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Lack of interaction between concurrent caffeine and mobile phone exposure on visual target detection: An ERP study

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ABSTRACT

Background: Caffeine affects information processing by acting predominantly on cortical activation, arousal and attention. Millions consume caffeine and simultaneously use their mobile phone (MP) during everyday activities. However, it is not known whether and how MP-emitted electromagnetic fields (EMFs) can modulate known psychoactive effects of caffeine. Here we investigated behavioral and neural correlates of caffeine and simultaneous MP exposure in a third generation (3G) Universal Mobile Telecommunication System (UMTS) signal modulation scheme.

Methods: We recorded electroencephalography (EEG) and event related potentials (ERP) in an oddball paradigm to frequent standard ($p = 0.8$) and rare target ($p = 0.2$) stimuli in a placebo controlled, double blind, within-subject protocol in four experimental sessions: 1) no caffeine and no MP, 2) caffeine only, 3) MP only, and 4) caffeine and MP. The subjects' task was to discriminate between standard and target stimuli and respond to the latter by pressing a button while reaction time (RT) and EEG were recorded. To provide a complete analysis of any possible caffeine and/or MP treatment effects that may have occurred, we analyzed the P300 ERP wave using four different ERP measures: 1) peak latency, 2) peak amplitude, 3) 50% fractional area latency (FAL) and 4) area under the curve (AUC).

Results: Caffeine significantly shortened RT and decreased AUC of the P300 component compared to the control or the UMTS MP alone conditions. However, no effects were observed on RT or P300 in the UMTS MP exposure sessions, neither alone nor in combination with caffeine.

Conclusion: Overall, the present results did not demonstrate any interactive or synergistic effects of caffeine and UMTS MP like EMF exposure on basic neural or cognitive measures. However, we found that caffeine consistently enhanced behavioral and ERP measures of visual target detection, showing that present results were obtained using a pharmacologically validated, consistent and replicable methodology.

1. Introduction

Caffeine is one of the most widely consumed stimulant of the central nervous system with known behavioral and neurophysiological effects (Fredholm et al., 1999; Lorist and Tops, 2003; Tieges et al., 2004, 2006; Barry et al., 2007; Brunyé et al., 2010a, 2010b; Snel and Lorist, 2011). The effects of caffeine are thought to result from its inhibitory action on adenosinergic neurotransmission (Fredholm et al., 1999), enhancing vigility. Caffeine also exerts indirect effects on Ca^{2+} channels (Dunwiddie and Masino, 2001), which is thought to play important role in processes underlying learning and memory via plasticity (Lynch, 2004). Furthermore, several studies showed that radio-frequency (RF) electromagnetic fields (EMFs), too, may also modify Ca^{2+} related processes in biological systems. For example, EMFs have been reported to significantly increase Ca^{2+} efflux in chick brain samples (Bawin and Adey, 1976; Blackman et al., 1980, 1985, 1991) and in monolayer cultures of human neuroblastoma (Dutta et al., 1984). In addition, in the past few years, the widespread use of mobile phones (MP) raised the concern of possible health hazards due to continuously increasing exposure to various EMFs in the population worldwide. Thus the EMF research interest turned into a hot topic in the

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bioelectromagnetic scientific area (Kwon and Hämäläinen, 2011). Although several studies investigated the effects of different types of MPs on human cognitive function and brain physiology (Stefanics et al., 2007; Bak et al., 2010; Croft et al., 2010; Kwon and Hämäläinen, 2011; Schmid et al., 2012; Leung et al., 2011; Trunk et al., 2013), existing evidence on MP EMF-related effects on the human cognitive functions are not yet convergent. Studies reporting the effects of MP EMF on cognitive functions usually elude replication (Kwon and Hämäläinen, 2011). Generally, the inconsistencies in the MP EMF-related results are thought to be caused by differences in study designs applied by the different research groups (Kwon and Hämäläinen, 2011).

