** | **0.67** | **1.47** | **1.44** | **1.32** | **1.03** | **1.20** | **1.17** |

parable. This is also true for median values calculated by averaging data from all electrode positions. A comparison of the data of the three arms of the study is therefore justified. These values are set to 100% and serve for determination of the change of spectral power in the presence of either Placebo or extracts. Changes of spectral power are documented in % of this baseline value.

### 3.3. Effect of Herbal Extracts Alone (Series I)

Since brain function relates to different anatomically defined regions, analysis of the local electric circuits provides information on externally induced physiological changes. Spectral analysis therefore was confined to frontal, temporal and centro-parietal brain areas as regions of interest (ROI). The frontal area was represented by the electrode positions $F_{3,4,7,8}$. The temporal area was represented by electrode positions $T_{3,4,5,6}$. The centro-parietal area was represented by electrode positions $C_{3,4}$, $P_{3,4}$. Spectral power in these regions was followed during 1, 2 and 3 hours after administration of Placebo or the two extracts.

Under the condition of performing the d2-concentration test *Bacopa* extract (320 mg) seemed to induce a little bit more spectral power in the delta range, which 3 hours after ingestion became statistically relevant (**Figure 1**). In the temporal area *Sideritis* extract (500 mg) induced increases of spectral theta power, which did not reach statistical significance. The spectral power in the faster alpha and beta waves was increased significantly only in the presence of *Sideritis* extract. In the centro-parietal area only *Sideritis* extract induced increases of spectral power in the alpha range. An overview of time dependent changes of spectral power is given in **Figure 1**.

In order to better analyze spectral changes during mental work with respect to different electric brain circuits, maps were constructed by non-linear interpolation (s. methods). The map now mathematically corresponds to a 64 channel EEG. In the presence of the two extracts much higher beta power (blue) is registered. In addition, *Sideritis* extract produces much more green color, corresponding to increases of spectral alpha2 power besides some increases of alpha1 power seen as yellow spots in the temporal lobe. *Bacopa* extract affects both hemispheres in a different manner. Main differences to Placebo are happening in the left hemisphere. Brain maps are depicted in **Figure 2**.

Under the condition of performing the arithmetic calculation CPT-test no statistically significant changes of spectral power were registered in the frontal brain area. However, in the temporal area a reduction of spectral power with respect to all frequencies was observed nearly exclusively in the presence of *Bacopa* extract, which occasionally became statistically relevant. In the centro-parietal area only beta spectral power is reduced in the presence of *Bacopa* extract. **Figure 3** gives an overview.

The corresponding maps reveal obvious differences with respect to changes of spectral power between Placebo and *Bacopa* extract but less with respect to *Sideritis* extract at 2 hours after administration. Reduction of spectral power induced by *Bacopa* is represented by darker spots in central areas. Maps are depicted in **Figure 4**.

Results obtained during performance of the memory-test reveal similarities to the changes as observed during performance of the arithmetic calculation CPT-test, especially the attenuation of spectral alpha and beta power. In addition, *Bacopa* extract induced some increases of delta and theta activity in the frontal area, which became statistically relevant during the first hour after administration. In the temporal lobe *Sideritis* induced a reduction of delta and theta power during the last hour after intake. With respect to alpha waves a slight reduction of spectral power was observed in the presence of both extracts. With respect to beta waves, only *Bacopa* extract induced an attenuation, which was statistically significant or conspicuous in comparison to Placebo. In the cento-parietal area no consistent changes were observed in the presence of both extracts in comparison to Placebo. Results are documented in **Figure 5**.

The maps showed some differences induced by the herbal extract in comparison to Placebo. *Sideritis* extract induced some increases of slow waves in the right frontal area (interpolated region not covered directly by a physical electrode). *Bacopa* extract changed spectral power in the left fronto-temporal area in comparison to Placebo. Maps are depicted in **Figure 6**.

### 3.4. Effect of Herbal Extracts in Combination (Series II)

The second series was undertaken in order to find out the best combination of *Sideritis* extract and *Bacopa* extract. Therefore, another two combinations were tested and are shown for the sake of clarity together with the results from the mixture of the first series (500 mg *Sideritis* extract and 320 mg of *Bacopa* extract).

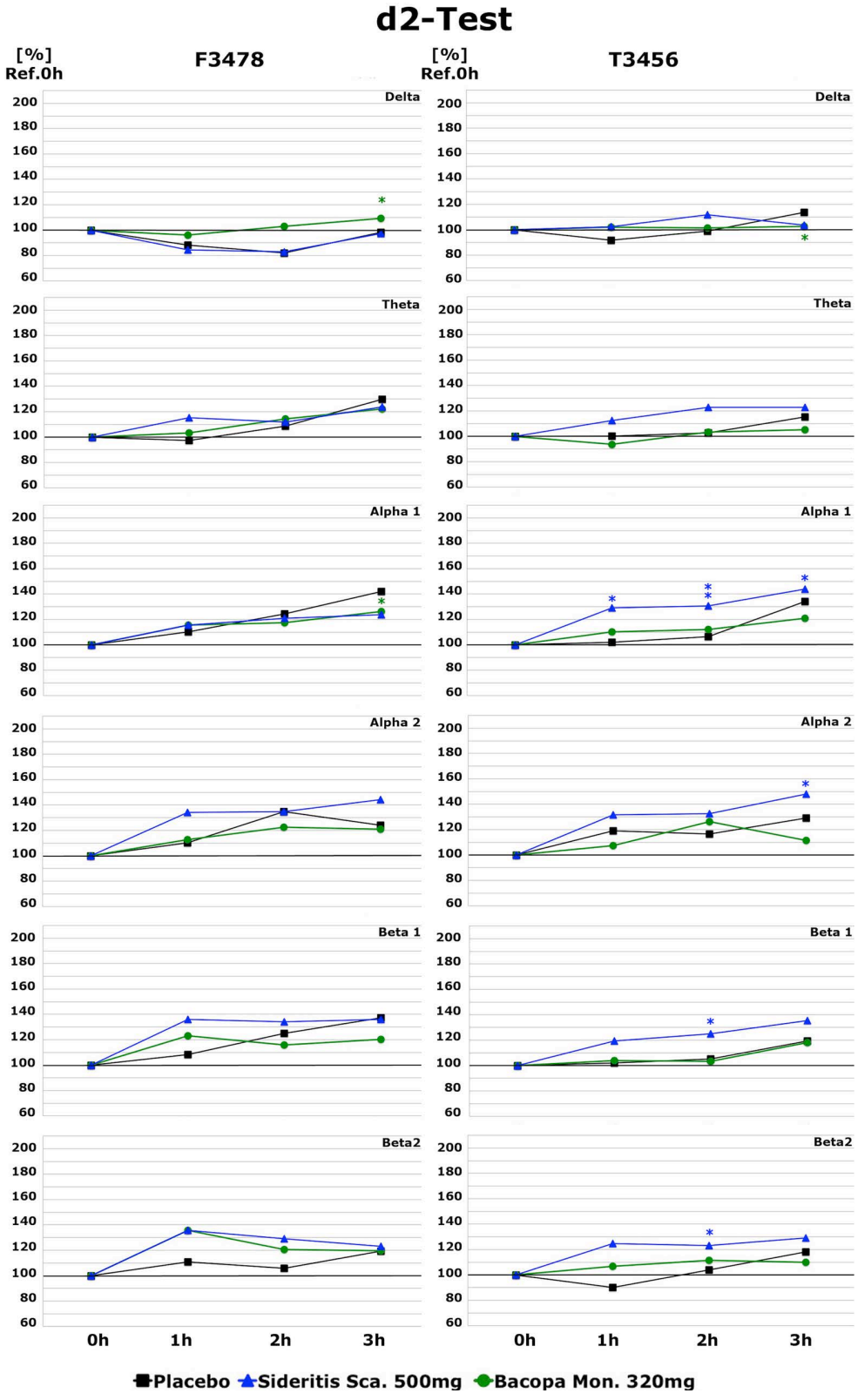


**Figure 1.** Time line of spectral power changes in three regions of interest (ROI = frontal and temporal electrode positions) in the presence of Placebo, *Sideritis* and *Bacopa* extract. Data were recorded during performance of the d2-concentration test. Statistical significance in comparison to Placebo is documented by stars: $^{*}p < 0.10$; $^{**}p < 0.05$.

