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Neurophysiological effects of Rhodiola rosea extract containing capsules (A double-blind, randomised, placebo-controlled study)

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Abstract: In 1947 Dr. Nicolai Lazarev introduced the term "adaptogen" in order to define special plant-derived extracts like Ginseng, which seemed to help to cope with stress-induced physical and psychic weakness. Extracts from *Rhodiola rosea* L. were recognized to belong to this category of food supplements. Due to contradictory results in the literature it was decided to examine the neurophysiological effect of *Rhodiola rosea* extract on surrogate parameters of cognitive and emotional brain processing in 20 volunteers. Spectral signatures of regional electric brain activity were recorded under control of an Eye-Tracking device, by means of which different challenges were presented. Among the cognitive challenges was a Stroop test, a memory test and a picture comparison for search of small deviations; among the emotional challenges were three pictures:a crying child, a bird spider and a picture taken from the TV series "Jungle Camp". Additionally, three film excerpts were shown: a boring and an exciting animal film as well as a horror trailer. Evaluation of all challenges against looking at a fixation cross on the screen revealed highly statistically significant differences. These consisted (among others) in considerable higher spectral power values of delta and theta power in frontal and occipital brain areas during all cognitive and emotional tasks except for the crying child and bird spider, where only occipital power increased. Exactly these parameters changed in the presence of *Rhodiola rosea extract*, where increases of delta and theta power in these regions were documented in comparison to placebo. These statistically significant increases indicate mental activation according to literature. Likewise, an increase of alpha2 spectral power was observed during performance of the memory test indicating activation of memory processes as known from literature. In summary, the extract from *Rhodiola rosea* modulated cognitive and emotional surrogate parameters indicating improvement of mental processing in a stimulatory and activating sense.

Keywords: Rhodiola rosea, EEG, Eye-Tracking, Neurocode-Tracking, Cognition, Emotion, CATEEM

1. Introduction

Food supplements are believed to protect and retain health. However, if special claims for its use are formulated and if they are intended to be used for marketing purposes, these claims have to be proven by scientific studies following the same criteria as known from pharmacological studies aiming at synthetic drugs to be used for the treatment of disease. Since there are no guidelines for testing food supplements, the same criteria as in pharmacological studies should be followed. However, no ethic vote or indication to authorities is recommended in Germany for this type of study. Thus, the present study was conducted according to the declaration of Helsinki and GCP guidelines were followed wherever possible.

Years ago, we have developed a neurophysiological methodology based on EEG recording that proved to be very suitable to quantify effects of drugs, food supplements and functional food. It has been named CATEEM® which is an abbreviation for Computer Aided Topographical Electro Encephalo Metry [1,2]. On the base of spectral signatures of regional electric activities surrogate parameters were defined related to cognitive and emotional features of brain activity [2-5]. Likewise electrophysiological imaging was used to follow cognitive decline in normal elderly within a longitudinal study in the past [6]. These surrogate parameters - also called "biomarkers" -, which are related to cognitive and emotional processing of the brain are taken to prove special claims within neurophysiological information

handling (Neurocode-Tracking).

Since modern working life very often leads to lack in drive, weakness in concentration and exhaustion, people look for help by functional food and food supplements. One of the most interesting plant-derived extracts in this respect is that of *Rhodiola rosea* L. *Rhodiola rosea* extract was recognized to belong to the category of so-called "adaptogens" as named by Russian scientist Dr. Nicolai Lazarev in 1947. An adaptogen leads to normalization of stress-induced psychic and physical exhaustion. However, extracts from Rhodiola rosea have been used for more than thousand years for coping with demanding life during hunting and wars in China, Russia, Japan, Korea and even Europe.

Root extract from *Rhodiola rosea* contains quite a number of ingredients, but not much is known about effects of single compounds. Adaptogenic properties were discussed with respect to modulation of neurotransmitters but also in terms of heart protection against stress-induced weakness of heart muscle activities. According to a large number of studies the following effects were described: stimulating action against physical weakness, tiredness and lack of performance; positive influence on sleep disturbance, loss of appetite and headache; increase of cognitive performance, improvement of mood and induction of shorter recreation time. However, a systematic search of literature revealed contradictory results [7].

It was therefore decided to examine the effect of a single dosage of 2x200 mg of native *Rhodiola rosea* extract containing capsules by using the most advanced neurophysiological technique in combination with Eye-Tracking in order to find out, if this extract was able to change spectral signatures of regional electrical brain activity related to cognitive and emotional brain processing. This idea was also based on the fact that *Rhodiola rosea* extract was able to change spectral signatures of deep field potentialsin freely moving rats indicating stimulatory effects[8]. Goal of the present study was therefore to quantitatively identify possible effects of *Rhodiola rosea* extract containing capsules on neurophysiological parameters related to cognitive and emotional brain processing as indicated by changes of spectral signatures of regional electric activity in human volunteers.

