Effects of a *Rhodiola rosea* extract on mental resource allocation and attention: An event-related potential dual task study

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*Rhodiola rosea* extract is widely used to alleviate stress and improve cognition and mental resources. A total of 50 adult participants were treated with 2 × 200 mg *R. rosea* extract (Rosalin®, WS® 1,375) for 12 weeks and were subjected to a neuropsychological test battery as well as an event-related brain potential measurement in a dual task paradigm prior to administration, after 6 weeks and after 12 weeks. The study followed a single-arm open-label design. Reaction times improved for the attention network task (ANT), the Go/Nogo task, and the divided attention task. Moreover, the orienting effect and the executive effect in the ANT showed an improvement. The P3 component in a dual task paradigm was increased in amplitude. The results of this pilot study show an improvement of mental speed and moreover, suggest improved mental resources. As the current study is single-armed these findings need to be replicated in a double-blind placebo controlled study.

**KEYWORDS**
attention, dual task performance, event-related potentials, mental resource allocation, neuropsychology, *Rhodiola rosea*

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**INTRODUCTION**

1.1 *Rhodiola rosea*

*Rhodiola rosea* L., also variously named Rhodiola, Arctic Root, Golden Root, or Roseroot, is a member of the Crassulaceae family of plants (Farhath, Amarinder, & Brahm, 2005). It has been used extensively in European and Traditional Chinese Medicine which ascribes positive effects on blood circulation, mental functioning, and asthma to this plant (Ma et al., 2018). The active ingredients of the plant are thought to be rosavin, rhodiosin, salidroside, and p-tryosol (Zhang, Yu, & Zhang, 2006). Of the Rhodiola species, *R. rosea* L. has been extensively studied regarding its phytochemical and toxicological properties (Kurkin & Zapesochnaya, 1985).

Many studies suggest that *R. rosea* improves cognition (Al-Kuraishy, 2015; Jówko et al., 2018; Spasov, Wikman, Mandrikov, Mironova, & Neumoin, 2000), alleviates symptoms of mental stress (Anghelescu, Edwards, Seifritz, & Kasper, 2018; Cropley, Banks, & Boyle, 2015; Edwards, Heufelder, & Zimmerman, 2012; Lazarova, Petkov, & Markovska, 1986; Vasilova et al., 2017; Xia, Li, Wang, Wang, & Wang, 2016), and reduces mental fatigue (Ishaque, Shamseer, Bukutu, & Vohra, 2012; Kang, Hong, Kim, & Choi, 2015; Lekomtseva, Zhukova, & Wacker, 2017; Punja, Shamseer, Olson, & Vohra, 2014; Shevtsov, Zhulos, & Shervary, 2003). Moreover, Ma et al. (2018) in a recent meta-analysis of 36 rodent studies summarized...
effects on learning and memory reported a positive effect compared with placebo in a number of paradigms.

The mechanization of action of R. rosea is not entirely known. It appears to interfere with the HPA axis, to act on a number of molecular pathways and has been reported to modulate a number of markers including glutathione, NADH/NADPH, superoxide dismutase, malondialdehyde, NO/NOS, acetylcholine, caspase-3, tumor necrosis factor-α, nuclear factor xB, Bcl-2 and Bax protein (reviewed in Ma et al., 2018).

Rhodiola rosea has been proposed to be an adaptogen, a concept defined some 50 years ago which refers to substances “that increase resistance to a broad spectrum of harmful factors (stresors) of different physical, chemical, and biological natures.” (Brekhman & Dardymov, 1968; Wagner, Norr, & Winterhoff, 1994). Adaptogens are plant derived natural compounds of no specific substance class which have in common a presumed effect on the adaptability of an organism to stress (Panossian, ). In particular, they have been ascribed antifatigue effects during stress and have also been recommended for age-related disorders (Panossian & Gerbarg, 2016, Panossian & Wikman, 2009, P2010). Obviously, the term adaptogen is very loosely defined and thus leaves room for discussion. From a cognitive neuroscience standpoint, however, one would expect that substances with these properties should increase mental resources and thus enable a better performance in situations with multiple task demands. These situations are captured by so-called dual task paradigms.