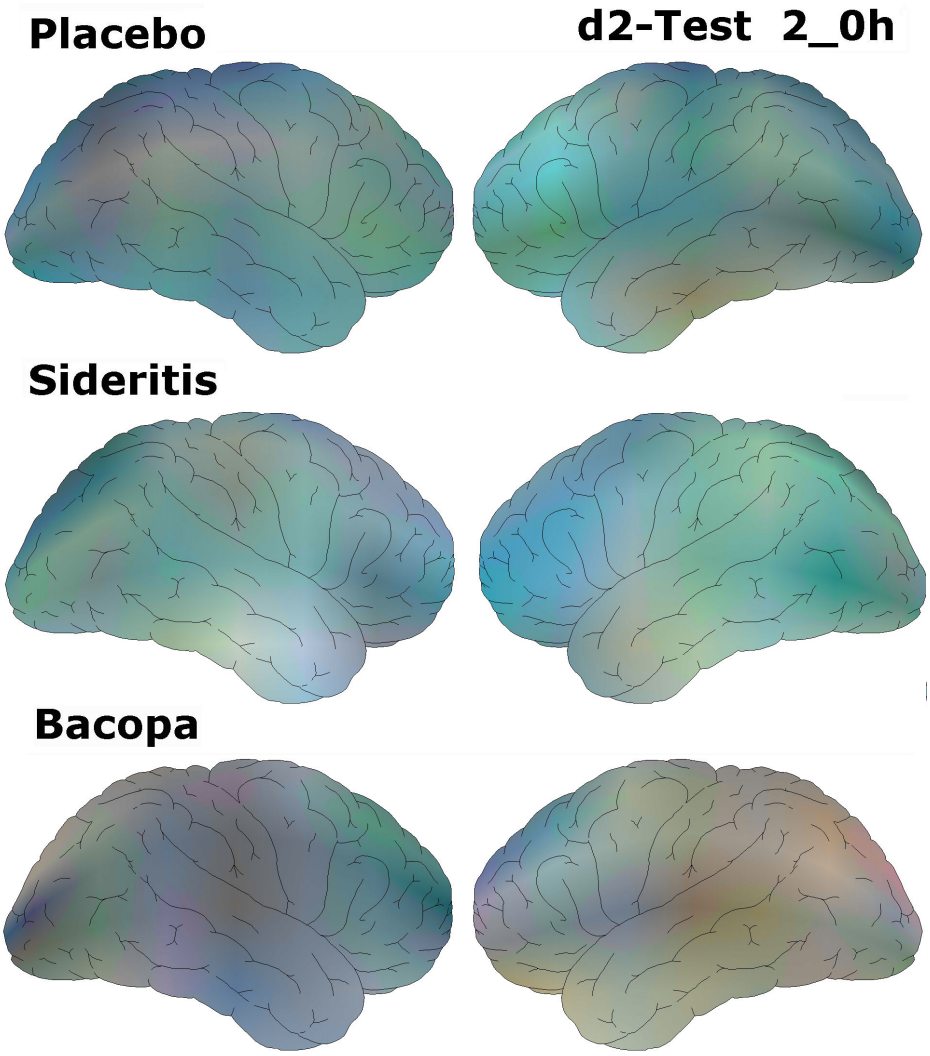


**Figure 2.** Comparison of electric maps (enkephaloglyphs) in the presence of Placebo, *Sideritis* extract (500 mg) and *Bacopa* extract (320 mg) alone at 2 hours after administration during performance of the d2-concentration test. Difference to baseline is depicted in %. Left side: right hemisphere. Please note frontal increases of beta wave activity (blue color) in the presence of the two herbal extracts.

### 3.5. Results of Psychometric Tests (Series II)

The psychometric results of the three mixtures (500 mg of *Sideritis* extract plus 160, 320 or 480 mg of *Bacopa* extract revealed increases of success in general. During performance of the d2-concentration test baseline values were significantly higher in the *Bacopa* 160 mg group, but similar values were reached in the other baseline test. Somewhat higher values were only reached during performance of the three different tests, with occasional statistical significance in comparison to Placebo data. An overview is given in **Table 3**.

### 3.6. Baseline Characteristics EEG (Series II)

As mentioned in the first series the absolute spectral power was documented for each electrode position and each frequency range as shown in **Table 4**. As one can see from these baseline values, data are quite comparable. This is also true for median values calculated by averaging data from all electrode positions. A comparison of the data of the three arms of the study is therefore justified. These values are set to 100% and serve for determination of the change of spectral power in the presence of either Placebo or extracts. Changes of spectral power are documented in % of this baseline value.

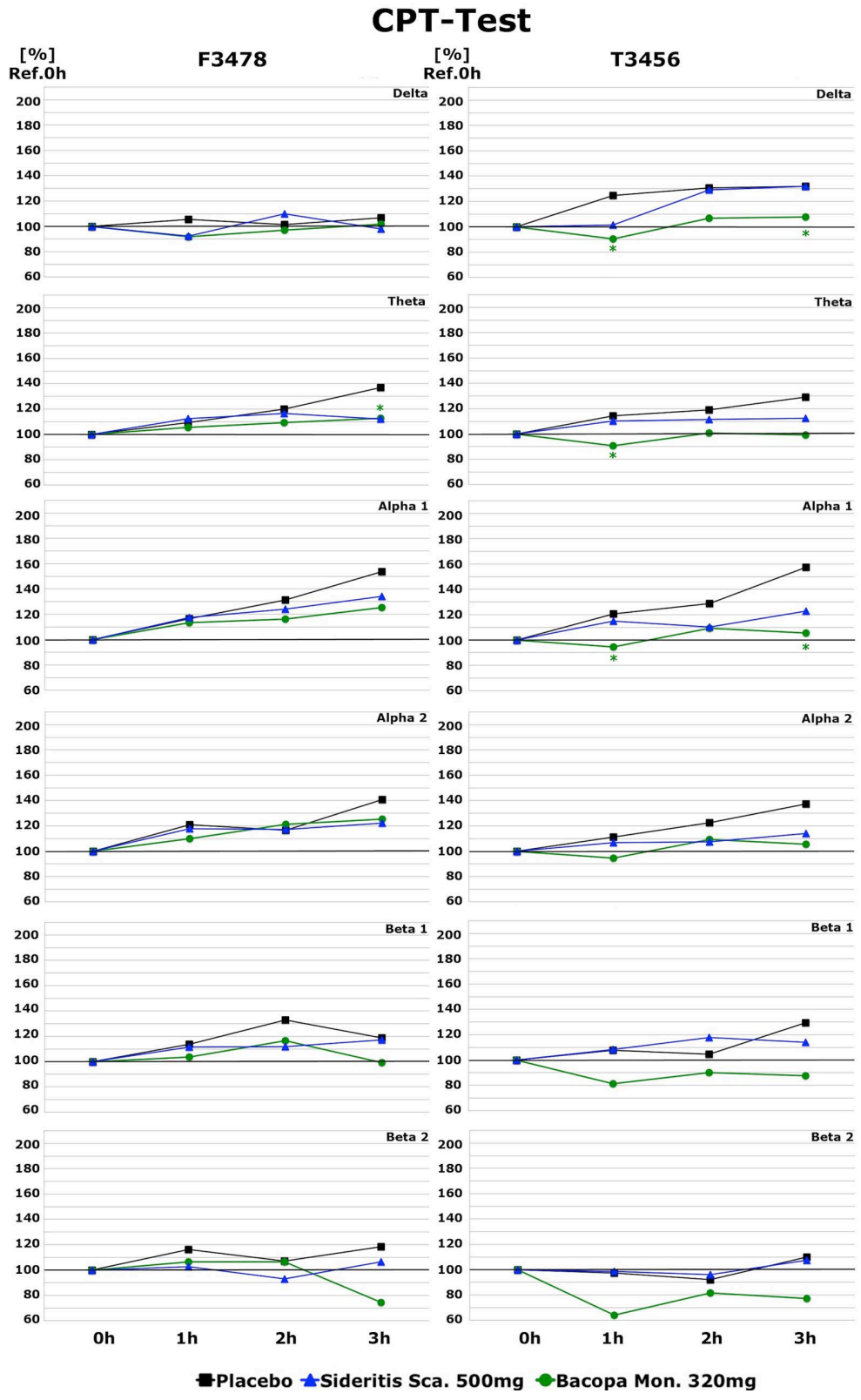


**Figure 3.** Time line of spectral power changes in three regions of interest (ROI = frontal and temporal electrode positions) in the presence of Placebo, *Sideritis* extract (500 mg) and *Bacopa* extract (320 mg). Data were recorded during performance of the arithmetic calculation CPT-test. Statistical significance in comparison to Placebo is documented by a star: $^{*}p < 0.10$.