2. Methods

2.1. Subject

Twenty healthy subjects (11 males and 9 females, on average 50.7 ± 12.6 years old) were recruited from our pool of volunteers and participated in this study. Subjects reporting neurological or psychiatric disturbances or having a history of alcohol abuse were excluded. None had participated in another study within the last six months. On the day of testing it was ensured that they were not on alcohol. The study was performed according to declaration of Helsinki (1964), and Guidelines for Good Clinical Practice were followed. Since the preparation to be tested was a food supplement and only EEG measurements were undertaken, no ethic vote or report to government authority was required. All subjects were informed about the goal of the study and gave their written informed consent to participate. Each subject was randomly allocated to either the functionally active preparation or placebo within a crossover design. The two experimental days were one week apart.

2.2. EEG Recording

In this study a 16 channel EEG recording was combined with Eye-Tracking [9,10]. Details of the EEG recording have been published earlier [2,3] but a new modified software for analysis of shorter time epochs of 364 ms duration was used (neo-CATEEM®, supplied by MEWICON CATEEM-Tec GmbH, 4164 Schwarzenberg, Austria). A manuscript containing details and validation of the software package now called "Neurocode-Tracking" has been published [10]. In short: For the new approach EEG frequency ranges to be analyzed had to be adjusted slightly to give the following exact ranges. Delta:1.375 - 4.125 Hz; Theta: 4.125 - 6.875 Hz; Alpha1: 6.875 - 9.625 Hz; Alpha 2:9.625 - 12.375 Hz; Beta1:12.375 - 17.875 Hz; Beta2:17.875 - 34.375 Hz. This adjustment is a precondition for the new fast dynamic frequency analysis (Neurocode-Tracking) because under this condition each frequency range from delta up to alpha2 contains only one frequency (middle frequency within the particular frequency band). Data were analyzed in the voltage mode and were not calculated as current source density. All other features remained identical to the classic analysis used now for nearly 20 years. Maps were constructed by transforming spectral power values into spectral colors followed by additive color mixture (RGB-mode like in TV).

The recording was performed in the presence of a video clip, which contained several different cognitive and emotional loads in series. At the beginning, after a gong for synchronization purposes, a fixation cross was presented for 1 minute as reference. Then a non-exciting animal film (3,14 min) was presented. Next parts of the video consisted of a Stroop test (16 images) and a memory test. Four tasks asking for memorizing a row of 8 letters and numbers were presented, which appeared for 4 s on the screen, followed by 10 s black screen. After this a multiple choice test of four possible answers was presented. Next part of the video contained 3 emotional pictures for 4 s each: a crying child, an image depicting a bird spider and a picture taken form the "Jungle Camp" (a famous TV series). Finally a picture comparison for differences was presented, and the end of the video contained an exciting animal film (3,14 min) and a horror trailer (2,20 min). The video was presented twice: during baseline recording and one hour after intake of two 200 mg *Rhodiola rosea* extract containing capsules (Rhodiolan 200®) on each of the two examination days. Placebo capsules only contained corn flour.

2.3. Eye-Tracking

Eye-Tracking (equipment and software from Interactive Minds GmbH, Dresden, Germany), was performed concomitantly with Neurocode-Tracking (fast dynamic quantitative EEG recording). All mental challenges were presented as a single video clip. Single mental loads were first collected as a power point file and then converted into a final video clip (by Adobe Captivate Software). For offline analysis and synchronization with the eye-track data a screen grabber (Adobe Captivate) was used to produce a video containing all successively calculated EEG maps. A second video was obtained from the eye-tracker software running on a separate computer. It is called a "gaze overlay" movie depicting the presented pictures, tasks or video film. In this gaze overlay video the momentary gaze of the subject is documented by a red spot. Since the presentation always started with an audio signal (gong) and this audio signal was also registered by screen capture of the EEG computer, it was used for synchronization of both videos by means of a video cut software (Adobe Premiere Pro). Due to the processing time of the brain (300 to 400 ms) plus that of the computer (depends individually on the type and number of active processors!) the gaze overlay video is shifted in our case (quad core, 3.4 Giga-Hz) for one second in order to obtain synchronized images between gaze and the particular EEG epoch of 364 ms. For detailed offline documentation a movie was exported and analyzed image by image. Single images containing the gaze and corresponding EEG map (called an Enkephaloglyph [11]) were cut from the screen by a software tool available on all computers.

2.4. Statistics

EEG data from the first recording session before intake of the capsules are given as absolute numbers (μV^2). For explorative statistical evaluation the nonparametric sign test was used. For mathematical differentiation of the different mental loads the linear discriminant analysis according to Fischer was used. Results from the first three discriminant functions were projected into space (X, Y and Z coordinates), whereas results from the fourth to sixth discriminant functions were coded into red, green and blue colour, respectively, followed by an additive color mixture (so-called RGB-mode). In order to document statistically the different electric reaction of the brain to various cognitive and emotional loads, data from each part of the presentation were divided by the data obtained during fixation of the cross on the monitor (1 minute) at the beginning. Comparison of *Rhodiola* versus placebo was accomplished by evaluation of the second recording of the day one hour after intake. Data in the presence of placebo were set to 100% and electrophysiological changes produced by *Rhodiola* are depicted as %-changes thereof.

