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Effects of Lozenge Containing Lavender Oil, Extracts from Hops, Lemon Balm and Oat on Electrical Brain Activity of Volunteers

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Abstract: Within a randomized double blind, placebo controlled trial the electrical activity of the human brain has been monitored using charge mode technology (Laplacian estimates) after exposure to a lozenge containing 4 different herbal preparations (lavender oil, extracts from hops, lemon balm and oat) or a matching placebo without any active ingredients. Sixteen healthy volunteers (8 males and 8 females) were tested within a crossover design. After baseline recording each subject sucked a lozenge and 2 hours later a second one. Recording was performed immediately after finishing the lozenge and in hourly intervals thereafter. Comparison to reference periods of 10 min eyes open and 5 min eyes closed, respectively, revealed increases in alpha1, alpha2 and beta1 electrical power at the electrode positions Cz, P3, T3 and T5 which were even more pronounced after a second application two hours later.

Since alpha1 changes repeatedly have been attributed to attentional states, increases of this electrical activity must be seen as indicator of a relaxational psychophysiological state. Changes in the alpha2 frequencies have been related to working memory indicating that an increase can be seen as a correlate for attenuating this circuit. Increases of beta1 activity have been seen in the presence of anxiolytic drugs including major and minor tranquilizers. The changes as observed after the application of this herbal composition are therefore in line with the idea of having induced a state of relaxation and regeneration. This interpretation suggests that one could expect from the ingestion of this lozenge to better cope with psychological and emotional stress. The data are further proof that recording computer aided quantitative EEG is a very fruitful and promising approach in psychophysiology.

Key words: EEG, Psychophysiology, CATEEM, Laplacian estimate, Human, Herbal extracts

Introduction

Monitoring the electrical activity of the human brain has been a major challenge since the first report on the feasibility of its measurement by the German researcher Hans Berger in 1929. As early as 1932 he together with Dietsch suggested to use the mathematical approach of frequency analysis in order to quantitatively describe the informational content of the recorded signals (Dietsch and Berger, 1932). But this brilliant idea had to await the availability of modern computer technologies since the 1960ies to perform the necessary calculations within a reasonable time. Since then an ever increasing literature describes changes of electrical activity of the brain in response to disease states, drug application and behavioural states. (Saletu and Grünberger, 1988; Itil et al., 1991; Itil and Itil, 1995). There is no doubt that - in terms of neurobiology - the electrical activity of the brain also reflects the emotional state of the individual subject and consequently can be used to quantitatively describe psychophysiological states by means of natural science parameters, the m/kg/s system (Machleidt et al., 1987). Later on also the reflection of mental work in the dynamic quantitative topographical EEG has been proven (Schober et al., 1995).

The aim of the current prospective study was to detect any topological differences in electrical processing of the human brain in response to sucking a lozenge consisting of herbal extracts of 4 different plants (lavender, hops, lemon balm and oat) assumed to have "calming" properties.

Materials and Methods

Subjects

Sixteen healthy volunteers (8 females and 8 males) participated in this study. All subjects were between 35 and 50 years old (average of 43 years) and underwent a medical examination before entering the trial. Subjects reporting neurological disturbances of the central nervous system (using DSM-III criteria) were excluded from the study. Subjects with a history of drug or ethanol abuse or participation in another study within the last six month were also excluded. It was ensured that they were not on drugs. On the day of examination no caffeine containing beverages were allowed within the last 12 hours preceding the EEG recording. The study was carried out according to the Declaration of Helsinki on Human Rights and was approved by the local ethic committee. All subjects were informed about the goals of the study in detail and gave their written informed consent to participate.

EEG Recording

Subjects were sitting alone in a quiet separate room in a comfortable easy chair. The light was dimmed. Baseline recording of 10 min under the condition of eyes open was followed by recording for 5 min under the condition eyes closed. Next recording period was performed immediately after sucking the lozenge and then in hourly intervals thereafter. A second lozenge was applied 2 hours after the first one. Again recording was performed immediately thereafter and 1 and 2 h later. Between the measurement sessions the subjects spent their time in the facility`s breakroom. All experiments took place at the same time of the day (starting at 8 h in the morning).