1.2 | Dual task paradigm

The execution of two (or more) concurrent tasks is instrumental to the cognitive performance of a person and requires attentional control to allocate resources to each of the tasks (Fernandes & Moscovitch, 2000; Naveh-Benjamin, Craik, Guez, & Kreuger, 2005). Physiological aging but in particular neurodegenerative diseases such as Alzheimer’s or Parkinson’s disease have been associated with reduced cognitive resources and, moreover, an impairment to adequately control resource allocation (Baddeley, Baddeley, Bucks, & Wilcock, 2001; Balota & Faust, 2001; Logie, Cocchini, Della Sala, & Baddeley, 2004). While examination of DT has immense promise for the early detection of cognitive decline in these and other conditions (Baddeley et al., 2001), it has only rarely been used in clinical practice, because of difficulties in testing and lack of normative data. Examination of DT entails to have the participant perform two tasks separately and then together. The difference between the single task performance and the DT condition provides a measure for DT ability. We have previously used the DT methodology in conjunction with electrophysiology (Johannes et al., 2001), for example, to study fatigue (Schubert, Johannes et al., 1998).

To mimic mental stress associated with DT in everyday life, we employed a paradigm that required the parallel execution of a visual and an auditory task while participants’ electroencephalogram (EEG) was recorded to obtain event-related brain potentials (ERPs): These can be used as an index for mental resources required by a specific task (Hahn, Wild-Wall, & Falkenstein, 2011; Isreal, Chesney, Wickens, & Donchin, 1980; Isreal, Wickens, & Donchin, 1980; Kida et al., 2004; Kida, Kaneda, & Nishihira, 2012; Nash & Fernandez, 1996; Singhal, Doerfling, & Fowler, 2002; Singhal & Fowler, 2004). This experiment was repeated twice, once before and once after 12 weeks of treatment with 200 mg of R. rosea extract [Rosalin®, WS 1375®, (DER 1.5–5:1, extraction agent: ethanol 60%), Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany] twice daily.

We hypothesized that treatment with R. rosea should improve DT performance as well as the performance in a number of complex attention tasks [Go/Nogo, divided attention, attention network task (ANT)]. Moreover, we expected the P3 component, as index of mental resources (Hahn et al., 2011; Polich, 2007; Sirevaag, Kramer, Coles, & Donchin, 1989), to increase in amplitude. The study followed an open-label single-arm design, as it was conducted as a pilot study.

2 | METHODS

All procedures were approved by the local ethical review board. The study was registered with EudraCT (2010–024312-33).

2.1 | Participants

A total of 50 healthy adults (25 women, 25 men) between 30 and 50 years (mean age 41.2 ± 5.4 years), free of chronic illnesses and centrally acting medication were recruited through advertisements. They did not have a history of neurological or psychiatric diseases. Study participants were subjected to a general physical and neurological examination on the screening visit including vital signs, laboratory parameters, and neuropsychological measurements.

All participants worked with a computer for 27.0 ± 6.8 hours per week and reported symptoms of occasional visual and mental fatigue during their work (scores ≥ 5 on at least 3 questions by a questionnaire “Fatigue and Computer Work”).

2.2 | Study medication

Rhodiola rosea contains the cinnamoyl glycosides rosavin, rosin and rosarmin (the rosavins) which are thought to be the active ingredients beside salidrosides. The study medication WS® 1,375 was chosen as it is standardized to 3–8% rosavins. Rosavins have been demonstrated by electrophysiological studies to determine the biological activity of extracts (Dimpfel, Schombert, & Panossian, 2018).

2.3 | Trial organization

An open-label single-arm design with one group (verum only) was used. At the baseline visit (day 1), participants were examined for vital...
signs and underwent electrophysiological and neuropsychological measurements. They received the investigational medicinal product with the instruction to take one film-coated tablet of 200 mg R. rosea extract: (Rosalin®, WS® 1,375) twice daily (one before breakfast and one before lunch). All participants were enrolled in a single treatment group. At study midterm (week 6), and at study termination (week 12) the participants were examined again, underwent the same electrophysiological and neuropsychological tests as on screening visit.