Both caffeine and EMFs have been reported to separately influence the Ca^{2+} homeostasis of the living cells. Here we set out to investigate possible interactive effects of simultaneous caffeine and EMF exposure via Ca^{2+} related processes on human visual cognitive functions. In the present study we focused on RT and the P300 ERP component; the latter being a positive deflection observed in late cognitive ERP at about 300–400 ms after stimulus onset (Duncan et al., 2009) being usually elicited in 'oddball' paradigms where subjects actively detect and respond to rare target stimuli embedded in a series of frequent unattended standard stimuli (Picton, 1992). It is known to be affected by various factors such as the actual arousal state, fatigue, age or drugs (Duncan et al., 2009). Furthermore, P300 is known to be sensitive to effects of caffeine as pharmacological manipulation (Lorist and Tops, 2003). Thus, in the present study caffeine exposure also served as a validating (positive control) protocol for hypothesized EMF effects.

Although several studies investigated the effects of either caffeine or MP exposure on human information processing, up to date, there are no comprehensive studies available about the possible acute combined action of simultaneous MP EMF and intraoral caffeine exposures on human information processing. Therefore, the main purpose of the present study was to investigate the combined effects of caffeine and acute UMTS MP-like exposures on vigilance measured by RT and brain electrophysiology measured by the P300 potential in healthy young human volunteers. We hypothesized that UMTS exposure may exert combined or even superadditive (synergistic) effects on caffeine-induced facilitation of cognitive function. We applied a double-blind placebo-controlled and crossover experimental design. Besides the traditional analysis of average ERP waveforms, single-trial analysis methods were also applied to detect possible acute effects that might have occurred during the exposure itself.

2. Materials and methods

2.1. Subjects

Twenty-five young, right-handed, and healthy university students (9 female, age from 18 to 38 years, mean age = 21.07, SD = 3.58 years) volunteered for the study. Because the half-life of caffeine in the human body is reduced by 30 to 50% in smokers compared to non-smokers (Fredholm et al., 1999), only nonsmoker volunteers were enrolled. Participants were asked to abstain from all kinds of caffeine- and alcohol-containing substances for at least 10 to max. 24 h prior to each session. All subjects gave their written informed consent after the nature of the experiment had been fully explained. The protocol of the study was approved by the Ethical Committee of the University of Pécs. Recording sessions were carried out in the Electrophysiological Laboratory of the Department of Experimental Neurobiology, University of Pécs, Hungary.

2.2. Quantitative determination of caffeine concentration in saliva samples

Two saliva samples were taken from each participant: one at the beginning and one at the end of each session (four sessions by 2 samples, altogether 16 samples per participant). Salivary caffeine concentrations were determined by high-performance liquid chromatography (HPLC), as it is considered to be a reliable and sensitive method for identification and confirmation of caffeine in biological samples from variable sources. For details about the HPLC analysis see Supplementary_Data_1.

2.3. UMTS exposure device

The exposure device was identical to the one used in previous experiments in the EMF NEAR project in our research group and elsewhere (Stefanics et al., 2008; Parazzini et al., 2009; Trunk et al., 2013). UMTS exposure was administered using a standard Nokia 6650 MP and its RF source was controlled via an external software [Phoenix Service Software (v. 2005/44_4_120; Nokia, Espoo, Finland)]. The MP was connected to an external patch antenna, which was mounted on a plastic headset (Fig. 1). The peak specific absorption rate (SAR) in brain tissue-equivalent liquid was 1.75 W/kg or 0.73 W/kg averaged on 1 g or 10 g liquid, respectively, at 2 cm depth from the shell surface of the phantom. The SAR values corresponded to the position of the inner ear region and met the limit of public exposure to RF requested by the 1999/519/EC Recommendation (EU, 1999). The exposure limit of the localized emitted power was 2 W/kg as proposed by the International Commission of Non-Ionizing Radiation Protection (ICNIRP). For details on the exposure device and conditions, see Supplementary_Data_2.

2.4. EEG recording

EEG was recorded with a 32-channel BrainAmp amplifier (Brain Products GmbH, München, Germany) using 30 Ag/AgCl electrodes mounted on an elastic cap (Easycap, Munich, Germany) according to the International 10–20 system. The nose served as reference and the forehead as ground. On-line band-pass filter between 0.016 Hz and 450 Hz with an additional 50 Hz notch filter were used. Raw data were digitized at 1 kHz sampling rate with 16 bit precision. For off-line artifact rejection electro-oculogram (EOG) was recorded from an additional electrode placed below the right external canthus. The impedance threshold at the beginning of each session was set under 5 kΩ for all electrodes. At the beginning of each session, subjects were asked to keep their head as still as possible and their eye movements at the minimum for the duration of the recording sessions.