The EEG was recorded bipolarly from 17 surface electrodes according to the international 10/20 system with Cz as physical reference electrode (Computer aided topographical electroencephalometry: CATEEM® from MediSyst GmbH, 35440 Linden, Germany), using an electrocap. The raw signals were amplified, digitalized (2048 Hz/12 bit) and transmitted via fiber optical devices to the computer. The automatic artefact rejection of the CATEEM®-System, which eradicates EEG-alterations caused by eyeblinks, swallows, respiration etc. during the recording was visually controlled and individually adjusted by the investigator. Electrocardiogram (ECG) and Electrooculogram (EOG) were recorded in one channel each in order to facilitate detection of those signals superposing on to the EEG. The artefact rejection set-up was observed for about 5 minutes prior to the start of the recording to ensure, that all artefacts were correctly eliminated from further evaluation. For safety purposes the original raw data were saved on optical disk in order to allow re-evaluation of the artefact rejection mode if necessary. In these cases the experimental session was reexamined offline with a newly adapted rejection mode. The amount of rejected data was determined automatically and given in percent of total recording time. Nevertheless the entire recording and the computer-based automatic artefact rejection were continuously supervised and adjusted by a trained scientist (Schober and Dimpfel, 1992).

In this study the EEG was computed not in the potential mode measured as voltage, but in a surface charge mode obtained by Laplacian estimates also known as current source density analysis (CSD, Harmony et al., 1993; Dimpfel et al., 1996). The charge is the 2. derivation of the potential and gives the curvature of the potential curve according to the space. All calculations are based on the standard set-up of the 10/20 system of recording. Under the condition of using a homogenous, steadily conducting medium the surface charge mode provides the source density of the electrical flow on the cortex surface. Whereas the EEG in the potential mode tends to produce a more extensive and diffuse picture of changes, the Laplacian estimate acts as a spatial filter emphasizing local sources over distant sources. There is a sharply contrasted display of cortex areas with highly activated generators in the depth of the brain and brain areas with less intensely working generators. Harmony et al. (1993) were able to demonstrate, that spectral parameters obtained from the CSD showed higher correlations with Computer tomography measures than those calculated from the potential mode of the EEG. We therefore used this methodology in order to describe the focal changes of brain activity.

Using a Lagrange interpolation, signals from 82 additional virtual electrodes were calculated to provide high resolution topographical maps. The signals of all 99 electrode positions (17 real and 82 virtual) underwent the Fast Fourier Transformation (FFT) based on 4-second sweeps of data epochs (Hanning window). Data were analysed from 0.86 to 35 Hz using the CATEEM® software. In this software the resulting frequency spectra are divided into six frequency bands: delta (1.25 - 4.50 Hz), theta (4.75 - 6.75 Hz), alpha1 (7.00 - 9.50 Hz), alpha2 (9.75 - 12.50 Hz), beta1 (12.75 - 18.50 Hz) and beta2 (18.75 - 35.00 Hz). This frequency analysis is based on absolut spectral power values. Color coding of the maps is achieved by transforming the content of the power spectrum into the socalled glow mode pictures (i.e. as in glowing iron from dark (no electrical power) to red and white (highest electrical power). Data acquisition and analysis were carried out simultanously and provide topographical maps displayed on-line on the computer screen. The maps show the relative, time averaged, functional changes of electrical brain activity of each specific recording condition in comparison to the reference period at the beginning. For statistical evaluation the nonparametric sign test was used.

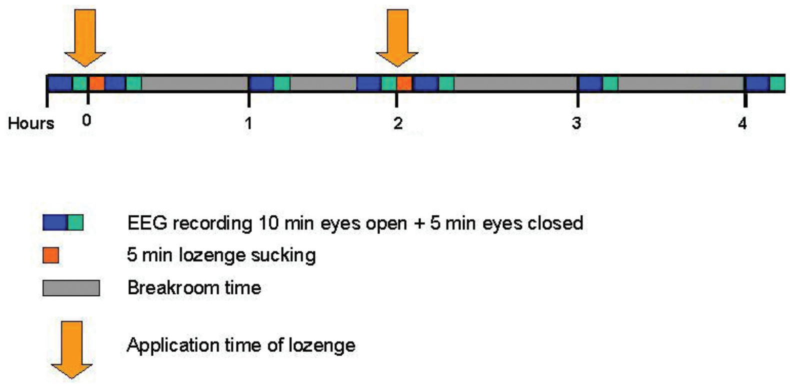

Table 1. Time schedule of electrophysiological recordings.