2.5. Extract

Extract from Rhodiola rosea was obtained from Swedish Herbal Institute, SE 31250 Vallberga, Sweden. Ethanol (70%) was used for extraction. Dr*ug Extraction Ratio was 2.5–5.0*: 1. One Capsule contained 200 mg of Rhodiola extract and 50 mg Maltodextrin.

3. Results

The combination of Eye-Tracking with Neurocode-Tracking (fast dynamic quantitative EEG mapping) provided a unique possibility to follow active brain processes during cognitive and emotional challenges in real time and with a time resolution of 364 ms. After synchronization of the Eye-Tracking gaze overlay film with the screen captured Neurocode-Tracking film one can follow single events in an up to now unknown manner. Representative enkephaloglyphs of 364 ms duration showing the relative distribution of electric power (maps were constructed by calculation of % of the median of power values of the different electrode positions for the corresponding frequency) are documented in Fig. 1 A, B and C. During the decision phase of the memory test a tremendous increase of frontal theta power is observed. Focusing on the bird spider right frontal delta power (red) and occipital alpha2 power (green) is seen. A scene of the horror trailer induced left occipital delta power, right frontal theta power and left temporal beta1 power.

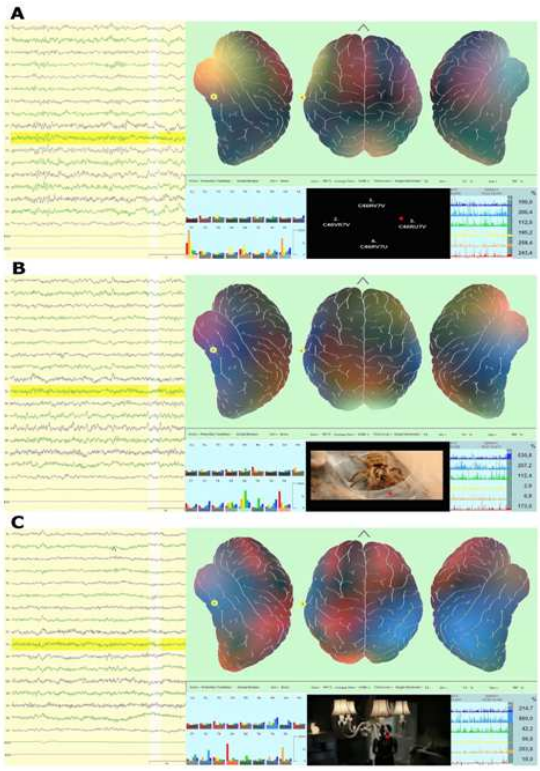

Figure 1. *Representative enkephaloglyphs obtained during performance of a memory task (A), watching an emotional picture (bird spider) (B) and watching a horror film trailer (C). Raw signal of EEG is depicted on the left side. Changes of the frequency content are shown as a map. Changes of electric power at different regions of the brain are documented in the lower middle as bar chart. Actual gaze of the subject is depicted by the red spot right besides the bar chart. Lower right corner: time line of frequency changes with numeric values of the last epoch of 364 ms for position T_3 (marked yellow at the raw signal on the left side).*

Before coming to the purpose of the study, namely to examine the effect of *Rhodiola rosea* extract containing capsules under various conditions of mental challenges, it is meaningful to show that these challenges are able to change the cortical pattern of electricity with respect to frequency content. For gaining information on this topic data were averaged over the particular time, as long as the challenge lasted. The absolute voltage values for the base line recording condition "fixation of a cross on the screen" are depicted in table 1.

Table 1. *Absolute spectral power values during the baseline given in μV^2. Med=Median; E=electrode positions; Pl=placebo, Ve=verum=Rhodiola.*