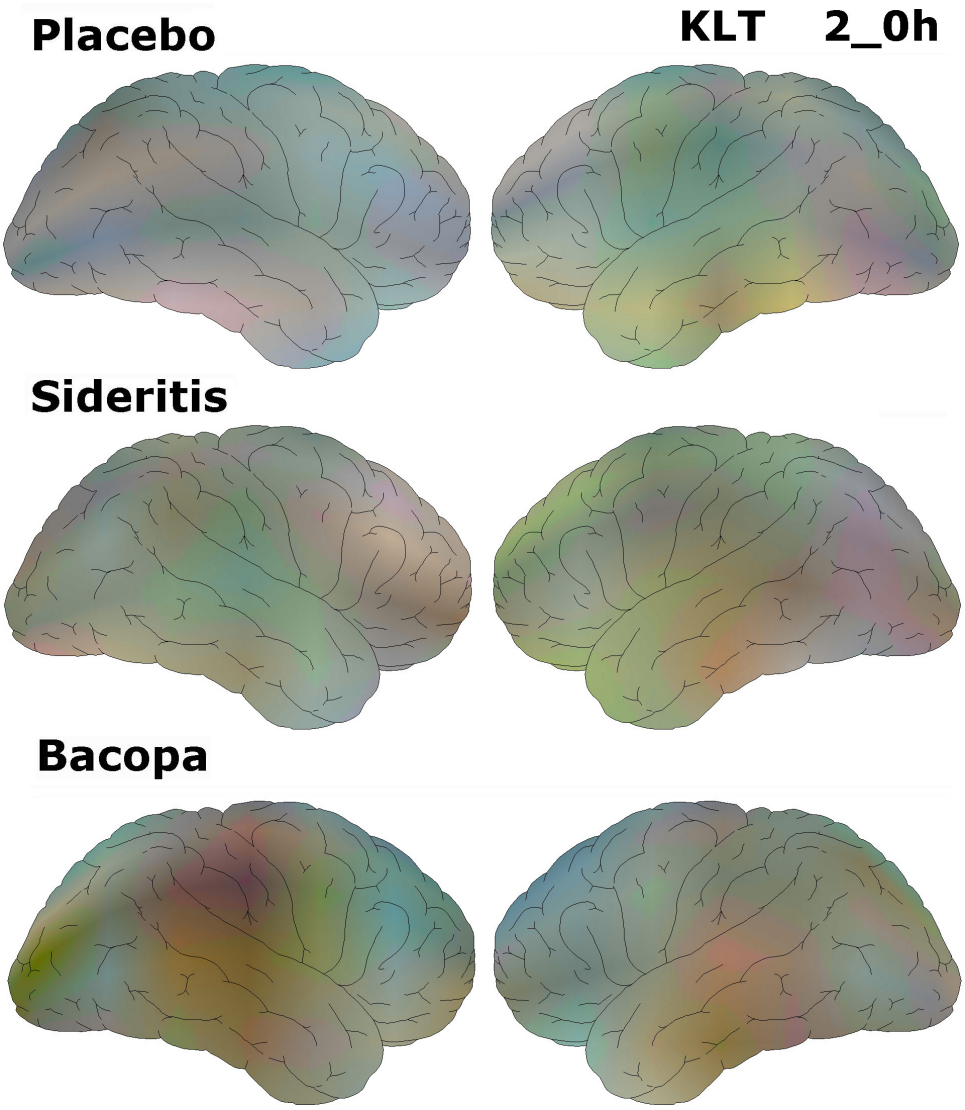


**Figure 4.** Comparison of electric maps (enkephaloglyphs) in the presence of Placebo, *Sideritis* extract (500 mg) and *Bacopa* extract (320 mg) alone at 2 hours after administration during performance of the arithmetic calculation test (CPT). Left side: right hemisphere.

### 3.7. Effect of Mixtures of Herbal Extracts (Series II)

With respect to the frontal brain the mixture of 500 mg of *Sideritis* and 320 mg *Bacopa* induced some increase of spectral alpha and beta power during performance of the d2-concentration test, however without statistical significance in comparison to Placebo. In the temporal lobe increases of alpha and beta spectral power emerged in the presence of the low *Bacopa* addition of 160 mg, which became statistically conspicuous at 2 hours after intake for the alpha1 range. No major changes were observed in the centro-parietal brain area during performance of the d2-concentration test (not shown). The changes in the presence of the low addition of *Bacopa* were rather similar to those measured in the presence of *Sideritis* alone with respect to temporal increases of alpha and beta power! Results are documented in **Figure 7**.

The corresponding maps produced during performance of the d2-concentration test revealed quite drastic differences with respect to the 3 different extract mixtures. Low addition of *Bacopa* induced increases of slow waves in fronto-temporal areas (red-orange colours), whereas the middle addition of 320 mg did not induce major changes. The highest amount of *Bacopa* added (480 mg) induced strongest spectral changes in the occipital area. A comparison of the maps is given in **Figure 8**.

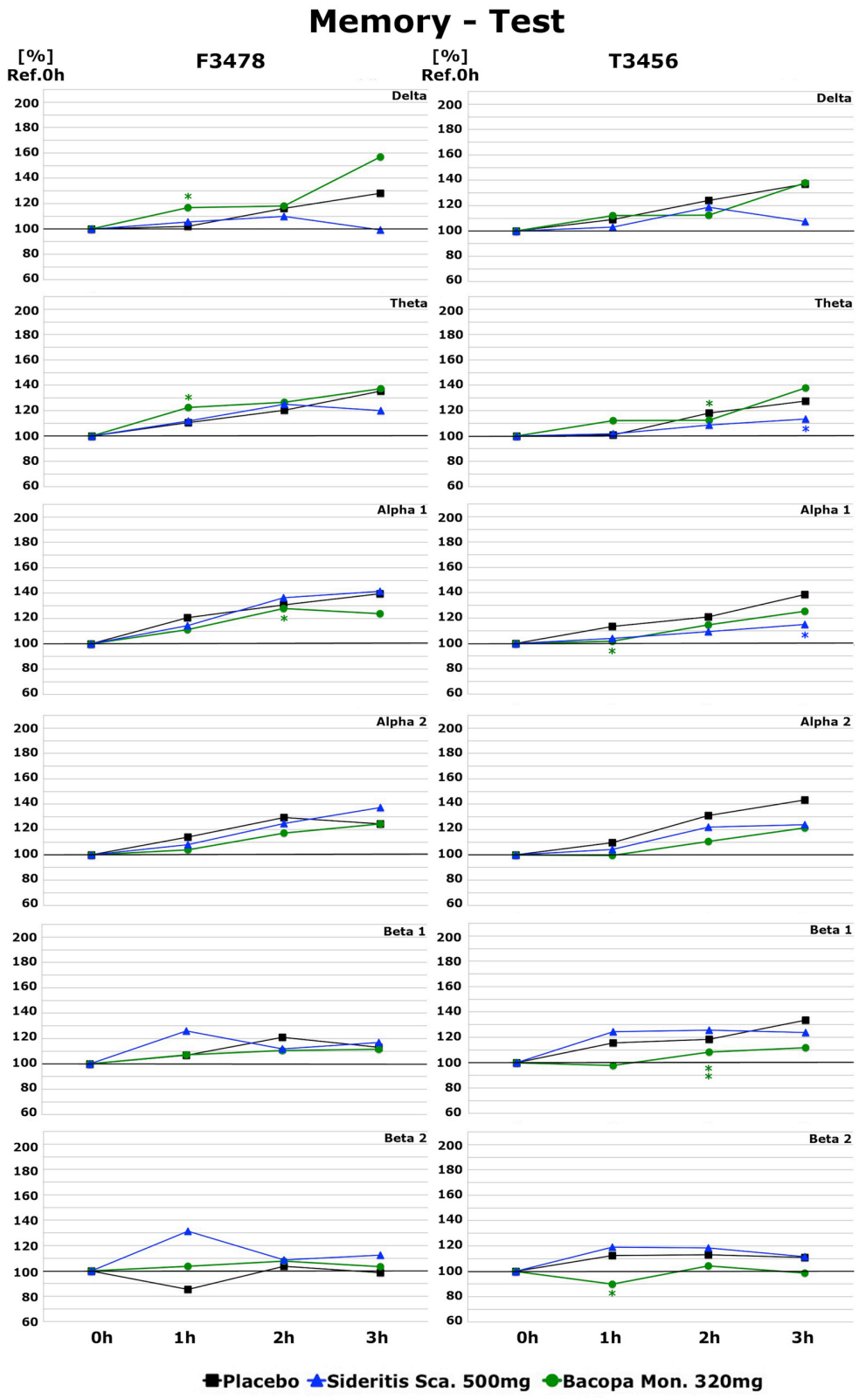


**Figure 5.** Time line of spectral power changes in three regions of interest (ROI = frontal and temporal electrode positions) in the presence of Placebo, *Sideritis* (500 mg) and *Bacopa* extract (320 mg). Data were recorded during performance of the memory-test. Statistical significance in comparison to Placebo is documented by stars: $^{*}p < 0.1$; $^{**}p < 0.05$.

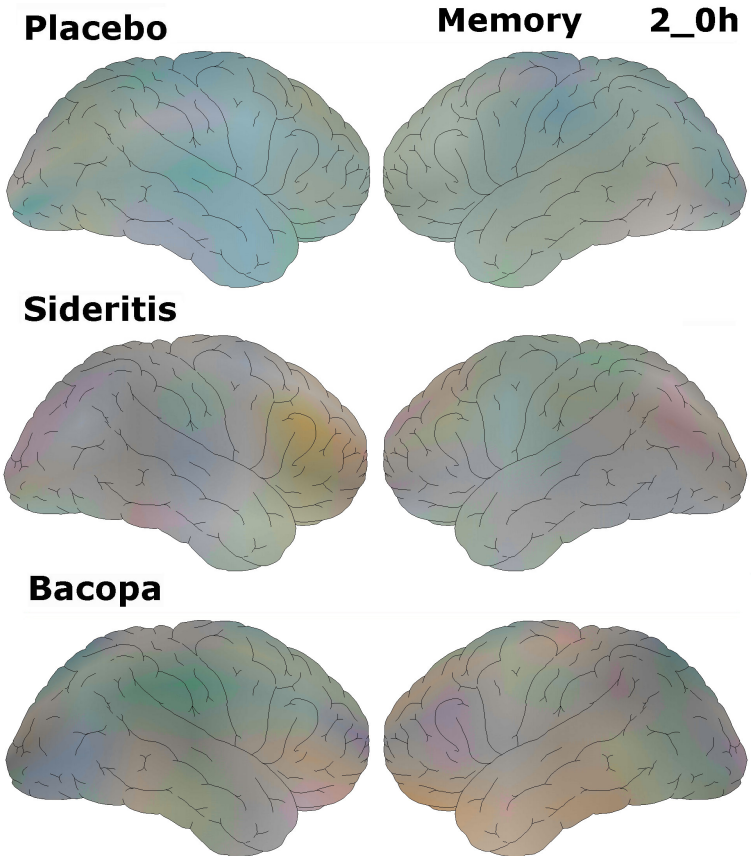


**Figure 6.** Comparison of electric maps (enkephaloglyphs) in the presence of Placebo, *Sideritis* extract (500 mg) and *Bacopa* extract (320 mg) alone at 2 hours after administration during performance of the memory-test. Difference to baseline is depicted in %.