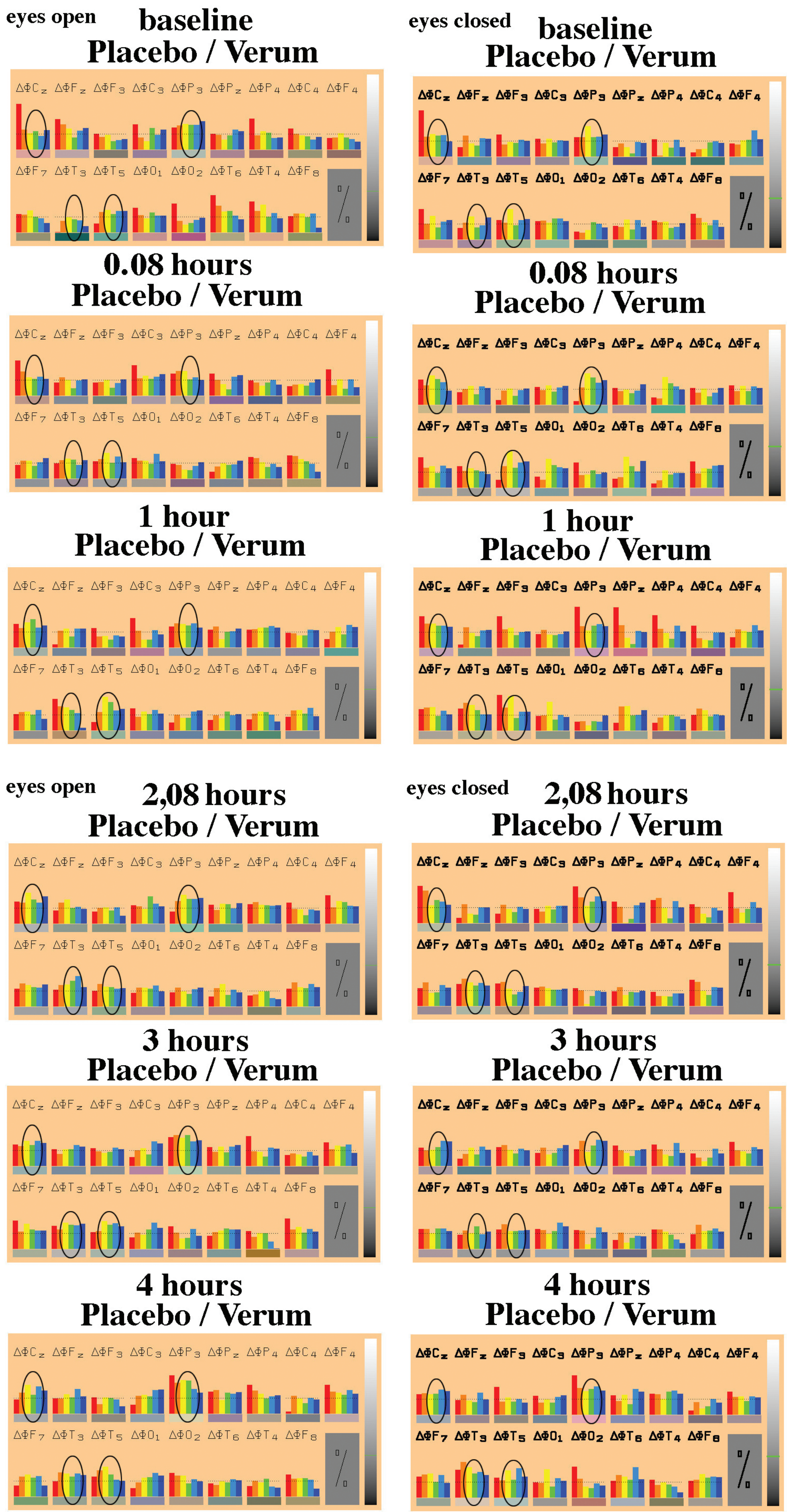

Fig. 1. Frequency changes at single electrodes (10/20 system) for the condition eyes open (left row) eyes closed (right row). Time course (begin of recording time) on the base of placebo = 100% (dashed line) at corresponding timing. Frequencies (delta, theta, alphal, alpha 2, beta 1 and beta 2 are shown as coloured bars from red (delta) to blue (beta 2). Horizontal bars represent an additive colour mixture of the single frequencies. A second lozenge was sucked at 2 h. Electrode positions representing regions of interest (roi) are marked by a cycle and evaluated to give the median values of Fig. 4 and Fig. 5.