2.5. Caffeine treatment

Gelatin capsules containing caffeine or glucose (placebo) were packed in hard gelatin capsules and were administered to the volunteers in each session. For caffeine treatment 5, 10, 20, and 100 mg caffeine-filled capsules were used to enable precise calculation of the chosen dose of 3 mg/kg. For placebo treatment, glucose filled gelatin capsules were used. All capsules were taken with 200 ml still mineral water. Placebo capsules contained less than 0.5 g glucose per capsule without any additional substance. Identical (white) capsules were used for each treatment. To avoid possible influences caused by subjective bias on the number of capsules taken, volunteers received the same amount of capsules in the control (placebo) sessions as in the caffeine sessions.

2.6. Stimuli and procedure

In a double blind, crossover design volunteers took part in four experimental sessions, each corresponding to one of the four exposure conditions: 1) Control — placebo caffeine & sham UMTS, 2) UMTS alone — placebo caffeine & genuine UMTS, 3) Caffeine alone — genuine caffeine & sham UMTS, and 4) Combined — genuine caffeine & genuine UMTS) with a minimum two and maximum seven days between sessions.

At the beginning of each session, the first saliva sample was taken. Thereafter, subjects received either caffeine or placebo capsules. EEG experiments started at 45 min after caffeine or placebo ingestion and

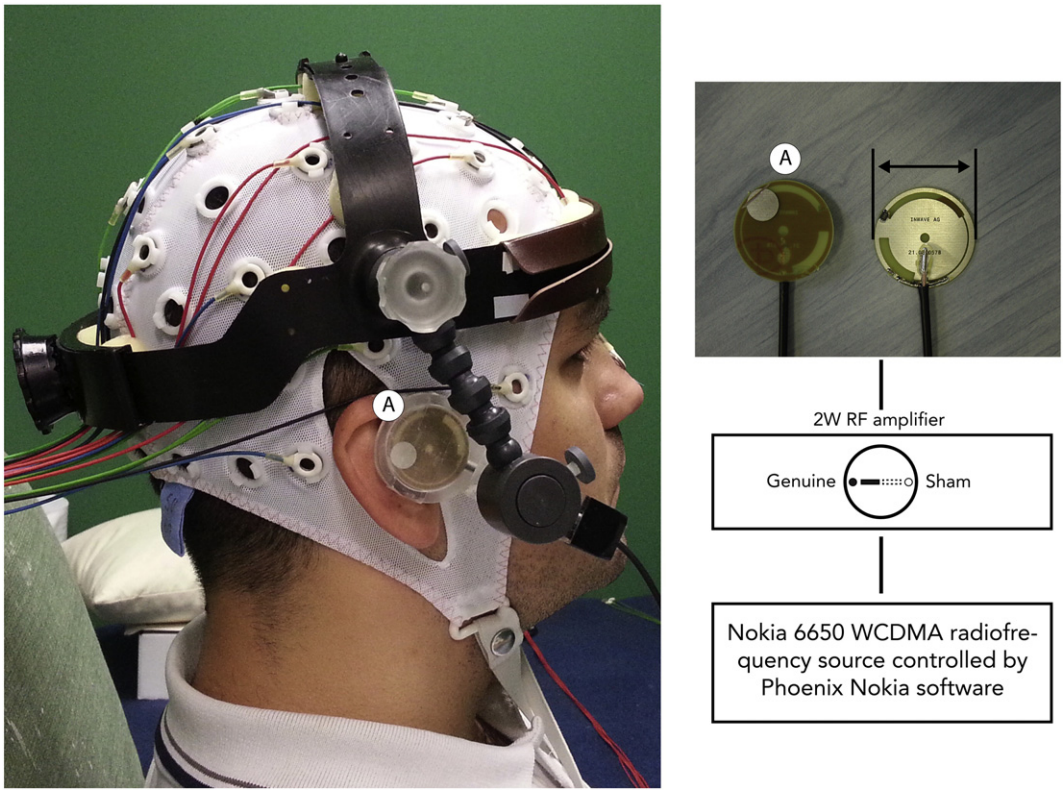

Fig. 1. During the whole EEG recording session the patch antenna was unilaterally placed at a distance of 4 to 5 mm from the right ear above the tragus, mimicking the most frequent normal position of MP in use as reported by the subjects. The phone was connected to a 2 W RF amplifier and controlled by Phoenix Nokia software.

lasted approx. 20 min. We choose this period for the experiments because available pharmacokinetic data indicates that peak caffeine concentration is reached between 15 and 120 min after intake (Fredholm et al., 1999). Finally, at the end of each session, a second saliva sample was taken.