During all visits the study center (baseline, weeks 6 and 12) as well as on weeks 3 and 9 by telephone interview, participants were asked about any noted adverse events (AEs) and any concomitant medication in order to assess safety of the study drug. In addition, blood was drawn for routine parameters including hemoglobin, RBC, WBC, platelet counts, creatinine, HbA1c, triglycerides, total bilirubin, cholesterol, TSH, ASAT, ALAT, γ-GT, prothrombin time, partial thromboplastin time, sodium, and calcium.

Due to the pilot character of the study, no differentiation in primary and secondary outcome variables was intended. Treatment effect outcome variables included neuropsychological and neurophysiological measurements.

2.4 | Neuropsychological measurements

2.4.1 | Attention network task

The ANT has been used extensively to assess different aspects of attention (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005; Fan, McCandliss, Sommer, Raz, & Posner, 2002; Gooding, Braun, & Studer, 2006). Participants view visual stimuli on a video screen that consist of a row of 5 visually presented horizontal black lines, with arrowheads pointing leftward or rightward. The central symbol is the relevant target stimulus and has to be responded to by a left index finger button press, if the arrowhead is pointing to the left, and by a right index finger button press, if the arrowhead is pointing to the right. This target symbol is flanked on either side by two arrows pointing either in the same direction (congruent condition), or in the opposite direction (incongruent condition), or by lines (neutral condition). Cue stimuli appear 400 ms before the target with four cue conditions occurring in a random order: (1) no-cue; participants are shown a cross which is the same as the first fixation for 100 ms; (2) central-cue, which is at the central fixation point; (3) double-cue, in which cues are presented on the two possible target locations simultaneously (both above and below the fixation point); and (4) spatial-cue, cue is presented right on the target location (either above, below the central fixation point). A session consists of a 24-trial practice block and three experimental blocks of trials. Each experimental block consists of 96 trials (4 warning levels × 2 target locations × 2 target directions × 3 congruency conditions, with 2 repetitions). Participants are instructed to focus on a centrally located fixation cross and to respond as fast and accurately as possible. Several different measures are obtained.

2.4.2 | Go/Nogo-test

The Go/Nogo-test is part of the “Testbatterie zur Aufmerksamkeitsprüfung” (“Battery of attentional tests”, TAP) (Zimmermann & Fimm, 2007), a widely used computerized battery of attention tests in Germany. It assesses the ability to react to specified target stimuli and—at the same time—to withhold reactions to similar nontarget (nogo) stimuli. The more difficult variant of this task was used which comprises the presentation of 5 square stimuli filled by different patterns, of which two are designated as target (go) stimuli and three as nontarget (nogo) stimuli. Reaction time and error rate were scored.

2.4.3 | Divided attention test

This test is also part of the TAP (Zimmermann & Fimm, 2007). It assesses the ability to divide one’s attention between two concurrent streams of stimuli. Thus, a dual task situation is created. A visual and an auditory task were presented concurrently. In the visual task the participant viewed a video screen on which several cross stimuli appear at different places simultaneously for a short time. The participant had to decide whether or not the crosses form a square. If yes, a button needed to be pressed. In the auditory task, a sequence of tones which can be either low or high were presented. Usually, low and high tones alternate. If either the high or the low tone are repeated, the participant should press a button. Reaction times for visual and auditory targets separately and overall number of errors were scored.

2.4.4 | Number connection test

The number connecting test (Oswald & Roth, 1987) is a language-free, timed test to assess the speed of cognitive function. Numbers from 1 to 90 are displayed on a letter-size sheet of article and have to be connected by the participant in their natural order starting at 1 and finishing at 90 as fast as possible by pencil lines. The time needed to connect all 90 numbers was scored on four versions of the task and the average time was calculated.

2.4.5 | Beck depression inventory II

The Beck depression inventory II (BDI-II; Hautzinger, Kühner, & Keller, 2006) is a 21-item measure designed to assess symptoms of depression such as sadness, guilt, loss of interest, social withdrawal, and suicidal ideation. The instrument assesses the patient’s mood and behavior over the previous 2 weeks, and can be used either as a screening tool or to assess response to treatment. Items are scored on a 0–3 scale, yielding a score range of 0–63 where higher scores indicate greater depression severity. According to Beck, Steer, and Brown (1996), scores in the range of 0–13 indicate minimal
2.4.6 | Recent perceived stress questionnaire