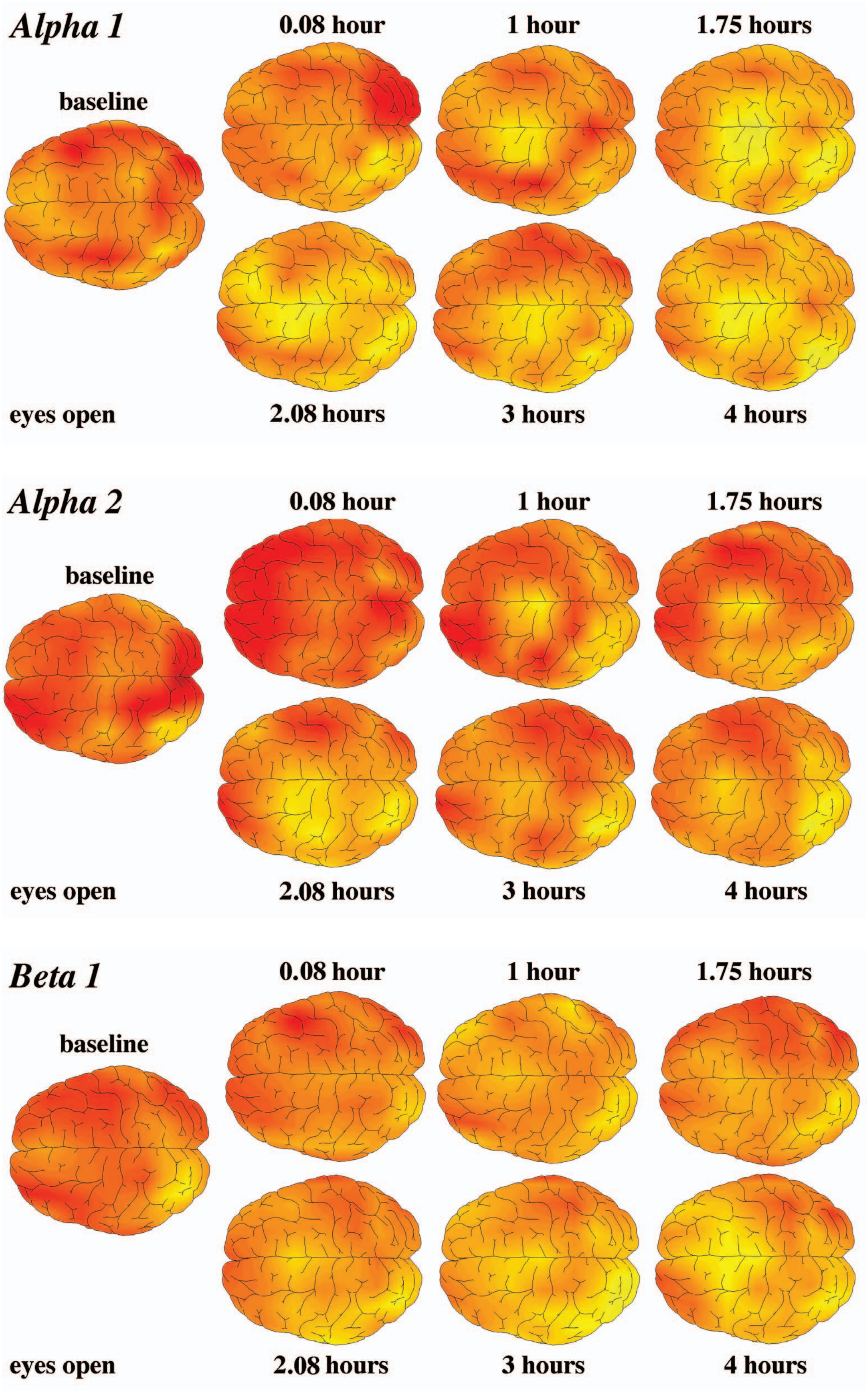

Fig. 2. qEEG-changes of electrical activity in 3 frequencies (alphal, alpha 2 and beta 1) presented as glow mode maps (the higher the electrial power the lighter the color like in glowing iron). Front of the brain: left side. Please remark that a second lozenge was taken immediately at 2 h . Data are given for the condition eyes open. Values are depicted in percent of the changes seen after application of placebo at the corresponding time.

The Preparation

A lozenge composed of a proprietary formula (nutrifin relax) composed of 93 mg of a blend of active components from extracts of lemon balm, hops, and oats as well as lavender oil was sucked twice during the recording session 2 hours apart. The placebo lozenge did not contain active ingredients, but was similar to the verum in taste and appearance.