A plastic antenna holed was used to mount the exposure device mimicking the position of a hand-held MP during conversation. The subjects' head was exposed to either genuine or sham MP exposure only in the Exposure Block (Fig. 1). To avoid possible interference with circadian regulation effects, each participant performed both sessions (genuine and sham) at the same time of the day with balanced number of subjects in each 2-hour recording session between 8 a.m. and 2 p.m.

In the visual oddball paradigm simple geometrical shapes were presented to the subjects on a computer screen in the center of the visual field subtending 5° both in vertical and horizontal directions (Fig. 2). A square served as the frequent standard ($p = 0.8$) and a circle as the rare target ($p = 0.2$) stimulus. The subjects' task was to press a button when a target was detected, while reaction time (RT) and EEG were recorded. Each recording session consisted of three consecutive recording blocks: 1) a block of 2.5 min preceded the exposure (Pre), followed by 2) a recording block of 15 min during exposure (Exposure), and 3) a 2.5 min post exposure block (Post) with no breaks in between blocks (Fig. 2). In each session, a total of 800 stimuli were clustered into 80 micro-sequences. The Pre/Post blocks contained 10 sequences each, and the Exposure block 60 micro-sequences.

3. Data analysis

Reaction time and EEG data were analyzed off-line in Matlab (MathWorks, Natick, MA) using built-in and self-developed scripts, as well as the freeware EEGLAB toolbox (Delorme and Makeig, 2004). Based on the well-known scalp distribution of the visual P300 ERP (Duncan et al., 2009), data from parietal and occipital electrodes (P3, P4, O1, O2, P7, P8, Pz, Cp1, Cp2, Cp5, Cp6) were selected for the analysis (Fig. 3A). To test the possible laterality and treatment interaction on the P300, electrode sites were divided into two regions of interests (ROIs) (Left ROI: P3, O1, P7, Cp1, Cp5; Right ROI: P4, O2, P8, Cp2, Cp6) corresponding to their position on the scalp (Fig. 3B). Mean ERPs across electrodes were calculated within each ROI.

To assess the potential possible interaction of caffeine and UMTS MP exposure on RT and P300 measures, we adopted an additive analysis model previously applied by several studies (Giard and Peronnet, 1999; Molholm et al., 2002; Boll and Berti, 2009) and used the following formula:

$$[\text{Caffeine–Control}] + [\text{UMTS–Control}] = \text{Combined–Control}.$$

Hereafter, "[Caffeine − Control] + [UMTS − Control]" and "Combined − Control" are referred to as 'sum' and 'simultaneous' data, respectively. We hypothesized that violation of the linear additivity of the analyzed RT or ERP measures would indicate synergistic interactions. This hypothesis was tested on both RT and P300 measures as described later.

Where applicable, data were further analyzed by Tukey's honestly significant difference (HSD) post-hoc tests. The null hypothesis was rejected at a significance level of 0.05 (alpha).

3.1. Reaction time

Behavioral responses to targets occurring between 200 ms and 1000 ms post-stimulus were accepted as hits (Ruijter et al., 2000; Boksem et al., 2005). Responses outside this interval, or lack of responses were considered as errors (omission and commission errors altogether).

3.1.1. Pre vs. Post blocks

In the Pre vs. Post analysis the maximum acceptable commission or omission error rates were 20% altogether (10% = two errors in the Pre