**Table 3.** Overview on psychometric results with respect to the three mixtures used: Ba160 = 500 mg *Sideritis* extract plus 160 mg *Bacopa* extract. Ba320 = 500 mg *Sideritis* plus 320 mg *Bacopa* extract. Ba480 = 500 mg of *Sideritis* extract plus 480 mg *Bacopa* extract. Data are given for the baseline (0 h) as well as 1, 2 and 3 hours after intake. in comparison to Placebo at each time. SD = Standard Deviation, SEM = Standard Error of the Mean, h = hours. Conspicuous statistical evidence is indicated by a star: $^{*}p < 0.10$.

| | | Performance of d2-concentration test (d2) | | | | | | Performance of Arithmetic Calculation Test (CPT) | | | | | | Performance of Memory-test (MEM) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | PL | Ba160 | Ba320 | Ba480 | | | PL | Ba160 | Ba320 | Ba480 | | | PL | Ba160 | Ba320 | Ba480 |
| | **Mean** | **10.79** | **12.55*** | **12.20** | **11.84** | | **Mean** | **3.26** | **4.04** | **3.57** | **2.83** | | **Mean** | **8.41** | **10.52** | **8.94** | **10.09** |
| **0 h** | SD | 1.85 | 2.23 | 3.46 | 2.15 | **0 h** | SD | 2.97 | 2.56 | 3.52 | 2.91 | **0 h** | SD | 3.31 | 4.28 | 2.43 | 2.76 |
| | SEM | 0.66 | 0.79 | 1.09 | 0.76 | | SEM | 1.05 | 0.90 | 1.11 | 1.03 | | SEM | 1.17 | 1.51 | 0.77 | 0.98 |
| | **Mean** | **11.30** | **12.78*** | **12.35** | **12.54*** | | **Mean** | **3.68** | **3.66** | **3.56** | **4.86** | | **Mean** | **10.05** | **11.00** | **10.55** | **10.17** |
| **1 h** | SD | 1.85 | 2.23 | 3.33 | 2.23 | **1 h** | SD | 2.87 | 2.82 | 3.96 | 1.98 | **1 h** | SD | 2.92 | 4.68 | 3.13 | 2.64 |
| | SEM | 0.65 | 0.79 | 1.05 | 0.79 | | SEM | 1.01 | 1.00 | 1.25 | 0.70 | | SEM | 1.03 | 1.65 | 0.99 | 0.93 |
| | **Mean** | **11.87** | **13.46** | **13.12*** | **13.09*** | | **Mean** | **3.75** | **4.07** | **3.68** | **4.70** | | **Mean** | **8.85** | **9.40** | **10.72** | **10.40*** |
| **2 h** | SD | 1.89 | 2.71 | 3.16 | 2.11 | **2 h** | SD | 2.41 | 3.97 | 2.55 | 3.27 | **2 h** | SD | 3.10 | 4.17 | 3.18 | 2.66 |
| | SEM | 0.67 | 0.96 | 1.00 | 0.75 | | SEM | 0.85 | 1.40 | 0.81 | 1.16 | | SEM | 1.10 | 1.47 | 1.00 | 0.94 |
| | **Mean** | **11.30** | **12.78** | **13.42*** | **12.54** | | **Mean** | **4.30** | **4.88** | **3.03** | **5.51** | | **Mean** | **9.67** | **9.78** | **9.88** | **12.28** |
| **3 h** | SD | 1.85 | 2.23 | 2.99 | 2.23 | **3 h** | SD | 3.29 | 3.22 | 2.77 | 2.86 | **3 h** | SD | 3.77 | 3.57 | 3.18 | 2.52 |
| | SEM | 0.65 | 0.79 | 0.94 | 0.79 | | SEM | 1.16 | 1.14 | 0.88 | 1.01 | | SEM | 1.33 | 1.33 | 1.01 | 0.89 |

**Table 4.** Starting values of absolute EEG spectral power in relaxed condition with eyes open. Data are given in $\mu V^2$ for each electrode position and each frequency range. Ba160 = 500 mg *Sideritis* extract plus 160 mg *Bacopa* extract. Ba320 = 500 mg *Sideritis* plus 320 mg *Bacopa* extract. Ba480 = 500 mg of *Sideritis* extract plus 480 mg *Bacopa* extract. E = electrode position, Med = median over all electrode positions.

| Absolute values of "eyes open" Baseline | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Delta | | | | Theta | | | | Alpha1 | | | |
| E | PL | Ba160 | Ba320 | Ba480 | PL | Ba160 | Ba320 | Ba480 | PL | Ba160 | Ba320 | Ba480 |
| **Cz** | 2.87 | 2.85 | 2.07 | 2.49 | 0.49 | 0.63 | 0.57 | 0.59 | 0.57 | 0.64 | 0.60 | 0.66 |
| **Fz** | 3.02 | 4.28 | 2.93 | 2.85 | 0.76 | 0.76 | 0.75 | 1.11 | 0.62 | 0.81 | 0.55 | 0.86 |
| **F3** | 5.24 | 5.43 | 3.00 | 2.59 | 0.82 | 1.07 | 0.69 | 0.90 | 0.66 | 0.91 | 0.66 | 0.80 |
| **C3** | 2.92 | 2.10 | 1.72 | 3.22 | 0.44 | 0.50 | 0.49 | 0.53 | 0.50 | 0.67 | 0.47 | 0.65 |
| **P3** | 2.04 | 0.72 | 1.14 | 1.66 | 0.35 | 0.23 | 0.31 | 0.37 | 0.52 | 0.36 | 0.39 | 0.38 |
| **Pz** | 1.46 | 1.27 | 1.36 | 1.96 | 0.60 | 0.43 | 0.41 | 0.51 | 0.63 | 0.53 | 0.44 | 0.54 |
| **P4** | 1.52 | 0.93 | 1.12 | 1.34 | 0.38 | 0.28 | 0.30 | 0.40 | 0.53 | 0.47 | 0.39 | 0.44 |
| **C4** | 1.96 | 2.11 | 2.29 | 2.39 | 0.40 | 0.49 | 0.47 | 0.51 | 0.48 | 0.57 | 0.56 | 0.80 |
| **F4** | 3.53 | 4.77 | 4.20 | 4.29 | 0.93 | 0.74 | 0.70 | 1.02 | 0.92 | 0.79 | 0.64 | 1.01 |
| **F7** | 11.82 | 10.96 | 9.99 | 8.18 | 1.62 | 1.77 | 1.56 | 1.42 | 1.26 | 1.54 | 1.16 | 1.47 |
| **T3** | 4.12 | 3.75 | 3.03 | 4.84 | 0.68 | 0.94 | 0.69 | 0.85 | 1.02 | 1.43 | 0.91 | 1.16 |
| **T5** | 4.13 | 2.88 | 2.67 | 3.29 | 1.39 | 0.85 | 0.84 | 0.76 | 2.12 | 0.94 | 1.65 | 1.07 |
| **O1** | 4.07 | 6.18 | 3.10 | 6.75 | 0.70 | 1.13 | 0.62 | 0.84 | 0.67 | 0.96 | 0.63 | 0.85 |
| **O2** | 3.61 | 4.85 | 4.36 | 4.05 | 0.55 | 0.99 | 0.58 | 0.81 | 0.53 | 1.00 | 0.78 | 1.27 |
| **T6** | 2.60 | 3.18 | 2.93 | 2.62 | 0.99 | 0.94 | 0.86 | 0.94 | 1.39 | 1.92 | 1.23 | 1.49 |
| **T4** | 3.51 | 3.48 | 4.34 | 5.80 | 0.90 | 0.90 | 0.85 | 1.22 | 1.28 | 1.20 | 1.18 | 1.61 |
| **F8** | 8.50 | 6.27 | 8.11 | 9.33 | 1.71 | 1.47 | 1.55 | 1.46 | 1.73 | 1.46 | 1.24 | 1.84 |
| **Med** | **3.62** | **3.30** | **2.81** | **3.14** | **0.66** | **0.75** | **0.68** | **0.80** | **0.80** | **0.95** | **0.66** | **0.90** |