Results

Comparing electrical brain activity between the control series and the consumption of the herbal mixture

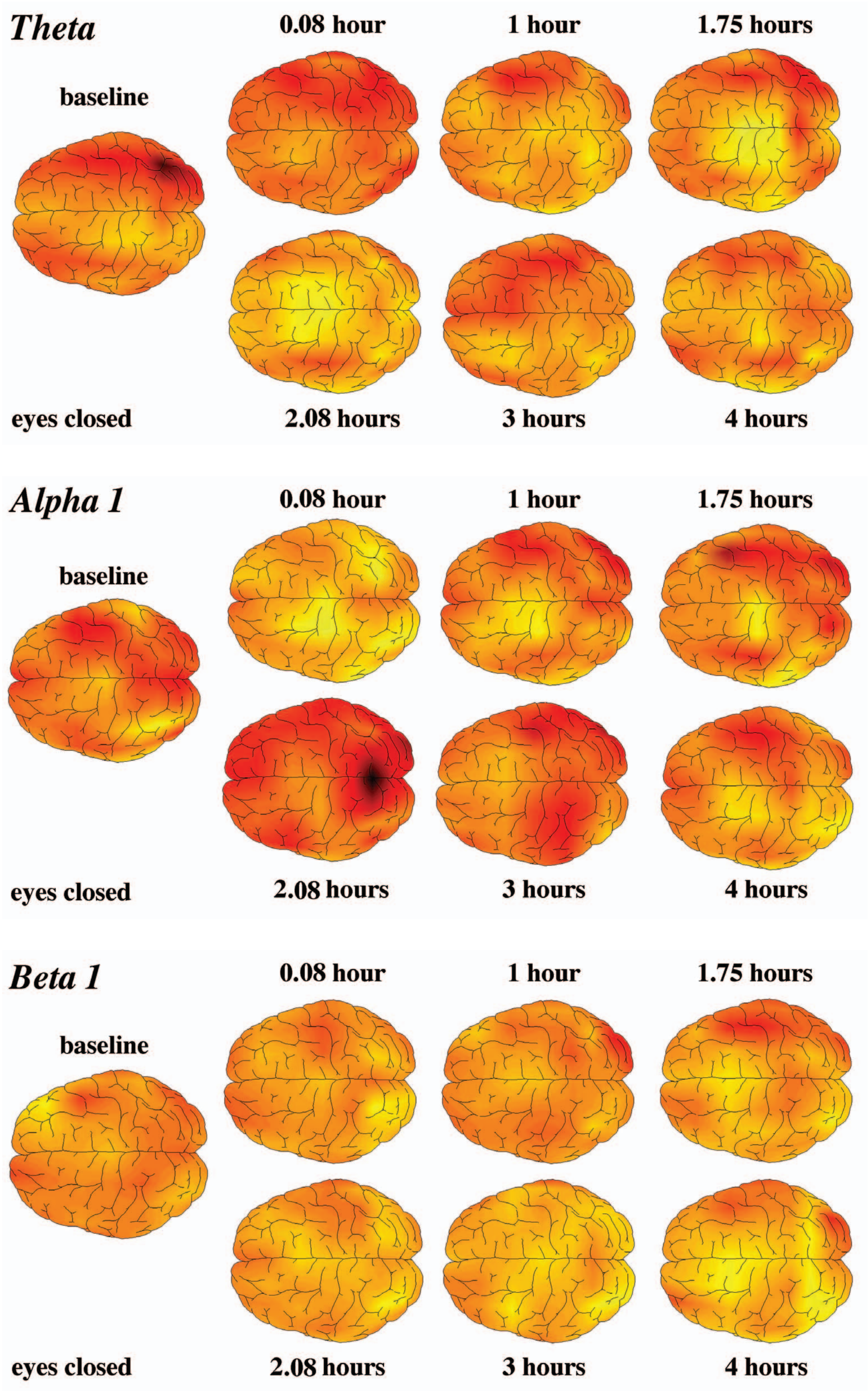

Fig. 3. qEEG-changes of eleetrical aetivity in 3 frequencies (theta, alpha 1, and beta 1) presented as glow mode maps (the higher the electrical power the lighter the color like in glowing iron). Front of the brain: left side. Please remark that a second lozenge was taken at 2 h. Data are given for the condition eyes closed. Values are depicted in percent of the changes seen after application of placebo at the corresponding time.

directly at each time of recording (by it circumventing changes caused by circadian rhythm) the application of the herbal lozenge resulted in focal changes of electrical activity. Under the recording condition of eyes open time dependent changes could be observed with respect to alpha1, alpha2 and beta1 frequencies. Despite the fact that there were some subtle differences at baseline recording between placebo and verum application more clearcut differences could be seen within the next two hours after application of the verum lozenge for alpha1, alpha2 and beta1 frequencies. As depicted in Fig.1 (for the condition eyes open and closed, respectively) differences to the application of placebo (each time of control recording was set to