Table of Absolute Values												
Fixation Cross	Baseline											
	Delta		Theta		Alpha 1		Alpha 2		Beta 1		Beta 2	
E	Pl	Ve	Pl	Ve	Pl	Ve	Pl	Ve	Pl	Ve	Pl	Ve
Cz	2,06	2,09	1,50	1,48	1,08	1,09	0,83	0,92	1,41	1,30	1,27	1,31
Fz	2,82	2,38	2,11	2,04	1,89	1,92	1,56	1,37	1,74	1,75	1,43	1,45
F3	2,09	2,24	1,89	1,87	1,59	1,74	1,51	1,44	1,88	1,91	2,28	2,22
C3	1,29	1,06	1,01	0,79	0,85	0,83	1,07	0,87	1,61	1,81	1,30	1,61
P3	1,30	1,28	0,97	0,93	1,04	1,01	1,28	1,21	1,39	1,65	1,55	1,60
Pz	1,60	1,88	1,08	1,12	0,93	0,95	0,89	1,05	1,33	1,23	1,15	1,14
P4	1,41	1,58	1,06	1,07	1,17	1,20	1,48	1,26	1,55	1,43	1,45	1,56
C4	1,45	1,40	1,25	1,10	1,22	1,03	1,43	1,19	1,91	1,82	1,18	1,79
F4	2,50	2,47	2,05	1,92	1,75	1,85	1,54	1,36	1,75	1,78	1,74	2,51
F7	3,29	3,84	2,20	2,26	1,64	1,88	1,55	1,62	2,30	2,36	4,00	3,52
T3	3,14	2,56	2,27	1,79	1,89	1,72	2,15	2,22	3,73	3,30	3,43	4,41
T5	2,39	2,38	2,24	2,19	2,64	2,32	2,22	2,49	3,13	3,78	2,64	2,50
O1	3,07	2,74	2,34	2,47	1,98	1,80	2,03	1,91	2,95	2,54	2,87	2,68
O2	2,16	2,20	1,63	1,79	2,46	1,56	1,75	1,47	2,74	2,21	2,40	2,74
T6	1,99	1,84	1,72	1,65	1,96	1,73	2,21	2,20	2,25	2,25	2,18	2,67
T4	2,55	2,23	1,95	2,25	2,13	2,17	2,23	2,22	2,58	2,88	2,39	3,37
F8	3,82	3,17	2,35	2,44	2,01	2,00	1,78	1,88	2,19	2,13	3,42	3,23
Med	2,21	2,19	1,80	1,67	1,59	1,71	1,51	1,44	2,02	2,09	2,04	2,12

Comparable values were obtained for both baseline recordings. Electrode positions are labeled according to the international so-called 10/20-system [12].

As can be seen from table 1, median values for each frequency range do not differ much from each other at the two days of examination and so provide a comparable base for measuring *Rhodiola*-induced changes of spectral parameters under placebo and active conditions.

In order to eliminate basic changes of visual processing as such, data from each challenge were divided by the data collected during one-minute fixation of the cross on the monitor at the beginning of the presentation. The electric power of each frequency range is depicted in % of this basic visual processing.

3.1. Changes of Spectral Signatures during Cognitive and Emotional Challenges

Results for cognitive challenges are given in Fig. 2. Statistically significant increases of delta and theta power are observed for all three tests, but somewhat quantitatively different among each other. With respect to the Stroop test mainly frontal and occipital increases of delta and somewhat less theta power were found. Parietal delta power also increased in a statistically significant manner.

Within the temporal lobe, beta2 power increased also significantly. During performance of the memory test also frontal and occipital delta and theta power increased significantly. Largest increases of frontal and occipital delta and theta power were seen during a comparison of pictures in order to recognize small differences. In addition, this time these frequencies were also significantly higher in the temporal lobe.

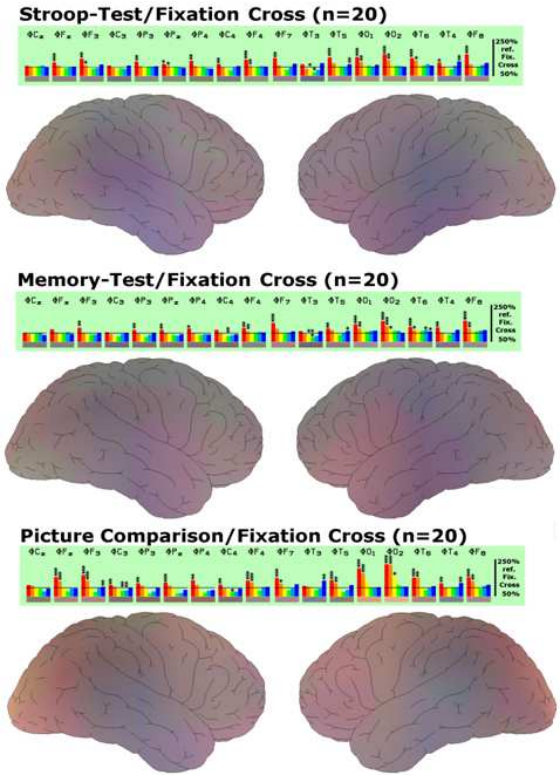

Figure 2. *Differences in electric power under various cognitive challenges to watching at the fixation cross as reference (%-change on the ordinate). Bar chart shows electric power changes within 6 frequency ranges: delta (red), theta (orange), alpha1 (yellow), alpha2 (green), beta1 (turquoise), beta2 (blue). *=p<0.05; **=p<0.01; ***=p<0.001.*

At electrode positions T_3 and T_4 higher beta2 power showed up. These slight differences between the different tasks were also visible when mapped according to the frequency content (s. "methods" for detail of map construction). Results are documented in Fig. 2.