We used the 30-item German version recent perceived stress questionnaire (PSQ-R; Fliege et al., 2005; Kocalevent et al., 2007) as an instrument to assess subjectively experienced stress. The questionnaire yields seven different subscales, that is, harassment (with four items and a range from 4 to 16), overload (with four items and values from 4 to 16), irritability (with two items and a range from 2 to 8), lack of joy (with seven items and values from 7 to 28), fatigue (with four items and values from 4 to 16), worries (with five items and values from 4 to 16), and tension (with four items and values from 4 to 16). Participants need to indicate whether a statement describes their own situation accurately “almost never,” “sometimes,” “often,” or “usually.” The PSQ-R stress score was calculated as sum of all items for each different subscale and standardized with respect to a range between 0 and 1, by means of “(sum of all items - 30) / 90.”

2.4.7 | Event-related potential task

ERPs were recorded in a dual task setting combining a visual search task and an auditory target detection task (Figure 1). The visual search task consisted of stimulus arrays occurring in rapid succession onset asynchrony 1,000–2,000 ms, rectangular distribution. The stimulus arrays contained red and blue circles and red and blue squares distributed over the video screen at random locations. For any given stimulus array, the participant had to decide if it contained a red square. Fifty percent of the arrays indeed contained such a target item. Several runs were applied in which the number of items per screen was manipulated (5 or 12 items), yielding two different levels of task difficulty ERPs were recorded in a dual task setting combining a visual search task and an auditory target detection task. The visual search consisted of stimuli occurring in rapid succession 1,000–2,000 ms, rectangular distribution. These stimuli contained red and blue circles and red and blue squares. For any given stimulus, the participant had to decide if it contained a red square. Several runs were applied in which the number of items per screen was manipulated (5–12 items), thus yielding two levels of task difficulty.

Concurrently with the visual task, an auditory stimulus series comprising short syllable stimuli (/ba/, /pa/, /da/, /ga/ interval 800–1,600 ms, rectangular distribution) was presented. In any given run, one of the syllables was designated the target and had to be responded to by a button press. Visual targets had to be responded to by the right hand, auditory targets by the left hand.

We presented 180 nontarget and 180 target visual stimuli per difficulty level (720 stimuli altogether). Likewise, 300 auditory nontarget and 100 target stimuli were presented per difficulty level of the visual task.

During these tasks, the EEG was recorded from 29 tin electrodes mounted in an elastic cap and placed according to the international 10–20 system. The reference electrode was placed on the right mastoid process. All channels were amplified (bandpass 0.01–100 Hz) and digitalized at a rate of 250 points per second using a BrainAmp system (BrainProducts, Germany). Stimulus locked ERPs were averaged for epochs of 1,024 ms length, starting 100 ms prior to each stimulus presentation. To enable the off-line rejection of eye movement artefacts, horizontal and vertical electrooculograms were recorded using bipolar montages between electrodes placed on the outer canthi of both eyes (horizontal EOG) and between electrodes place below and above the left eye (vertical EOG). The analysis was performed using EEGLab (Delorme & Makeig, 2004) and ERPlab (Lopez-Calderon & Luck, 2014) software packages running on a MatLab surface.

First, eye-blink artefacts and other artefacts were identified and removed using independent component analysis (Hoffmann & Falkenstein, 2008; Hou et al., 2016). Furthermore, visual inspection of the resulting EEG traces was performed in order to detect and remove further artefacts. Averages were obtained per subject and condition. For display-purposes, grand averages across participants were obtained. Displayed ERP curves were filtered with a digital low pass filter of 12 Hz. The ERPs were quantified by mean amplitude measures within specified time-windows by computer. Time windows were set based on similar earlier studies and are given in the result section.

2.4.8 | Statistical analysis

After 0, 6, and 12 weeks of treatment, the absolute values and the absolute and relative intraindividual changes during the time courses...
of the outcome parameters (neuropsychological tests and ERPs in a dual task setting) were evaluated. Descriptive statistics were computed to describe the empirical distributions; two-sided 95% confidence intervals for the expected values and medians were calculated, and descriptive p-values of the appropriate statistical tests are presented. In order to additionally analyse not only main effects, but also interaction effects on the different outcome variables, repeated measurement analysis of variance was applied.