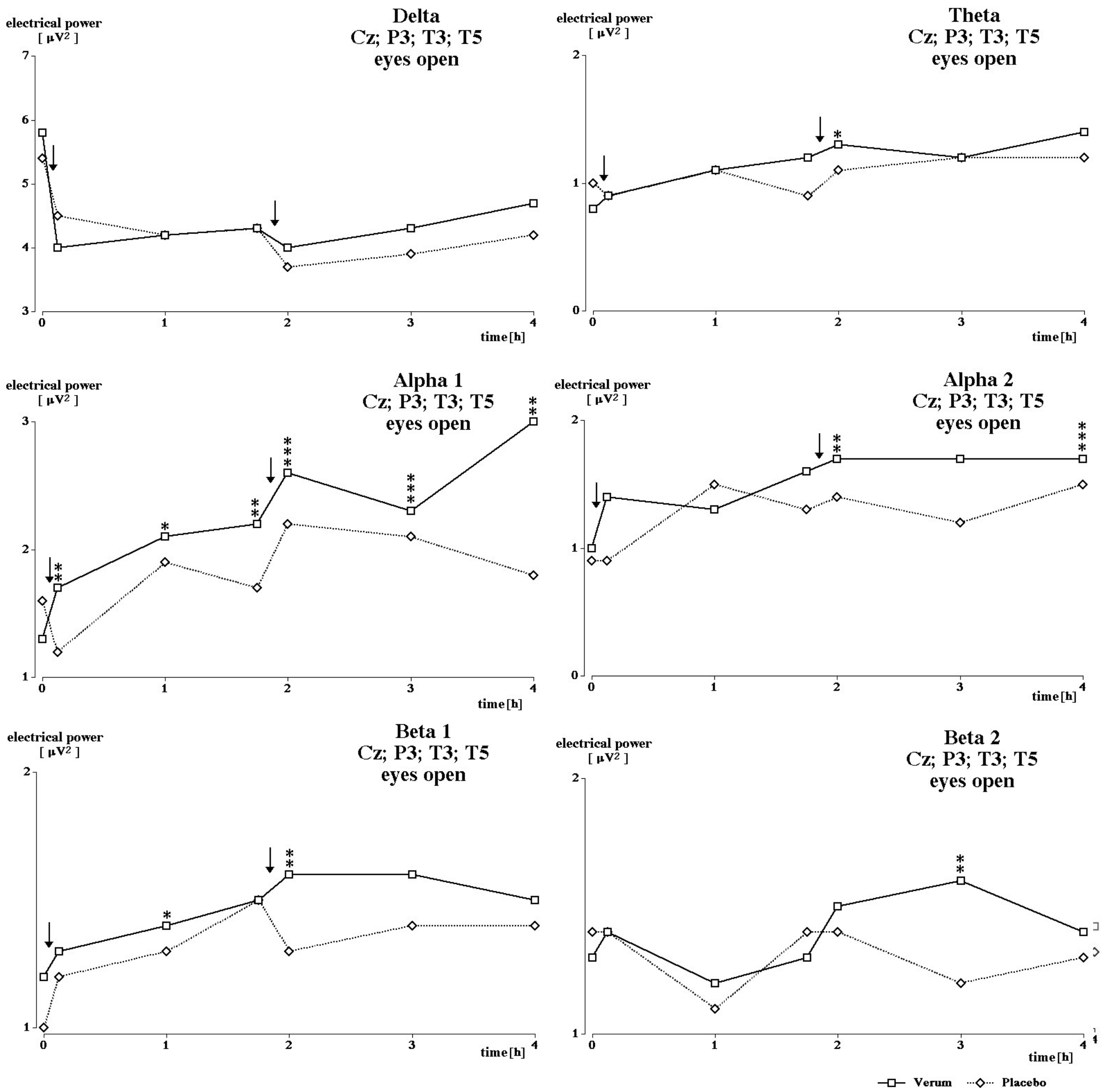

Fig. 4. Time dependency of qEEG-changes in 6 frequencies (for definition s. methods) after taking the herbal product. Please remark that a lozenge was taken at the times marked by an arrow. Statistieal evaluation according to the sign test revealed increases of electrical power at the regions of interest (ROI) represented by the electrode positions Cz, P3, T3 and T5 (central, parietal and temporal cortex on the left side as marked in Fig. 1). * corresponds to $p<0.10$, ** corresponds to $p< 0.05$ and *** corresponds to $p< 0.01$

100%) were mainly observed in central and temporal areas of the brain. Especially after the application of the second lozenge the difference to placebo becomes obvious. Largest differences between the application of placebo and the herbal lozenge were seen with respect to alpha1 frequencies as already observed after the first application.The second one (given about 2 h after the first one) led to much more pronounced differences. Fig. 2 and 3 document the changes by means of mapping the results as socalled glow mode pictures (derived from the picture of glowing iron where no electrical power is reflected by dark colors and higher activity by red to white colors).