Presentation of emotional pictures led to somewhat different results. Largest increases of delta and theta power emerged in the occipital lobe. No changes were seen in the left and right frontal lobe at electrode positions F_7 and F_8. However, slight elevations of mere delta power were seen in the middle frontal lobe at positions F_3, F_z and F_4. Finally, increases of beta2 power came up in the temporal lobe at T_4. Looking at an image of bird spider largest statistically significant increases were observed with respect to theta power even larger than delta power increases. Again, no changes at F_7 or F_8 happened. The most extensive increases of delta and theta power occurred when looking at an image taken from the TV series "Jungle Camp". Under this condition highest values emerged at frontal electrode positions F_7 and F_8 as well as occipitally (positions O_1 and O_2). Minor but also statistically significant increases of delta power were documented at the other frontal electrodes and also within the parietal lobe, which was not visible while looking at the other two pictures. The changes of electric power clearly were more pronounced while looking at the camp in comparison to the reaction to the other two pictures. Frequency changes are documented as bar chart and map in Fig. 3.

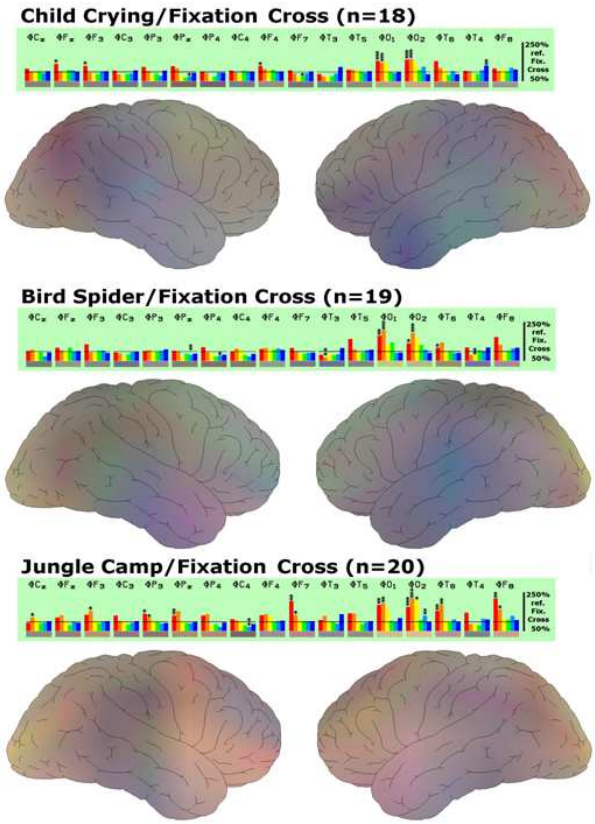

Figure 3. *Differences in electric power under various emotional challenges to watching at the fixation cross as reference (%-change on the ordinate). Bar chart shows electric power changes within 6 frequency ranges: delta (red), theta (orange), alpha1 (yellow), alpha2 (green), beta1 (turquoise), beta2 (blue). *=p<0.05; **=p<0.01; ***=p<0.001.*

Rather similar results were obtained when watching various films. Strongest reaction came up with looking at the horror trailer. In difference to the other films fronto-temporally statistically significant beta1 and beta2 increases became visible. Changes of electric power with respect to all frequencies are depicted in Fig. 4. Obviously, the more exciting the film the more delta and theta power develops in the occipital and frontal lobe concomitantly with increases in the parietal lobe as seen while watching the horror trailer.

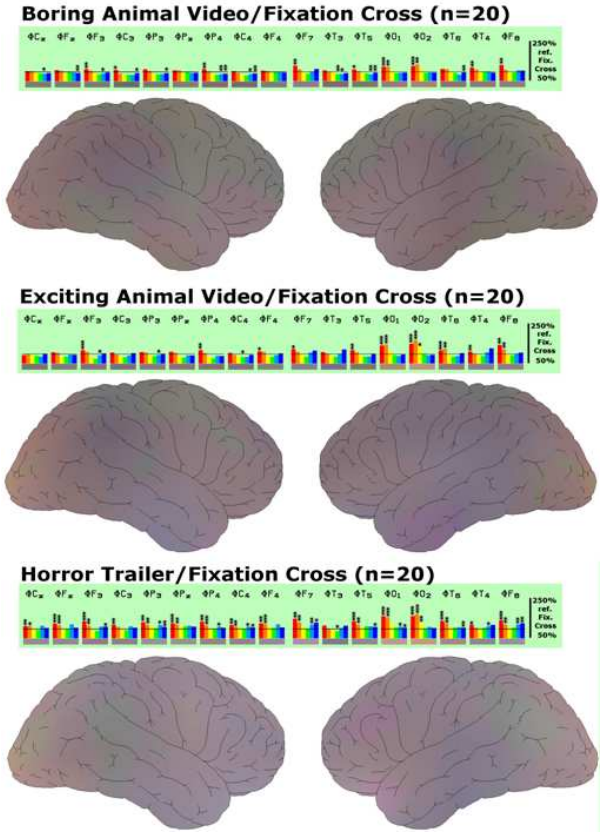

Figure 4. *Differences in electric power during watching of various films to watching at the fixation cross as reference (%-change on the ordinate). Bar chart shows electric power changes within 6 frequency ranges: delta (red), theta (orange), alpha1 (yellow), alpha2 (green), beta1 (turquoise), beta2 (blue). *=p<0.05; **=p<0.01; ***=p<0.001.*