Analysis was primarily based on the full analysis set (FAS) including all subjects having received the study drug at least once and having at least one measurement during the treatment period. Missing values of some items or total scores during treatment period were replaced by the last observation carried forward method. Three subjects (6%) had to be excluded due to protocol deviations. The remaining 47 subjects were also analyzed in a per protocol set (PPS). As there were no relevant differences between the analyses of the PPS and FAS, we present results from the FAS.

3 | RESULTS

3.1 | Safety

During the treatment period 3/50 (6.0%) subjects experienced a total of three AEs, all of mild intensity. Only one AE (exanthema triggered by heat starting at day 80) was assessed to have a causal drug relationship (unlikely) to the investigational medicinal product. No subject discontinued the study due to an AE. No serious AEs occurred during the duration of the study. No clinically relevant changes regarding mean values of laboratory parameters were observed.

3.2 | Neuropsychological measures

The pertinent results of the neuropsychological measures are given in Table 1. For the ANT changes were observed in three of five outcome parameters, that is, total reaction time, orienting effect, and executive effect. The alerting effect and error rate remained unchanged. In particular, the executive effect, that is, the difference in reaction time between compatible and incompatible trials showed a marked reduction over the course of the study.

The Go/Nogo-test yielded a statistically significant reduction of reaction time over the course of the study while the already low error rate remained unchanged.

In the divided attention task, a significant improvement of reaction times to both, auditory and visual stimulus sequences, as well as a lower error rate were seen over the course of the study. The time to finish the number connection test was significantly decreased at week 12 compared with the beginning of the study.

The screening values of the BDI-II total score were low and revealed only a minimal burden with symptoms of depression. Still, the BDI-II total scores decreased significantly during the study course.

| Item | Screening | Week 6 | Week 12 | p-value |
|------|-----------|--------|---------|---------|
| Alerting effect (ms) | 34 ± 28 | 41 ± 23 | 38 ± 15 | .3443 |
| Orienting effect (ms) | 53 ± 36 | 46 ± 19 | 42 ± 18 | .0495 |
| Executive effect (ms) | 130 ± 71 | 101 ± 28 | 93 ± 29 | <.0001 |
| RT (ms) | 505 ± 78 | 483 ± 76 | 469 ± 63 | <.0001 |
| Error rate (%) | 10.9 ± 2.7 | 9.6 ± 1.1 | 9.6 ± 1.0 | <.0001 |
| RT (ms) | 552 ± 74 | 525 ± 63 | 526 ± 73 | .0081 |
| # errors | 0.4 ± 0.7 | 0.2 ± 0.6 | 0.5 ± 1.6 | .6863 |
| RT visual (ms) | 568 ± 95 | 552 ± 87 | 540 ± 70 | .0032 |
| RT auditory (ms) | 831 ± 115 | 824 ± 128 | 801 ± 101 | .0455 |
| # errors | 8.4 ± 9.5 | 5.2 ± 4.6 | 4.6 ± 2.9 | .0001 |
| Average time (s) | 64.4 ± 15.8 | 58.5 ± 11.3 | 56.5 ± 12.5 | <.0001 |
| Beck depression inventory II | | | |
| Total score | 3.9 ± 3.5 | 3.3 ± 4.7 | 2.4 ± 3.9 | .0008 |
| Perceived stress questionnaire revised (PSQ-R) | | | |
| Total score | 0.27 ± 0.14 | 0.22 ± 0.13 | 0.20 ± 0.14 | .0001 |

Note: mean ± standard deviation; p-value computed using the Wilcoxon signed rank test. Abbreviation: RT, reaction time.
Likewise, while perceived stress as determined with the PSQ-R was very low at the beginning of the study, it further decreased significantly over the course of the study.

### 3.3 Dual task paradigm

Results from the dual task paradigm are summarized in Table 2. There was a significant reaction time reduction over the course of the experiment for both modalities and levels of difficulty (i.e., visual search difficult, visual search easy, auditory combined with visual search difficult, auditory combined with visual search easy). Moreover, we obtained a typical dual task cost, which was reflected in shorter reaction times for the auditory task when it was combined with the easy visual search task. Dual task costs were significantly reduced over the course of the experiment. In addition, there was a highly significant reduction of errors over the course of the experiment in all conditions.