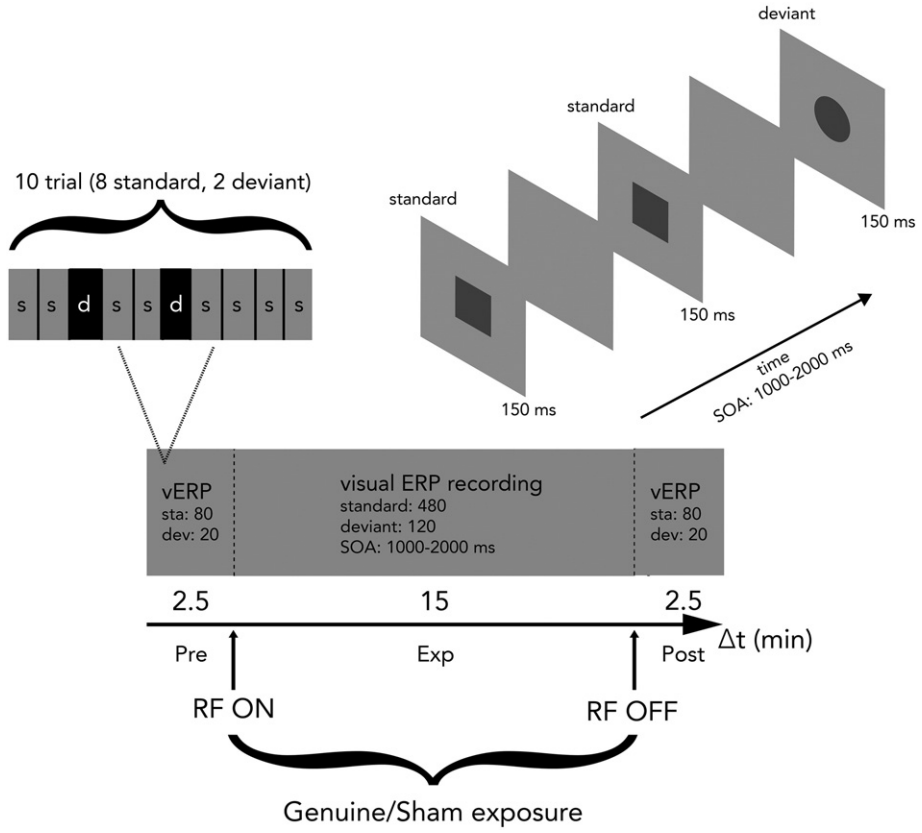

Fig. 2. Schematic illustration of the experimental design. During task performance, dark gray squares were presented as frequent standard ($p = 0.8$) and circles as rare deviant ($p = 0.2$) stimuli on a light gray background. In each session, a total of 800 stimuli were presented in a pseudo-random order. The total stimulus sequence was divided into 80 micro-sequences, each containing 8 standard and 2 deviant stimuli. Each recording session consisted of three consecutive recording blocks (Pre-exposure (Pre), Exposure (Exp), Post-exposure (Post)). The subjects' head was exposed to either genuine or sham MP exposure only in the Exp blocks.

and 10% = two errors in the Post block, respectively). Due to high error rates or data loss, data from 4 subjects were excluded from further analysis. The final sample comprised of 21 subjects. The Pre vs. Post block effects on RT were analyzed with two-way repeated measures analyses of variance (rANOVA) of Block (Pre vs. Post) × Session (Control vs. UMTS vs. Caffeine vs. Combined).