Focal changes of activity were analyzed quantitatively with respect to the region of interest (roi) represented by the electrode positions Cz, P3, T3 and T5, regions where emotional and working memory is anatomically located. The numerical data from this brain area were averaged and depicted with respect to time dependence in Fig. 4 and 5. As can be seen from this figure delta and theta waves do not change in a consistent manner whereas alpha1 activity on average is significantly higher than after the placebo applica-

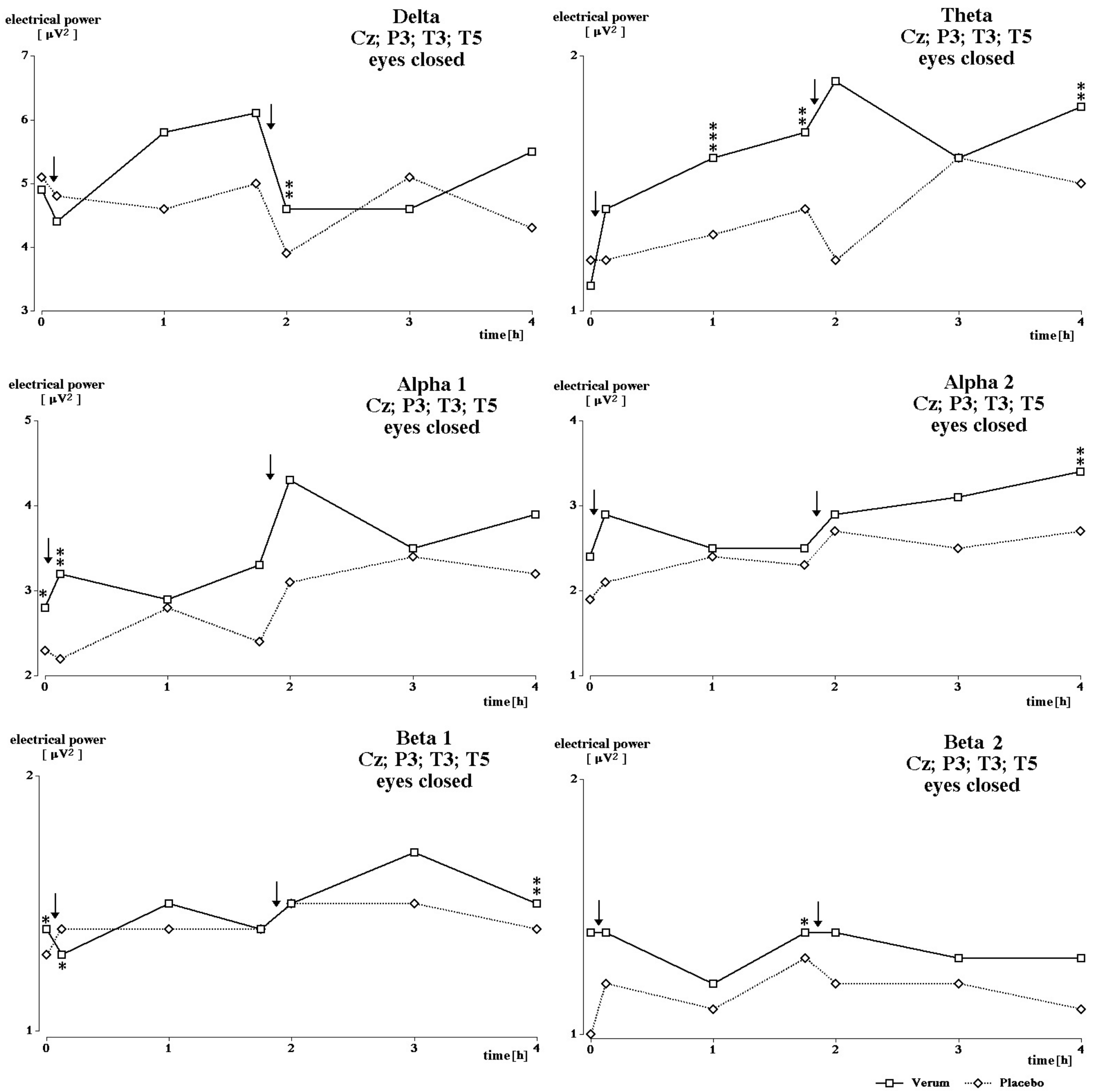

Fig. 5. Time dependency of qEEG-changes in 6 frequencies (for definition s. methods) after taking the herbal product. Please remark that a lozenge was taken a the times marked by an arrow. Statistical evaluation according to the sign test revealed increases of electrical power at the regions of interest (ROI) represented by the eleetrode positions Cz, P3, T3 and T5 (central, parietal and temporal cortex on the left side). * corresponds to p<0.10, ** corresponds to p< 0.05 and *** corresponds to p< 0.01