3.2. Changes of Spectral Signatures during Cognitive and Emotional Challenges in the Presence of Rhodiola Extract Containing Capsules

After showing that different cognitive and emotional challenges induced different changes of the frequency pattern of electric brain activity, data were analyzed with respect to a possible action of *Rhodiola* extract containing capsules. Data were grouped according to the random plan and evaluated with respect to the measurement one hour after intake of the active and placebo capsules, respectively. Results from the active group were divided by the results from the placebo group and changes are given as % of placebo. With respect to cognitive challenges results for the action of Rhodiolaare depicted in Fig. 5.

During fixation of the cross on the monitor - thus without mental load - virtually no eminent changes were seen. During performance of the cognitive tests statistically significant increases of delta and theta power emerged. Also in common were increases of beta2 power in the left temporal lobe (T_3). With respect to the Stroop test a tendency of theta increase was seen in the right temporal lobe (T_4). During performance of the memory test statistically significant increases of frontal delta and theta power were documented accompanied by a tendency of increases of alpha2 power in the temporal lobe (T_3 and T_4; p=0.12).

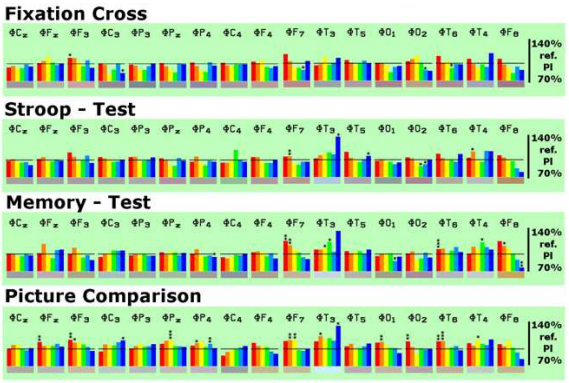

Figure 5. *Cognitive challenges: Bar chart documenting differences in frequency content between placebo intake and intake of the active ingredient. Rhodiola-induced change of electric power is given in % change with respect to placebo (100% represented by solid line) for each brain region and each of the 6 frequency ranges during three cognitive challenges. *=p<0.12; **=p<0.05; ***=p<0.002.*

Most prominent differences between placebo and active ingredient were observed during the comparison of two images and searching for slight differences between them. *Rhodiola*-induced increases of theta power were confined to the middle or left frontal brain and right temporal region. This cognitive task was the only one, where also increases of alpha1 spectral power emerged.

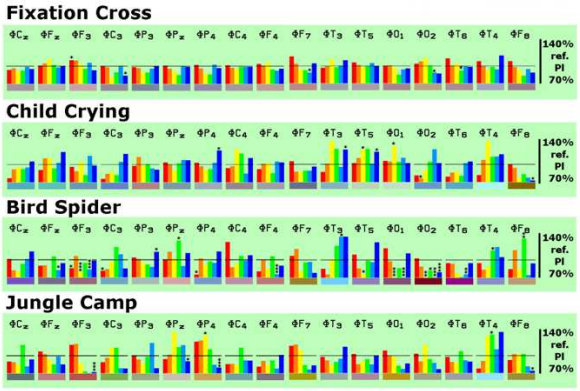

Figure 6. *Emotional challenges: Bar chart documenting differences in frequency content between placebo intake and intake of the active ingredient. Rhodiola-induced change of electric power is given in % change with respect to placebo (100% represented by solid line) for each brain region and each of the 6 frequency ranges during three emotional challenges. . *=p<0.12; **=p<0.05; ***=p<0.002.*

Completely different neurophysiological effects of *Rhodiola rosea* containing capsules were observed during emotional challenges. Results for looking at three emotional pictures are given in Fig. 6.

Looking at a crying child only a tendency of increases of alpha1 spectral power in the temporal lobe and occipital lobe was seen, whereas in some regions massive decreases of the slow frequencies were obvious (i.e. centrally at C_z and C_3 or temporally at T_6). There was also a tendency of beta increases, which nearly became statistically significant in the temporal lobe and parietal lobe. With respect to looking at the picture of the bird spider highly significant decreases of alpha1 and beta1 power in frontal and temporal regions emerged. Temporal beta2 increases did not reach statistical significance. Alpha2 power only increased at the right frontal brain in a significant manner.

Looking at the picture taken from "Jungle Camp" also revealed some significant differences between placebo and the active ingredient. A decrease of beta2 power was observed in general, but did not reach statistical significance everywhere. Decreases of beta2 power (F_3 and P_4) were highly statistically significant except for the electrode position T_4.