ERPs to both auditory and visual stimuli are shown in Figure 2. Following modality specific ERP components during the first 200 ms, both, visual and auditory targets, gave rise to a positive in the sense of a P3 component that was larger and earlier in the visual modality. There were clear amplitude modulations as a function of the measurement time-point. The P3 component showed a parietal maximum as illustrated by the topographic maps shown in Figure 3.

The P3 amplitude was quantified by a mean amplitude measure at the Pz electrode, the electrode showing the P3 component most prominently and consistently (Polich, 2007). The time window was 450–550 ms for the visual targets and 550–650 ms for the auditory targets. The analysis of the P3 amplitudes revealed a statistically significant increase of the P3 amplitude for visual targets under easy as well as difficult conditions (Table 2). The P3 component to the auditory targets, by contrast, showed no statistically significant change under medication.

As the P3 amplitude has been considered a measure of resource allocation and availability (Kida et al., 2004; Kranczioch & Dhinakaran, 2013), we computed the sum of auditory and visual P3 components separately for the easy and difficult conditions as a measure of available resources. There was a highly significant and clear increase of this aggregate measure over the course of the study (Table 2).

### 4 DISCUSSION

The current study set out to assess the possible effects of *R. rosea* extract on cognitive functions. As *R. rosea* is thought to modulate cognition (Al-Kuraishy, 2015; Jówko et al., 2018; Spasov et al., 2000) and to alleviate stress related symptoms (Anghelescu et al., 2018; Cropley et al., 2015; Edwards et al., 2012; Lazarova et al., 1986; Vasileva et al., 2017; Xia et al., 2016) and mental fatigue (Ishaque et al., 2012; Kang et al., 2015; Lekomtseva et al., 2017; Punja et al., 2014; Shevtsov et al., 2003), a dual task paradigm was implemented. Such paradigms tax the cognitive system, as they require the allocation of mental resources to two competing stimulus streams. They have also been shown to be particularly useful to identify diminished mental resources in beginning neurodegenerative diseases (Foley, Kaschel, Logie, & Della Sala, 2011; MacPherson, Parra, Moreno, Lopera, & Della Sala, 2012). Moreover, dual tasking is the rule rather than the exception in many everyday situations (Carriera, Rosen, Cheever, & Lima, 2015). In addition, we applied a number of attention tests that were able to identify changes in different aspects of attention.

| Item                                      | Screening | Week 6 | Week 12 | p-value       |
|-------------------------------------------|-----------|--------|---------|---------------|
| RT auditory (+ visual difficult) (ms)      | 762 ± 52  | 749 ± 52| 732 ± 44| <.0001        |
| RT auditory (+ visual easy) (ms)          | 643 ± 45  | 643 ± 66| 625 ± 38| .0103         |
| Dual task costs (ms)                      | 119 ± 51  | 106 ± 60| 107 ± 45| .041          |
| RT visual difficult (ms)                  | 691 ± 40  | 677 ± 42| 673 ± 42| <.0001        |
| RT visual easy (ms)                       | 473 ± 47  | 461 ± 45| 456 ± 48| <.0001        |
| # errors auditory (+ visual difficult)    | 31.2 ± 24.6| 16.9 ± 11.6| 14.5 ± 11.1| <.0001        |
| # errors auditory (+ visual easy)         | 30.7 ± 23.3| 16.2 ± 11.2| 14.0 ± 11.2| <.0001        |
| # errors, visual difficult                | 20.7 ± 14.5| 12.6 ± 11.1| 11.1 ± 9.0 | <.0001        |
| # errors, visual easy                     | 19.6 ± 12.6| 10.9 ± 6.7 | 10.3 ± 6.6 | <.0001        |
| P3 auditory target, (+ visual difficult) (μV) | 1.75 ± 2.6| 2.41 ± 2.2 | 2.18 ± 2.5 | .2718         |
| P3 auditory target, (+ visual easy) (μV)  | 1.75 ± 2.1| 1.86 ± 2.3| 1.73 ± 2.5 | .9570         |
| P3 visual difficult (μV)                  | 5.89 ± 3.7| 7.25 ± 3.9| 7.61 ± 3.6| <.0001        |
| P3 visual easy (μV)                       | 7.26 ± 3.8| 8.52 ± 3.3| 8.94 ± 3.9 | .0003         |
| P3 sum difficult (μV)                     | 7.64 ± 3.8| 9.66 ± 3.6| 9.79 ± 3.8 | <.0001        |
| P3 sum easy (μV)                          | 8.95 ± 3.9| 10.38 ± 3.9| 10.67 ± 3.5| <.0001        |