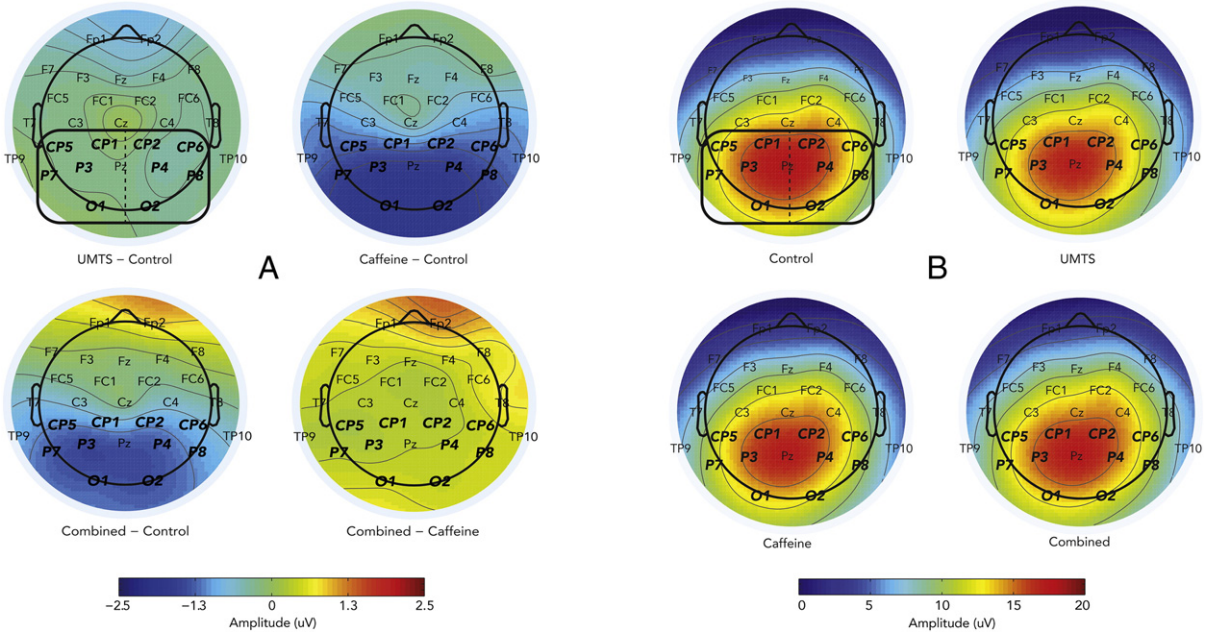

Fig. 3. A: Scalp topographic maps of ERP difference waves (UMTS minus Control, Caffeine minus Control, Combined minus Control and Combined minus Caffeine). Colors represent mean amplitudes from 400 ms to 700 ms after the onset of the stimuli. B: Scalp topographic maps of P300 in each treatment. Colors represent P300 amplitudes of each electrode site. Region of interests is marked with black rectangle. ROI was divided into two symmetrical parts (left: P3, O1, P7, Cp1, Cp5; right: P4, O2, P8, Cp2, Cp6) to test the possible laterality effects. Note that the dotted line was used as a separate sign between left and right analyzed side.

Furthermore, the possible after-effects of the UMTS MP exposure were tested in the Post exposure block with one-way rANOVA of Treatment (Control vs. UMTS vs. Caffeine vs. Combined). One-way rANOVA was applied on the additive model in the Post block. One out of 25 subjects was excluded from these analyses due to data loss.

3.1.2. Exposure block

We performed two different statistical analyses on the data of the Exposure block. In both analyses one-way rANVOA was used to test possible interactions of caffeine and UMTS MP exposure on the RT applying the summative model. The maximum number of acceptable target errors was 10% in each test. Due to high error rates or data loss, two subjects' data were excluded from the analyses. Thus, the final sample for Exposure block comprised of 23 subjects.

First, we tested the overall treatment effect on RT in the Exposure block by comparing RTs during the whole block. In this analysis the possible accepted target number was between 108 and 120. In the first analysis one-way rANOVA of *Treatment* (Control vs. UMTS vs. Caffeine vs. Combined) was applied. Second, to investigate possible short-term effects during exposure, we divided the Exposure block into six equally long consecutive sub-blocks (named as 'segmented Exposure' blocks). Since stimuli were presented in pseudo-randomized micro-sequences, the minimum number of accepted target trials in each sub-block was 18 (out of 20). Possible sub-block effects were tested by Pearson's correlations. We applied two-way rANOVA of *Sub-block* (1st vs. 2nd vs. 3rd vs. 4th vs. 5th vs. 6th) × *Treatment* (Control vs. UMTS vs. Caffeine vs. Combined).

3.2. Event related potentials

The continuous EEG data were off-line band-pass filtered between 0.5 Hz and 30 Hz using a zero phase-shift filter (filtfilt.m, Matlab built-in script). From the continuous EEG data epochs from 100 ms before to 800 ms after stimulus onset were extracted. Trials exceeding ± 100 μV amplitude were rejected from further analysis. Artifact-free ERP waveforms of the four experimental sessions were pooled together to calculate grand average ERP waveforms, which were used to define amplitude measurement intervals in each block at all analyzed electrodes. Time windows defined for amplitude and peak latency measurements are shown in Supplementary_Data_3.