| Absolute Values of "Eyes Open" Baseline | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Alpha2 | | | | Beta1 | | | | Beta2 | | | |
| E | PL | Ba160 | Ba320 | Ba480 | PL | Ba160 | Ba320 | Ba480 | PL | Ba160 | Ba320 | Ba480 |
| **Cz** | 0.64 | 0.57 | 0.38 | 0.50 | 1.00 | 1.16 | 0.61 | 0.87 | 1.41 | 1.18 | 1.06 | 0.98 |
| **Fz** | 0.57 | 0.70 | 0.47 | 0.83 | 0.96 | 0.98 | 0.86 | 1.37 | 1.28 | 1.32 | 1.07 | 1.58 |
| **F3** | 0.69 | 0.81 | 0.50 | 0.84 | 1.29 | 1.79 | 0.72 | 1.87 | 2.32 | 1.79 | 1.42 | 4.37 |
| **C3** | 1.07 | 1.05 | 0.49 | 0.85 | 1.56 | 1.73 | 1.22 | 2.16 | 1.64 | 1.51 | 1.47 | 1.69 |
| **P3** | 0.47 | 0.32 | 0.40 | 0.47 | 0.76 | 0.58 | 0.65 | 1.00 | 0.91 | 0.45 | 0.52 | 1.12 |
| **Pz** | 0.40 | 0.42 | 0.27 | 0.62 | 0.70 | 0.57 | 0.45 | 0.67 | 0.67 | 0.38 | 0.54 | 0.76 |
| **P4** | 0.43 | 0.48 | 0.37 | 0.48 | 0.86 | 0.74 | 0.57 | 0.69 | 0.75 | 0.66 | 0.58 | 0.55 |
| **C4** | 1.20 | 0.99 | 0.96 | 1.32 | 1.83 | 1.89 | 1.73 | 2.53 | 2.58 | 1.44 | 1.74 | 2.10 |
| **F4** | 0.94 | 0.61 | 0.60 | 1.65 | 2.00 | 1.19 | 1.17 | 2.67 | 4.66 | 1.20 | 2.05 | 5.74 |
| **F7** | 1.16 | 1.20 | 0.96 | 1.77 | 1.93 | 2.09 | 1.70 | 2.62 | 6.02 | 2.86 | 3.53 | 6.89 |
| **T3** | 1.03 | 0.90 | 0.80 | 1.56 | 1.78 | 2.44 | 1.19 | 4.04 | 3.35 | 1.99 | 2.30 | 2.98 |
| **T5** | 1.53 | 1.07 | 1.16 | 1.07 | 2.14 | 1.31 | 1.86 | 1.51 | 1.96 | 0.99 | 1.06 | 1.55 |
| **O1** | 1.11 | 1.16 | 0.71 | 0.98 | 2.03 | 1.82 | 1.34 | 2.16 | 1.80 | 2.51 | 1.65 | 2.54 |
| **O2** | 1.22 | 1.29 | 0.99 | 1.43 | 2.27 | 2.71 | 1.71 | 3.36 | 3.23 | 1.96 | 1.77 | 2.76 |
| **T6** | 1.41 | 1.25 | 1.02 | 1.68 | 1.68 | 1.46 | 1.71 | 2.70 | 1.44 | 1.10 | 1.16 | 2.19 |
| **T4** | 1.26 | 1.10 | 1.06 | 1.92 | 2.54 | 2.11 | 2.16 | 3.65 | 3.35 | 4.03 | 4.21 | 5.46 |
| **F8** | 1.37 | 1.22 | 1.02 | 1.39 | 2.15 | 1.97 | 1.69 | 3.25 | 3.94 | 4.72 | 3.00 | 11.00 |
| **Med** | **1.00** | **0.90** | **0.71** | **1.01** | **1.70** | **1.60** | **1.26** | **2.07** | **2.23** | **1.25** | **1.08** | **1.96** |

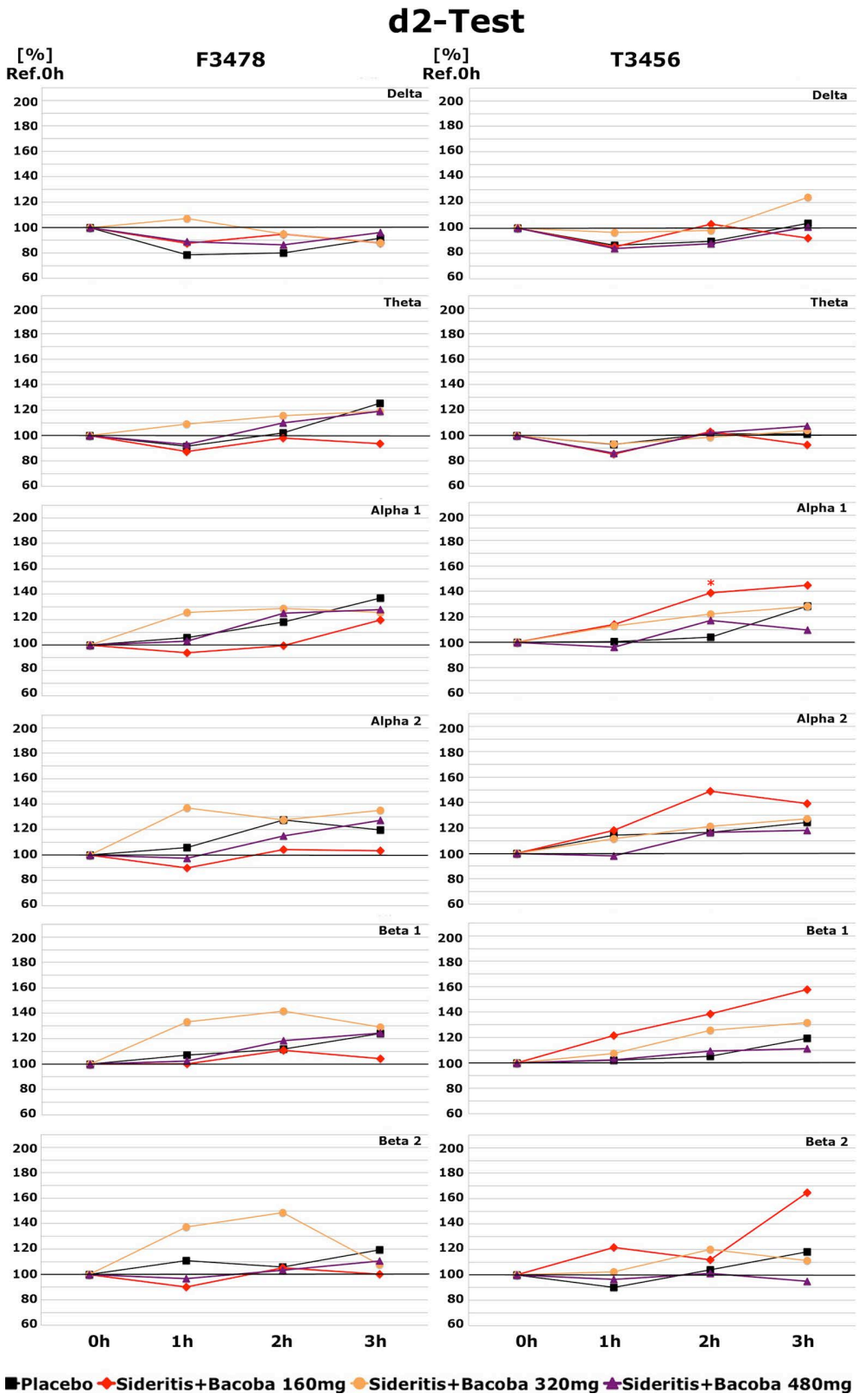


**Figure 7.** Time line of spectral power changes in three regions of interest (ROI = frontal and temporal electrode positions) in the presence of three extract mixtures (for identification see lowest line). Data were recorded during performance of the d2-concentration test. Statistical significance in comparison to Placebo is documented by star: $^{*}p < 0.10$.