Note: Behavioral results and ERP measurements. mean ± standard deviation, p-value of the Wilcoxon signed rank test. Abbreviation: RT, reaction time.
With regard to the ANT, we found a marked reduction in overall reaction time from baseline to week 12 accompanied by a significant reduction in the executive effect, that is, the difference in reaction time to congruent and incongruent stimuli, a significant modulation of the orienting effect and a reduction in error rate. These effects were already present at week 6, albeit in a slightly reduced manner. The ANT assesses alerting, orienting, and executive attention (Fan et al., 2002). It has been shown that the indices for the three different functions (alerting, orienting, and executive) are largely uncorrelated (Fan et al., 2002). A decrease in reaction time was also seen in the Go/Nogo task as well as the divided attention task with a reduction in error rate clearly apparent in the latter task as well. Taken together, these findings suggest a beneficial effect of *R. rosea* on complex attention functions. As both reaction time and error rate improved, this cannot be attributed simply to a speed accuracy trade-off (Heitz, 2014).

The main findings from the dual task paradigm were:

a. a significant decrease in reaction times for all conditions
b. a significant decrease in dual task costs, determined as the difference in reaction time between the auditory reaction times when paired with the difficult visual task and the auditory reaction times when paired with the easy visual task
c. a significant decrease in error rates in all conditions
d. an significant increase of P3 amplitude in the visual tasks at week 6 and 12, and
e. an increase of the sum of auditory and visual P3 (taken as an index of processing resources).

Taking into account previous literature on dual task effects on ERPs (Kramer, Wickens, & Donchin, 1985; Hoffman, Houck, MacMillan, Simons, & Oatman, 1985; Schubert, Johannes, et al., 1998), this pattern of results is compatible with the view of increased processing resources at week 6 and 12 compared with baseline, as the P3 amplitude has been (among other factors) related to the available (respectively, invested) processing resources (Hahn et al., 2011; Polich, 2007) in dual task and other paradigms (Matthews, Garry, Frances, & Summers, 2006; Sirevaag et al., 1989).
With regard to previous results obtained for *R. rosea*, several studies have shown a positive effect on mental fatigue (Ishaque et al., 2012; Kang et al., 2015; Lekomtseva et al., 2017; Punja et al., 2014; Shevtsov et al., 2003). Recent evidence suggests that mental fatigue is related to depleted resources and, moreover, that "dual-task tests are most effective for inducing mental fatigue whilst maintaining arousal" (O'Keeffe, Hodder, & Lloyd, 2020). We concur with this assessment and would like to stress that it is critical to define mental fatigue stringently. Recently, Tran, Craig, Craig, Chai, and Nguyen (2020) defined mental fatigue "as a subjective wakefulness state in which they begin to feel mentally tired, drowsy and sleepy, experienced during periods of sustained demand in which a person is required to concentrate and focus their attention on a cognitive or behavioral task of some nature such as sitting for an examination, driving a vehicle or operating machinery" (see also, Craig, Tran, Wijesuriya, & Boord, 2006). Mental fatigue causes a decline of behavioral and mental functioning, reflected by an increased error rate (Lorist, 2008). This has been linked a decline of “top-down” resources resulting in reduced capacity to effectively attend to tasks (Lorist, 2008). For example, extended driving might lead to mental fatigue and thus to a reduced capacity to process incoming information necessary to drive safely (Boksem, Meijman, & Lorist, 2005).