Four indices of the P300 ERP component were analyzed. First, we tested the possible treatment effects with conventional mean amplitude and peak latency analyses for better comparability of the results showed in previous studies. We also computed area-based measures, namely fractional area latency (FAL) and area under the curve (AUC) (Luck, 2005). The 50% FAL of the ERP gives a special latency value that divides the AUC in the given time range into two equal fractions. The FAL method is less affected by noise or latency-jitter than that of peak-based measures, thus it is more advantageous in single trial analysis. Furthermore, the FAL method is more useful to measure the accurate timing of the late ERP components (Luck, 2005). Similar to the FAL the AUC analysis also provides distinctive advantages over mean amplitude and peak latency analysis methods as AUC is also less sensitive to high frequency noise and in addition, it reflects the shape of the P300, which is ignored by the conventional mean amplitude-based analysis. In AUC analysis the area was calculated by the trapezoidal rule in the given time range. To investigate any possible treatment effects even more accurately we characterized P300 component through two different separated time windows (Kreher et al., 2008; Guillaume et al., 2009; Ditman et al., 2011). Data were selected from 245 ms to 400 ms (hereafter early AUC) and 400 ms to 700 ms (hereafter late AUC) after stimulus onset, which corresponds to the upslope and the downslope of the grand-average P300, respectively (Fig. 4). We believe that, by applying the above described four different analysis methods, any potential single or combined treatment effects would be reliably tested and evaluated.

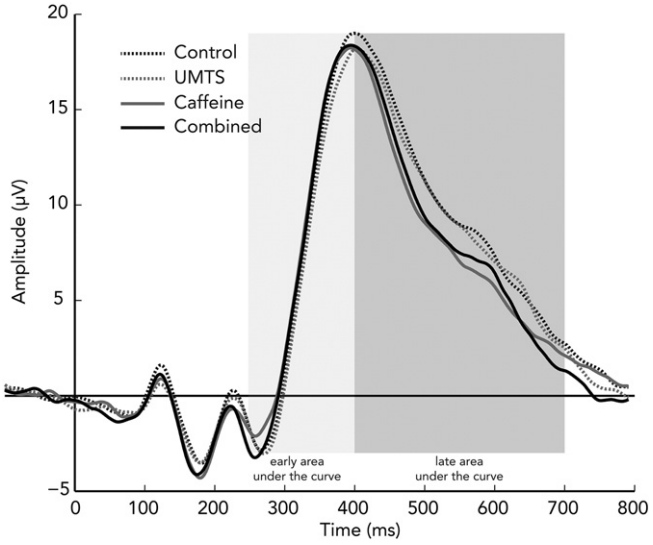

Fig. 4. Grand-average (n = 19) waveforms to target stimuli recorded from the Pz electrode in each treatment (Control, UMTS, Caffeine, Combined). Gray patches indicate the early (245–400 ms) and the late (400–700 ms) time windows of the area under the curve (AUC) analysis.

3.2.1. Pre vs. Post blocks

The accepted minimum trial number was 10 out of 20 per block. Due to excessive artifacts 9 subjects were excluded from further data analysis. Thereafter, the final sample comprised data from 16 subjects. Conventional and interval-based measures of the P300 were analyzed by three-way rANOVA of *Treatment* (Control vs. UMTS vs. Caffeine vs. Combined) × *Block* (Pre vs. Post) × *Electrode* (P3 vs. P4 vs. O1 vs. O2 vs. P7 vs. P8 vs. Pz vs. Cp1 vs. Cp2 vs. Cp5 vs. Cp6). The possible laterality effects of the treatments on the P300 were tested by three-way rANOVA of *Laterality* (Left ROI vs. Right ROI) × *Treatment* (Control vs. UMTS vs. Caffeine vs. Combined) × *Block* (Pre vs. Post). The possible interaction on the summative model in the Post block was tested by two-way rANOVA of *Interaction* (Sum vs. Simultaneous) × *Electrode* (P3 vs. P4 vs. O1 vs. O2 vs. P7 vs. P8 vs. Pz vs. Cp1 vs. Cp2 vs. Cp5 vs. Cp6).

3.2.2. Exposure block

First, similar to the RT analysis, we tested the overall treatment effect on the ERPs over the whole Exp. block. The minimum acceptable trial number was 40. Due to low trial numbers data of 6 subjects were omitted from further analysis. Thus the final sample comprised data of 19 subjects. The effects of experimental conditions were analyzed on the peak latency, amplitude, FAL, early and late AUC of the P300 component with two-way rANOVA (Treatment × Electrode). The possible laterality effects of the treatments on P300 measures were analyzed with two-way rANOVA of *Laterality* (Left vs. Right) × *Treatment* (Control vs. UMTS vs. Caffeine vs. Combined). Second, to find any possible acute effects on the ERPs the Exp. block was divided into 6 sub-blocks. In this analysis the minimum acceptable trial number was 10. Thus two additional subjects were excluded from further analysis. Thus, the final sample comprised data from 17 subjects. In the second analysis three-way rANOVA (Treatment × Sub-Block × Electrode) was applied on P300 measures. To test the possible equality of the additive model two-way rANVOA was used in both analyses.