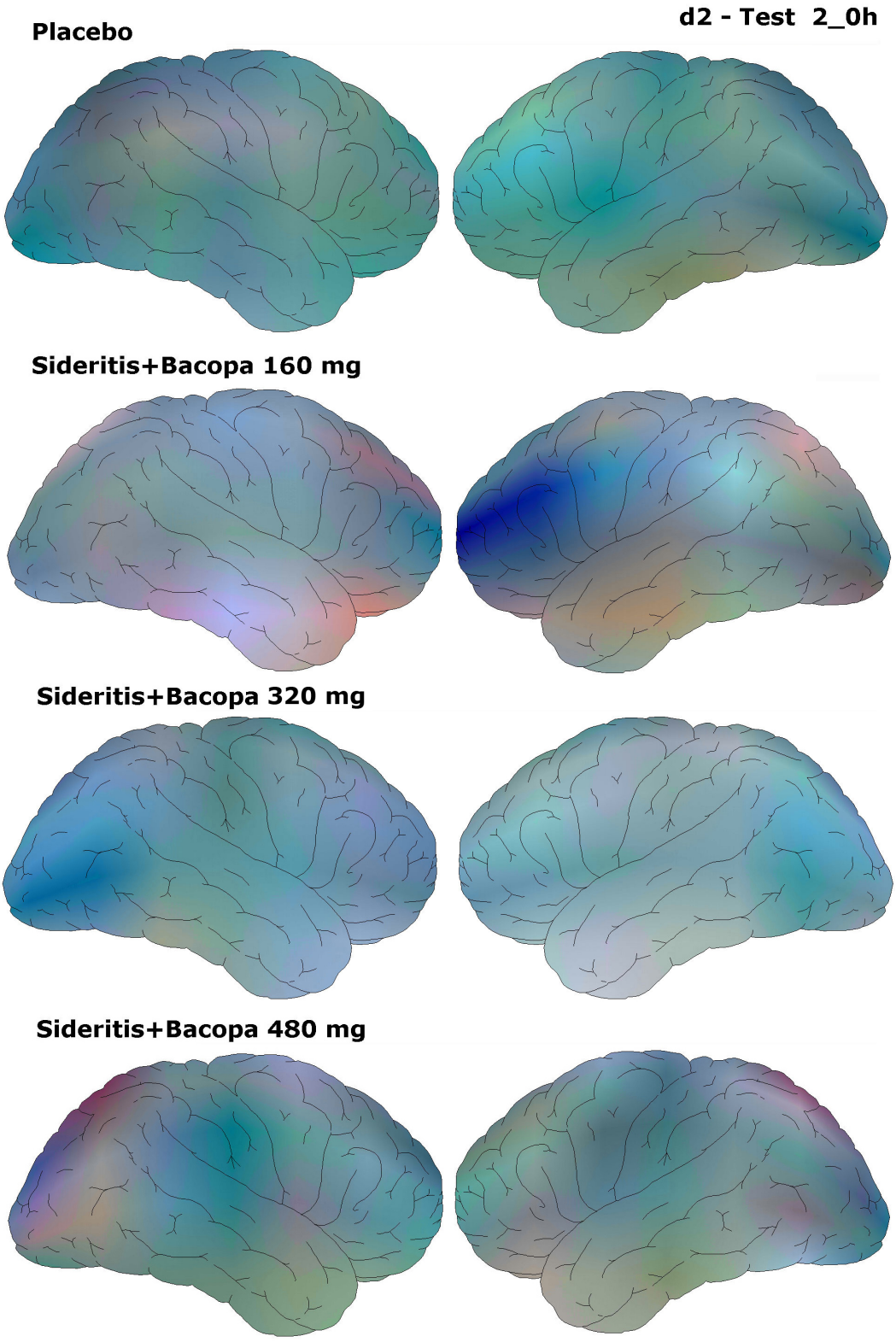


**Figure 8.** Comparison of electric maps (enkephaloglyphs) in the presence of three mixtures of *Sideritis* extract and *Bacopa* extract at 2 hours after administration during performance of the d2-concentration test. Difference to baseline is depicted in %. Left side: right hemisphere. Please note frontal increases of beta wave activity (blue color) in the presence of the two herbal extracts.

Taking now a look at the changes of spectral waves during performance of the arithmetic concentration test (CPT) a significant difference is observed with respect to low or high addition of *Bacopa*. Whereas addition of low *Bacopa* amount leads to increases of delta and theta spectral power, high amount of *Bacopa* leads to statis tically significant attenuation of delta and theta activity strongest in the temporal lobe but also significant for theta in the frontal lobe. Here also beta1 and beta2 waves are attenuated by high *Bacopa* amounts in comparison to Placebo, whereas beta2 waves are increased in the temporal lobe in the presence of low or middle *Bacopa* addition. Results are depicted in **Figure 9**.

With regard to electric brain maps (enkephaloglyphs) addition of a low amount of *Bacopa* extract led to higher prevalence of slow waves (red-orange) in the right temporal lobe. Further addition of *Bacopa* extract induced higher slow waves in the left temporal lobe. The highest amount of *Bacopa* extract added led to attenuation of spectral power leading to more dark areas. A direct comparison is given in **Figure 10**.

Finally, here are the results of the memory-test. In the presence of the low amount of *Bacopa* extract increases of delta activity are observed in the frontal and temporal area. Statistically, a conspicuous difference to Placebo is seen in the temporal lobe. Higher but non-significant values in comparison to Placebo are also seen with respect to theta waves. In the frontal lobe higher values in the beta range emerged during the first two hours after intake. Results are depicted in **Figure 11**.

With respect to maps quite a difference is observed to Placebo dependent on the amount of *Bacopa* added to 500 mg of *Sideritis* extract. In the presence of the lower amount of *Bacopa* added (160 mg) increases of frontal slow waves are visible as represented by red color. The middle amount of 320 mg *Bacopa* added also produces local increases of slow waves more dominant in the left temporal and right occipital lobe. The highest amount of *Bacopa* added changed the spectral content mainly in the frontal and temporal lobe resulting in brown color due to attenuation of spectral power. Maps are depicted in **Figure 12**.

In order to gather more information on the overall effects of the herbal extracts and the three combinations thereof, data were fed into linear discriminant analysis. A total of 102 parameters (17 electrode positions × 6 frequency ranges) were used from each preparation in the presence of all three mental challenges. Data from each preparation were projected according to the results of the discriminant functions. Results from the first three functions are displayed in space (x, y and z coordinates), results from the 4th to the 6th function are dis-played using the so-called RGB mode (like in TV). From the projections it is quite obvious, that spectral changes induced by *Sideritis* extract differ from those observed in the presence of *Bacopa* extract with respect to all mental challenges (**Figure 13**). Results obtained in the presence of the combinations are also discriminated from each other quite well. The results of the low amount of *Bacopa* added to *Sideritis* is projected near the pure *Sideritis* extract, whereas higher amounts of *Bacopa* added to *Sideritis* are projected more in the vicinity of the pure *Bacopa* extract.

With respect to tolerability all subjects evaluated their feeling after intake of the preparations as very well or well. Pulse and blood pressure measurements did not reveal any change in the presence of the preparations. There were also no differences between the preparations. There were absolute no adverse effects reported after intake of the different preparations.

## 4. Discussion

The current investigation resulted in a clear discrimination of the psychophysiological effects of *Sideritis scardica* extract from the effects of *Bacopa monnieri* extract in subjects suffering from mild cognitive impairment. *Sideritis* extract enhanced theta, alpha and beta spectral power during performance of the d2-concentration test, most clearly in the temporal lobe, a brain area involved in mental processing strongly influenced by the underlying hippocampus. *Bacopa* extract did not show such an effect, but reduced the spectral power within these frequencies during arithmetic calculations and for alpha2 and beta power during performance of the memory-test. This is interesting, because alpha spectral power and coherence have been shown to change during a three-level working memory task in subjects with mild cognitive impairment [18]. Further evidence comes from a report, where oscillations in the alpha2 band increase with memory load during retention in a short-term memory task [19]. The increase of spectral alpha power induced by *Sideritis* extract might therefore be related to the acute positive effects observed during psychometric testing. A working hypothesis might be therefore, that intake of *Sideritis* extract has a positive impact on short-term mental processing, whereas the effect of *Bacopa* extract confines to long term memory demands, which leads to a task-specific desynchronization in the alpha2 band as

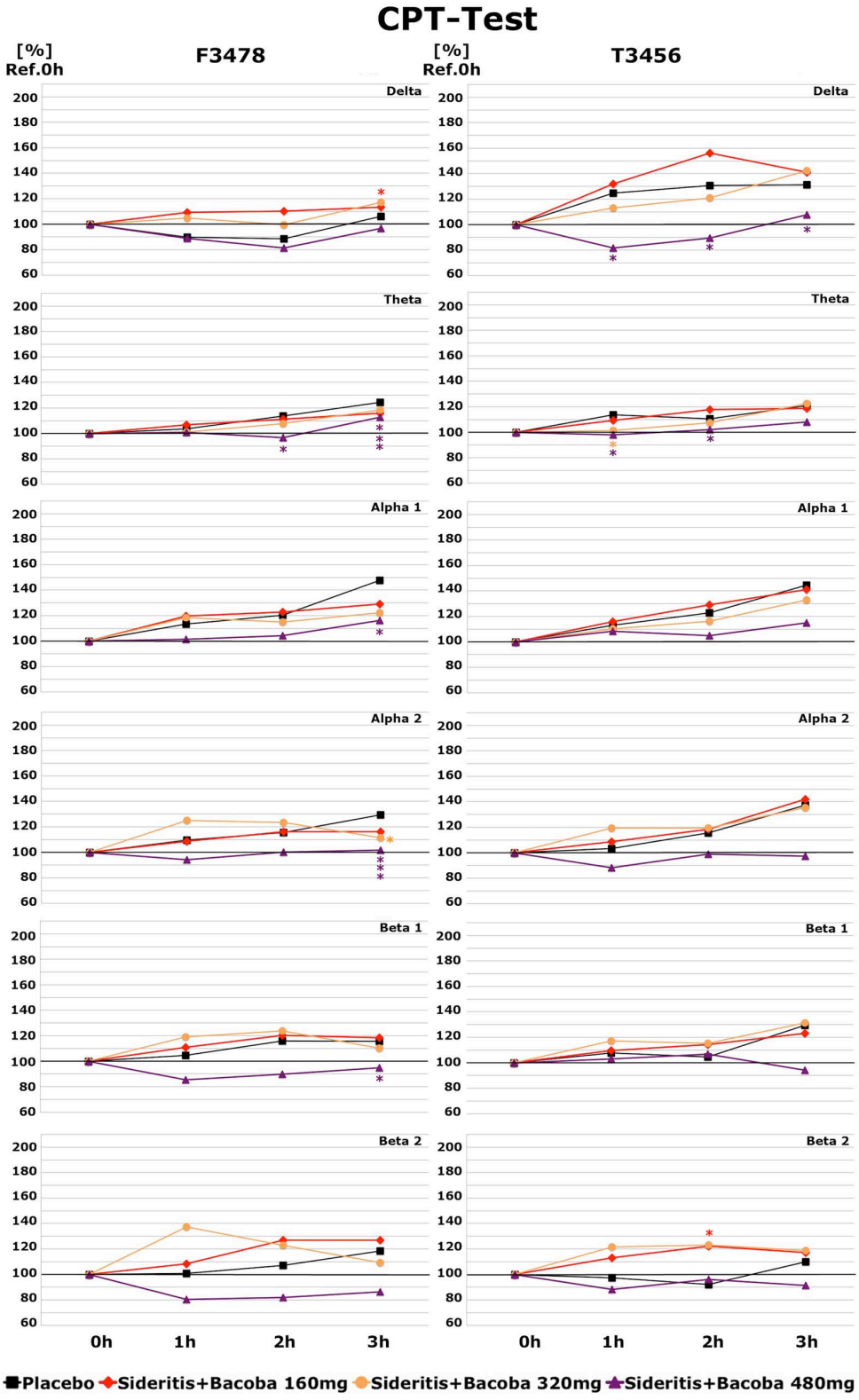


**Figure 9.** Time line of spectral power changes in three regions of interest (ROI = frontal and temporal electrode positions) in the presence of three extract mixtures (for identification see lowest line). Data were recorded during performance of the arithmetic calculation CPT-test. Statistical conspicuousness in comparison to Placebo is documented by a star: $^{*}p < 0.10$; $^{**}p < 0.05$, $^{***}p < 0.01$.