Besides EEG-based measures other noninvasive electrophysiological methods may be used to infer the mode of actions of medicinal plant preparation. In particular, a recent series of studies using transcranial magnetic stimulation (TMS) has investigated corticospinal excitability and plasticity in humans. (Concerto et al., 2018; Mineo et al., 2017). A comprehensive protocol assessing motor threshold, recruitment of motor-evoked potentials, cortical silent period, short interval intracortical inhibition, and intracortical facilitation was used in placebo controlled studies of single intake of *Hypericum perforatum* (Concerto, Boo, et al., 2018), *Valeriana officinalis* (Mineo et al., 2017), and *R. rosea* (Concerto et al., 2018) while cortical plasticity was induced using transcranial direct current stimulation (tDCS). The main finding in the R. rosea study was that in the verum condition cathodal tDCS induced Long-term depression-like plasticity was prevented, while no effect was found on cortical excitability (Concerto, Infortuna, et al., 2018). As TMS measures have been used to assess physical fatigue, for example, induced by walking, in multiple sclerosis (Schubert, Wohlfarth, Rollnik, & Dengler, 1998), it seems plausible to combine TMS/tDCS protocols and ERP-based assessments to assess the effect of *R. rosea* on both, physical and mental fatigue.

Other phytomedicines such as *Ginkgo biloba*, which is widely prescribed in Europe, for example, one recent study assessed a number of cognitive control functions (cognitive set-switching, maintenance of task-relevant information in the face of interfering stimuli; response inhibition and prospective memory) in elderly nondemented participants (Beck et al., 2016). These control functions critically depend on mental resources. Using a functional imaging approach the authors found improved cognitive flexibility on the behavioral level without changes in brain activation, which was interpreted to indicate increased processing efficiency. We suggest that a dual task approach might be particularly suited to compare the effects of different pharmacological interventions on mental resources.

### 4.1 Limitations

The current study was conducted as an open-label trial. While there were marked improvements in reaction time in the different tests (ANT; divided attention; Go/Nogo task; dual task paradigm) as well as the reaction time derived measures (e.g., alerting, orienting and executive effect in the ANT and the dual task costs in the dual tasks paradigm), the missing placebo control condition raises the question whether these effect might reflect learning or training effects. With regard to the ANT a number of papers have been published assessing test–retest-reliability and learning effects (Ishigami & Klein, 2010; MacLeod et al., 2010; Ta, 2013).

For example, Ta (2013) examined 55 healthy participants twice with the ANT within 7 months and found the means of the overall reaction time, alerting effect, and orienting effect very stable. Only the executive effect became smaller at retest. With regard to the tests divided attention and Go/Nogo Bühner et al. (2006) published an investigation which required healthy participants to repeat these test four times with only short breaks between the test runs and found no significant improvement of the Divided Attention task. For the Go/Nogo task the mean RT of the group was 495 ms for the first session and 480 ms for the third session. We would assume that a training effect should be smaller, if test sessions are spaced apart by 6 weeks (as in the current study) rather than a few minutes (as in the Bühner et al., 2006, study). We thus conclude that the marked behavioral effects in the current study are unlikely to be solely due to training effects.

With regard to the P3 component, a number of investigations have addressed test–retest reliability and learning effects. For example, Lew, Gray, and Poole (2007) assessed the stability of the auditory P3 component obtained in an oddball experiment with test sessions spaced 2 days to 2 months apart. They found a high reliability and the overall amplitude change between the two sessions was 0.28 μV (see also Huffmeijer, Bakermans-Kranenburg, Alink, & van Ijzendoorn, 2014).

The current study had a treatment time of 12 weeks. It might well be that a longer treatment time would have led to more stable effects but an extended treatment period was not feasible in the current study.

### 5 Conclusions

The current single-arm study set out to measure the effects of a 12 week treatment with *R. rosea* extract WS® 1,375 and found indications for a beneficial effect on performance in the sense of an improved reaction time and decreased error rate in several tasks. Moreover, the P3 component in a dual task paradigm was increased in amplitude suggesting an increase in available processing resources.
These encouraging findings need to be substantiated by a double-blind placebo-controlled study. Moreover, we propose that the dual-task methodology is excellently suited to assess mental fatigue and thus any possible beneficiary effects of *R. rosea* on mental resources.

**CONFLICT OF INTEREST**

We wish to draw the attention of the Editor to the following facts which may be considered as potential conflicts of interest and to significant financial contributions to this work: AD is an employee of the sponsor of the study, Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany).

**AUTHOR CONTRIBUTIONS**

TFM, GR, MH and AD designed the study. TV performed the experiments. TV, MH and TFM performed the analyses. All authors discussed the results and contributed to the interpretation. TV and TFM wrote the article. All authors critically revised the manuscript.

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