Finally, emotional film contents were looked at comparing placebo with *Rhodiola rosea* extract containing capsules. During watching a non-exciting animal film hardly any differences were detected. However, watching a very exciting scene (alligators hunting gnus) induced some statistically significant differences as documented in Fig. 7.

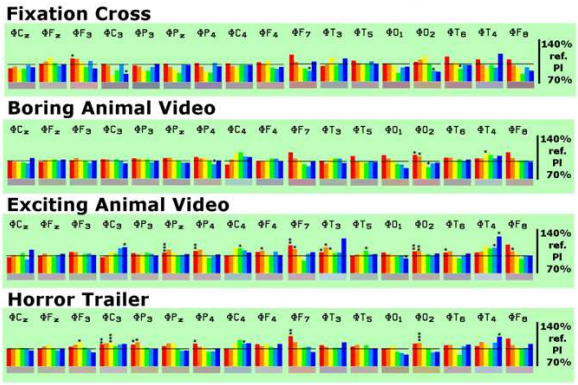

Figure 7. *Emotional film contents: Bar chart documenting differences in frequency content between placebo intake and intake of the active ingredient. Rhodiola-induced change of electric power is given in % change with respect to placebo (100% represented by solid line) for each brain region and each of the 6 frequency ranges during three emotional challenges. . *=p<0.12; **=p<0.05; ***=p<0.002.*

Higher values of delta and theta were seen in the frontal and occipital lobe as well as in the parietal lobe, where the highest statistical significance was reached. With respect to the horror trailer only marginal differences were detected, which consisted in a higher alpha1 spectral power at C_3 ($p<0.02$) and higher theta power at O_2 ($p<0.02$). The left frontal region showed statistically significant higher delta power.

Thus, time averaged electric brain patterns related to emotional loads were clearly influenced by the intake of

Rhodiola rosea containing capsules.

To sum it up, evaluation of spectral power values of the EEG in different brain regions revealed statistically significant differences between placebo and *Rhodiola rosea* extract containing capsules. However, assuming, that the complete pattern of spectral changes during a mental challenge accounts for the psychophysiological state of the subject, it would be nice to be able to compare the full pattern of 102 parameters (17 electrode positions x 6 frequency ranges). Exactly this was achieved by feeding the data into a discriminant analysis. Using this mathematical tool, differences between intake of placebo or active ingredient became visible. Fig. 8 documents the result of this analysis for each of the mental challenges. Part A depicts the result for cognitive loads, B for looking at pictures with emotional content and C for the recording during watching three films. The result obtained during the placebo condition is always linked to the particular verum condition to make comparison easier. As seen above, fixing the cross did not produce a large distance within the space coordinates for placebo and verum.

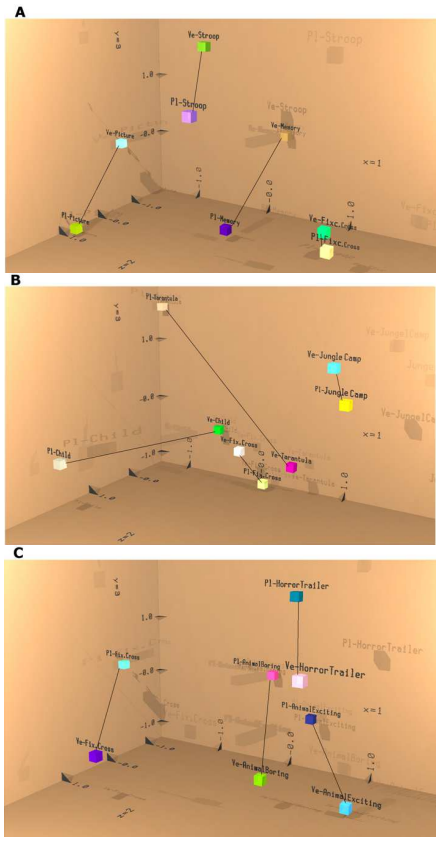

Figure 8.*Discriminant analysis showing changes of total electric power pattern in the presence of Rhodiola (Ve) or Placebo (Pl).Rhodiola and Placebo positions are always linked for better overview. Upper image A: performance of cognitive tests; middle image B: watching emotional pictures; lower image C: watching film clips. The bigger the distance, the larger the difference between placebo and Rhodiola rosea extract containing capsules (result from the first three discriminant functions are projected into space by x,y and z coordinates). Different color is also related to the result from the 4th to 6th discriminant function by using so-called RGB mode.*

From regarding all three different types of mental loads, clear statistically significant differences became visible and indicate that taking the active ingredient has changed the psychophysiological condition represented by spectral signatures within the different brain regions. Last not least no side effects have been reported by the subjects.

4. Discussion

Measurement and evaluation of the electric activity of the brain is regarded as a safe non-invasive methodology for assessment of cognitive performance and emotional states in human subjects. Neurophysiological changes are described using so-called surrogate parameters as published earlier [5,13,14].