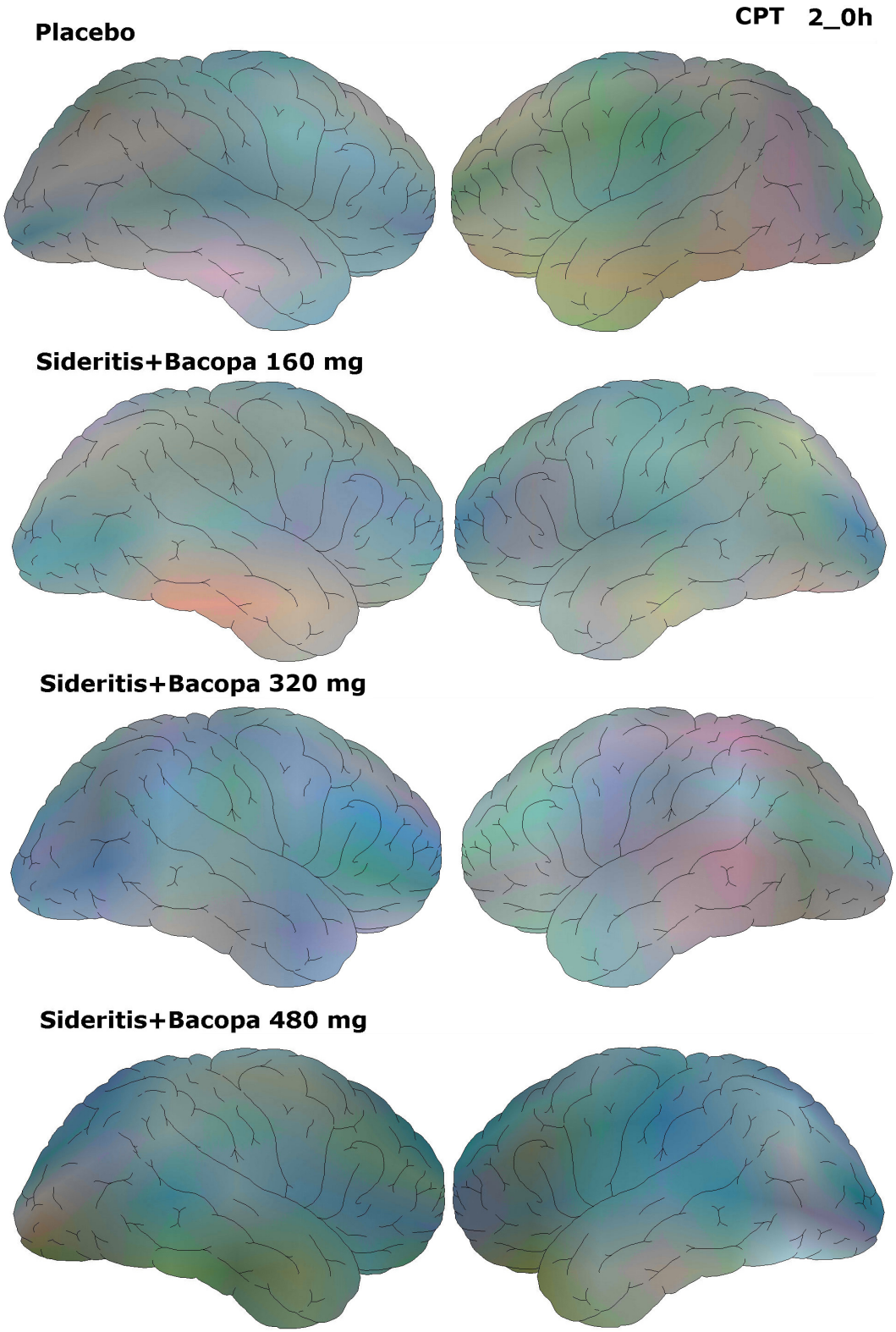


**Figure 10.** Comparison of electric maps (enkephaloglyphs) in the presence of three combinations of *Sideritis* extract and *Bacopa* at 2 hours after administration during performance of the d2-concentration test. Difference to baseline is depicted in %. Left side: right hemisphere. Please note frontal increases of slow wave activity (red-orange color in the second line) in the presence of the low *Bacopa* mixture as observed also during performance of the arithmetic calculation CPT-test.

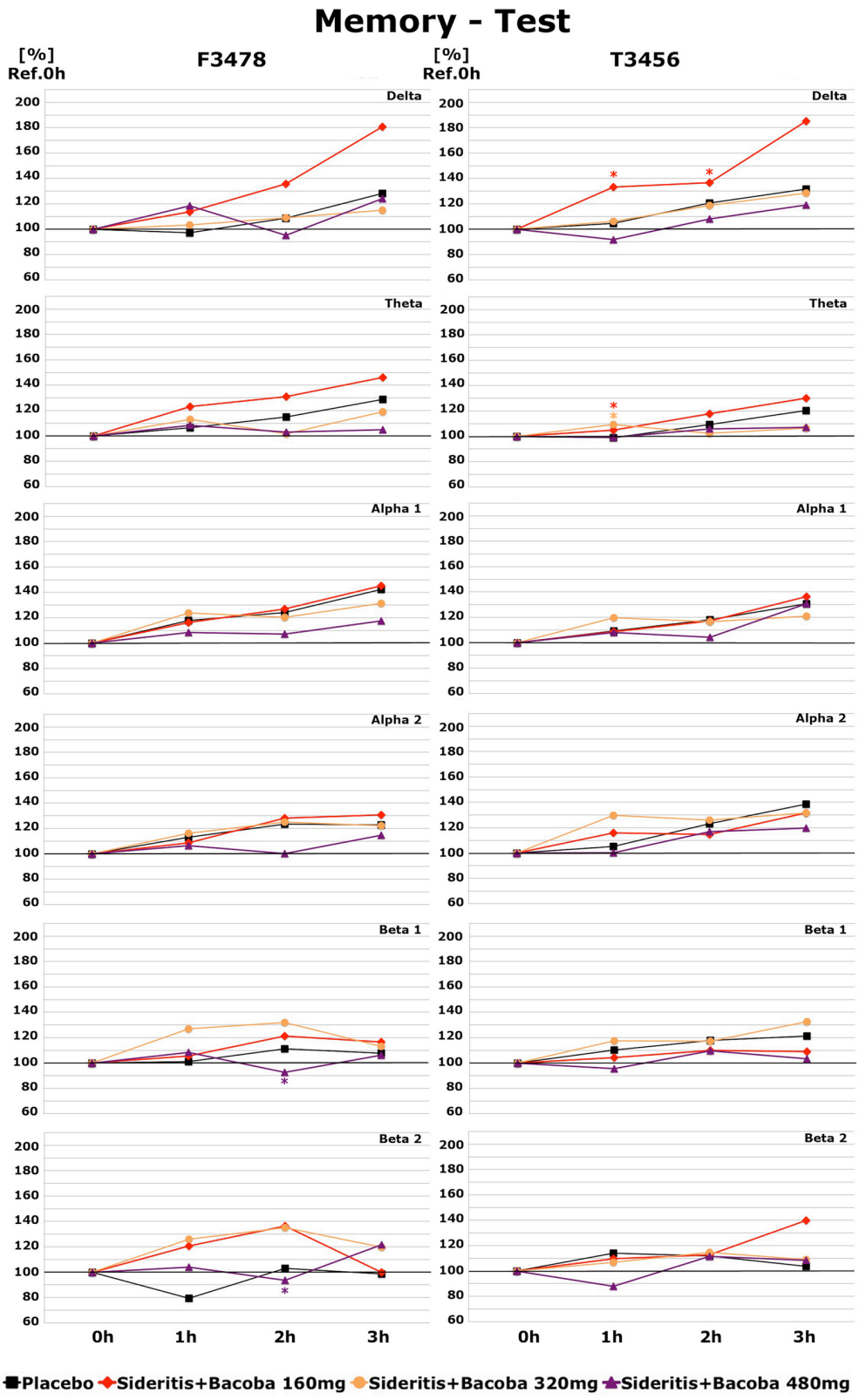


**Figure 11.** Time line of spectral power changes in three regions of interest (ROI = frontal and temporal electrode positions) in the presence of three extract mixtures (for identification see lowest line). Data were recorded during performance of the memory-test. Statistical conspicuousness in comparison to Placebo is documented by a star: $^{*}p < 0.10$.