tion. After the second sucking of the lozenge alpha2, beta1 and also beta2 activity are higher in comparison to placebo values. These changes are consistently visible but only partially statistically significant.

Under the recording condition eyes closed a similar picture arises except for the fact that also theta waves increase already after the first sucking period (Fig. 5). These consistent increases were statistically significant. Changes with respect to the other frequencies were not so pronounced and rarely reached statistical significance. In summary, consumption of the herbal composition resulted in significant time and dose dependent increases of middle frequencies of the EEG power spectrum under both recording conditions at the particular regions of interest.

Evaluation of the profile of mood questionnaire did not give statistically significant results. The items making up the term dejection and drive were somewhat diminished whereas items representing sleepiness increased somewhat in general. But there was no difference between sucking the verum lozenge in comparison to placebo.

Discussion

From the results mentioned above one can assume that the application of a herbal lozenge containing

Lavender, Hops, Lemon balm and Oat changes the pattern of electrical activity in particular brain regions. Since different brain regions serve specific aspects of mental activity (i.e. Bunge et al., 2003) changes of activity in particular regions of the cortex can be interpreted in a more detailed manner. The areas changing their activity in the presence of the lozenge represent attention (temporal lobe, Fiez et al., 1996) and working memory (parietal lobe, Olesen et al., 2004). With respect to frequencies changing after the consumption most prominent changes have been observed in the alpha1 range. This frequency repeatedly has been attributed to changes in attention. Thus, increase of the electrical power in this range signalizes lower attention and higher relaxation. Decreases in alpha2 frequencies have been observed during tasks involving working memory and in the presence of stimulating drugs (Stipacek et al., 2003). An increase may therefore be interpreted as a kind of attenuating the circuit responsible for mental work. Increases in beta1 activity have been observed in the presence of minor and major tranquilizers which resulted in anxiolysis. Thus, the pattern of changes as observed after the consumption of the lozenge under investigation must be seen as indicative for a relaxing and regenerating action of this herbal product.

The result is not quite unexpected since all four herbs have been regarded traditionally as having a calming effect on the psyche. In animal experiments (geller type conflict test) Lavender oil produced an action similar to the action of diazepam (Umezu, 2000). The action of Lavender could be due to one of its major constituents, linalool (Lis-Balchin and Hart, 1999). A critical review on the biological activities of lavender oil is given by Cavanagh and Wilkinson, 2002. Despite the fact that clinical studies are rare Holmes et al., 2002 could show modest positive effects on agitated behaviour in severely demented patients. Hops is applied traditionally most often in combination with Valerian and prescribed successfully for the treatment of sleep disturbance (Müller-Limmroth and Ehrenstein, 1977). Modulation of mood and cognitive performance following acute administration of lemon balm has been reported by Kennedy et al., 2002. These authors found dose-specific reductions in both Secondary Memory and Working Memory factors using their psychometric battery. Assessment by Bond-Lader mood scales revealed that self-rated "calmness" was elevated at the earliest time points by the lowest dose, whilst "alertness" was significantly reduced at all time points following the highest dose. But one has to consider that in these cases 10 times higher doses were applied. Nevertheless a combination of different herbs in low dosage might just be as effective leading to a much safer application, especially in the field of food supplements.

Since questionnaires obviously are not suited to gather information with small numbers of trial participants a more sensitive and quantitative methodology had to be used in order to visualize small changes in psychophysiological states. Here we know from earlier studies on mental work and induction of emotions during watching TV that recording of the electrical activity of the brain provides a very sensitive measurement of changes of the psychophysiological state (Dimpfel et al., 2003). Especially the central and parietal cortex is regarded as the anatomical location representing changes in mood (LeDoux, 2000). At a first glance it might be surprising that we could observe only focal changes of electrical activity but in view of learning more and more on the meaning of local electrical circuits the result is in favor of a very selective action on particular information processing units within the brain which have their psychophysiological correlates in mood (Marosi et al. 2001) and mental work (Schober et al. 1995).

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