The goal of the present study was to examine if the intake of 2 *Rhodiola rosea* extract containing capsules was able to change the spectral signature of electric brain activity in a different way than placebo. Electric brain activity is related to the psychophysiological state of subjects and can be quantified by frequency analysis of the electroencephalogram (EEG). Activity of electric circuits within defined brain areas changes according to different mental loads. Therefore three different types of mental challenge were used to find out if spectral patterns of the EEG react in a different way to the intake of *Rhodiola rosea* extract containing capsules or placebo. Differences within particular frequency ranges were taken as biomarkers for mental activation, visual perception or relaxation. In order to facilitate interpretation of bioelectric changes and to assure visual attention, an Eye-Tracking device was used concomitantly with the EEG recording (Neurocode-Tracking). This new combination of frequency-analyzed EEG with Eye-Tracking revealed for the first time that electric circuit activity changes dramatically from one period of 364 ms duration to the next one, dependent on a particular gaze. Surprisingly, focal increases of more than 2000 % were observed during single gazes at particular cognitive or emotional inputs with respect to single frequency ranges. This observation opens new aspects for interpretation of bioelectric activity during neurophysiological experiments [2].

However, for quantitative analysis of possible changes of bioelectric activity during different mental challenges data had to be averaged to give longer epochs according to the duration of the particular challenge. It was hoped that different cognitive and emotional challenges would produce different spectral signatures of brain electric activity. This was indeed the case, since statistically significant changes of electric power within particular frequency ranges were proven. These differences became especially obvious when basic visual processing represented by looking at a fixation cross was taken as reference and all other challenges were referred to it (calculation of the quotient between both).

These results were the precondition to examine the possible effects of the food supplement containing *Rhodiola rosea capsules*. Looking at the fixation cross did not reveal major

differences between the active ingredient and placebo despite some attenuation of spectral alpha power within the central and parietal lobe. Similar effects have been published in the presence of caffeine [15-17]. Three types of challenges have been presented: a) Stroop test, memory test and a picture comparison representative for cognitive loads, b) three images depicting a crying child, a bird spider and a picture taken from the TV series "Jungle Camp"for emotional challenge and c) a non-exciting and an exciting animal video followed by a horror trailer. In the presence of all three cognitive challenges further statistically significant increases of delta and theta power within the frontal brain were observed after intake of *Rhodiola rosea* extract containing capsules in comparison to placebo.

Exactly such increases during mental work have been reported already in 1995 [3].With respect to delta waves a relationship to cortical choline acetyltransferase was reported in the past [18]. This relation between delta waves and the cholinergic transmitter system was reported also for freely moving rats [19]. These results are in line with the view that lower delta in the relaxed state and higher delta during mental load are indicating higher wakefulness and better cognitive performance as reported earlier [20].

With respect to theta waves, it was reported that they increase during memory retrieval [21]. Also performance of visual memory tasks induced higher theta amplitudes in the right hemisphere compared to the left hemisphere [22].Theta power increases have also been observed during retrieval of lexical semantic information [23]. Furthermore, during performance of the memory test a tendency of alpha2 frequency increase was observed ($p< 0.12$). The only other challenge, where this happened, was the reaction to the picture showing abird spider. There is strong evidence from others that theta and alpha2 waves are related to memory [24].

Lower induction of delta and theta waves was observed during cognitive challenges in demented people [25] in comparison to healthy subjects. These authors also showed a high correlation between less induction of theta waves during mental performance and the degree of dementia. Suppressed production of theta waves was also reported for subjects suffering from mild cognitive impairment [26].Thus, high levels of theta waves during relaxation and less production during mental work are indicative for mild cognitive impairment [27]. This interpretation is also supported from published work [28]. From these facts it can safely be concluded that *Rhodiola rosea* extract containing capsules have shifted the psychophysiological state of the subjects to a higher degree of wakefulness and cognitive performance by induction of increases of delta and theta waves during mental challenges.

A difference between placebo and verum was also obvious during emotional challenges. Increases of beta power are in general observed during high tension. In the case of looking at the picture from the "Jungle Camp" beta activity was obviously attenuated in line with the view that a certain stress induced by the picture disappeared. Other spectral changes induced by verum with respect to emotional challenges have to await the recognition of further surrogate parameters in order to be interpreted. The combination of Neurocode-Tracking with Eye-Tracking might be of great help in this respect.

Finally, the results from discriminant analysis give also statistically valid information that *Rhodiola rosea* extract containing capsules have changed the spectral signature of electric brain activity in a different way than placebo did. In summary, intake of *Rhodiola rosea* extract containing capsules can be regarded as a safe booster of mental activity during cognitive and emotional challenges. It should be mentioned that also other authors already reported on improvement of cognitive performance after repetitive intake of *Rhodiola* extract in 120 subjects (e.g. [29,30]).

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