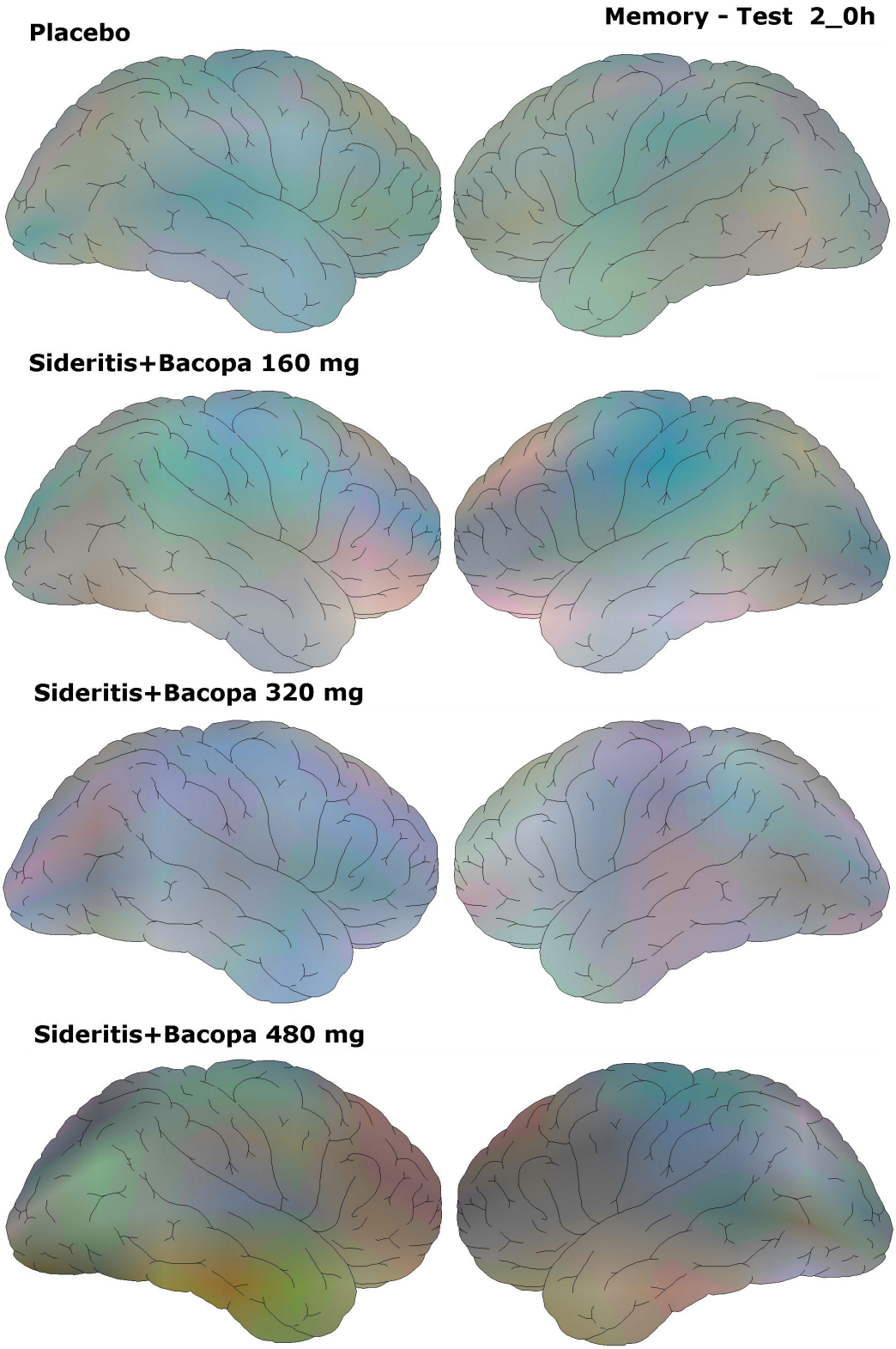


**Figure 12.** Comparison of electric maps (enkephaloglyphs) in the presence of three combinations of *Sideritis* extract and *Bacopa* at 2 hours after administration during performance of the memory-test. Difference to baseline is depicted in %. Left side: right hemisphere. Please note frontal increases of slow wave activity (red-orange color in the second line) in the presence of the low *Bacopa* mixture as observed also during performance of the memory-test.

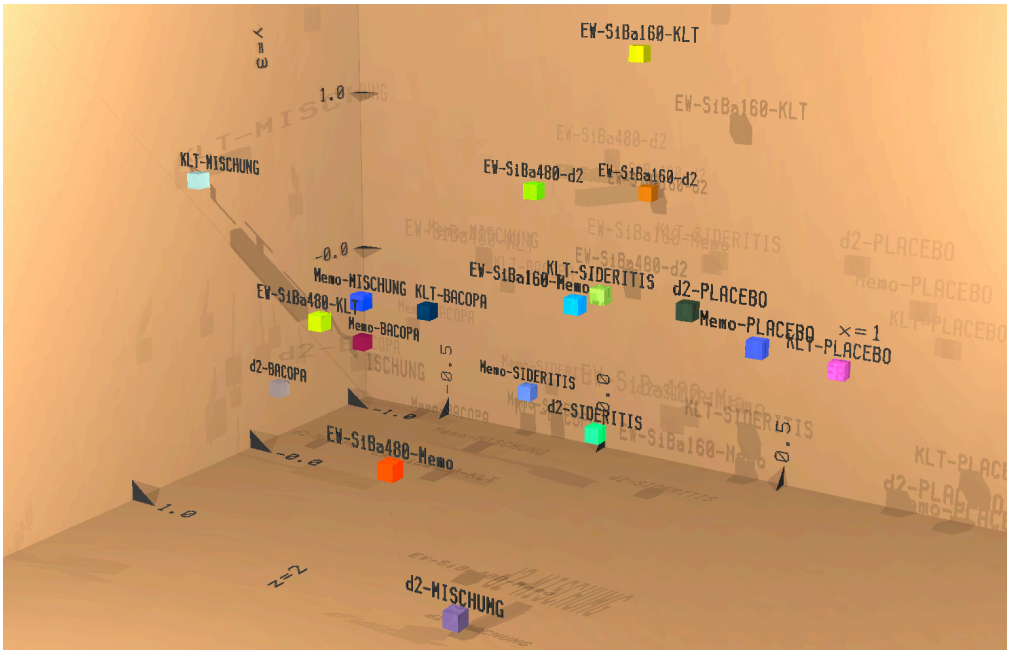


**Figure 13.** Result of discriminant analysis. Results from the first three discriminant functions are displayed in space (x, y and z coordinates), results from the 4th to the 6th function are displayed using the so-called RGB mode (like in TV). Mental challenges are labeled as d2 for the d2-concentration test, CPT for the arithmetic calculation test and MEM for the memory-test. Combinations of *Sideritis* and *Bacopa* extract are labeled by the amount of *Bacopa* added (Ba-160-320-480 mg). Please note that Placebo data group together on the right side.

reported in the literature [20].

With respect to the combinations of both herbal extracts the mixture with the low *Bacopa* content induced similar EEG changes as observed with *Sideritis* extract alone leading to increases of spectral power during performance of the d2-concentration test within the temporal lobe. During performance of the arithmetic calculation test (CPT) high *Bacopa* content led to attenuation of not only slow waves, but also of alpha and beta waves. Again the increases of spectral power in the presence of *Sideritis* extract plus low *Bacopa* confirm the main action produced by intake of *Sideritis* extract alone. Since improvement of psychometric testing during the performance of the d2-concentration test was observed in all three combinations, this probably was due to the presence of *Sideritis* extract, as hypothesized from the results with *Sideritis* extract alone. The effect of *Bacopa* might be seen only after repetitive dosing. For example: in 98 healthy elderly participating in a randomized, Placebo controlled, double blind clinical trial *Bacopa* extract at a dosage of 300 mg significantly improved memory acquisition and retention after a 12 weeks intake [21]. However, this extract caused gastrointestinal side effects (increased stool frequency, abdominal cramps and nausea). In 104 subjects suffering from mild cognitive impairment a combination of *Bacopa monnieri* extract with astaxanthin, phosphatidylserin and vitamin E was given for 60 days. Statistically significant improvements were observed with respect to ADAS.cog and clock drawing test scores [22].

Since *Bacopa* extract was effective in improving cognitive testing – at least according to the literature—the question was if and how a combination of *Sideritis* extract with *Bacopa* extract would be meaningful. The present investigation clearly showed differences not only with respect to quantitative EEG parameters but also with respect to psychometric results when given as a single intake. Obviously, *Bacopa* extract asks for a repetitive dosing in order to induce improvement of cognition parameters. Therefore the question came up, which dosage would be meaningful to be combined with *Sideritis* extract. According to the results of the combinations, the lowest dosage of 160 mg added to *Sideritis* extract came nearest to the results of *Sideritis* alone. At the same time low dosage as additive was only 50% of the dosage producing side effects in the gastrointestinal tract [21]. Thus, combination of the short term effects produced by *Sideritis* extract with the long-term effects expected from repetitive dosing of *Bacopa* extract might be a new promising option for treatment of subjects suffering from mild cognitive impairment.

## 5. Conclusion

There is hardly an effective treatment for mild cognitive impairment, yet. Therefore, the two botanicals *Sideritis scardica* extract and *Bacopa monnieri* extract are looked at in terms of improvement of cognition. *Sideritis* extract alone or in combination with a low amount of *Bacopa* extract lead to statistically significant improvement during performance of the d2-concentration test. Quantitative EEG assessment during the different experimental conditions shows massive differences between both extracts. A combination of *Sideritis* extract with a low amount of *Bacopa* extract to be tested within a repetitive dosing is therefore recommended for treatment of subjects suffering from MCI.

## Acknowledgements

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