Single-trial analysis was applied to examine the possible acute effects of either EMF exposure or the combination of EMF and caffeine. Data were smoothed by using a window of 10 trials from the 21st deviant trial to 130th deviant trial (corresponding to the exposure period in the conditions involving EMF) in the Exposure block. Possible treatment effects on the P300 measures were analyzed by two-way rANOVA of Treatment × Electrode on each single-trial. Only those time intervals

were considered significant where at least five consecutive single-trials showed significant treatment effects.

4. Results

4.1. Reaction time

4.1.1. Pre vs. Post blocks

Results showed that RT was significantly shorter [$F(1,20) = 65.311$, $p < 0.001$, $\eta^2 = 0.77$] in the Pre block (mean: 382 ms, SEM: 7.78) compared to the Post block (mean: 419 ms, SEM: 10.37). The analysis of Treatment in the Post block showed a significant main effect [$F(3,60) = 3.537$, $p < 0.02$, $\eta^2 = 0.15$]. Tukey HSD test showed that RT was significantly shortened ($p < 0.027$) in the Combined treatment (mean: 408 ms, SEM: 12.16) compared to Control (mean: 434 ms, SEM: 11.71) and a marginally significant effect ($p = 0.0537$) was found between Caffeine (mean: 411 ms, SEM: 12.69) and Control. The post hoc test showed no significant differences between the Combined and Caffeine treatment ($p = 0.99$).

4.1.2. Exposure block

a) The analysis of RT during the Exp. block yielded a significant treatment effect ($F(3,66) = 3.0$, $p < 0.037$, $\eta^2 = 0.12$). Post hoc Tukey's HSD showed that RT in Caffeine treatment (mean: 399 ms, SEM: 12.18) was significantly shorter ($p < 0.038$) than in the Control treatment (mean: 419 ms, SEM: 9.8) (Fig. 5A). However, RTs in the Combined treatment (mean: 405 ms, SEM: 10.61) did not differ from RTs in any other treatments ($p > 0.25$). To further test for possible linear interaction between caffeine and UMTS exposures, we applied the summative model. As we did not find significant difference between the summed data in individual exposures ([Caffeine − Control] + [UMTS − Control]) and the data in simultaneous exposures (Combined − Control) [$F(1,22) = 0.535$, $p = 0.47$, $\eta^2 = 0.02$], we do not suggest attenuating effects of the UMTS signal on caffeine-induced decrease of RT (Combined treatment).

b) Significant Pearson's correlations showed that RTs were increased over time from the first Exp sub-block in each treatment (Control: $R^2 = 0.79$, $p = 0.017$; UMTS: $R^2 = 0.93$, $p = 0.02$; Caffeine: $R^2 = 0.98$, $p < 0.001$; Combined: $R^2 = 0.92$, $p = 0.002$) (Fig. 5B). We found significant Sub-block [$F(5,110) = 37.596$, $p < 0.001$, $\eta^2 = 0.63$] and Treatment [$F(3,66) = 3.001$, $p < 0.037$, $\eta^2 = 0.12$] main effects on RT. The Tukey HSD post hoc test revealed that the RT in the Caffeine treatment (mean: 399 ms, SEM: 12.2) was significantly shortened ($p < 0.039$) compared to Control (mean: 419 ms, SEM: 9.8). No other significant differences were found between different treatments. Post hoc test revealed that the observed Sub-block effects were caused by caffeine. Furthermore, the analysis of the summative model did not reveal significant differences between the sum and simultaneous data in any of the sub-blocks either.

4.2. Event related potentials

We found clear caffeine-induced effects on area-based measures of the P300 ERP component. Thus, hereinafter, only results of area-based analyses will be discussed. For results derived from conventional ERP measures see Supplementary_Data_4.

4.2.1. Pre vs. Post block

We found that the P300 FAL significantly increased ($F(1,15) = 20.843$, $p < 0.001$, $\eta^2 = 0.582$) in the Post (mean: 455.22 ms, SEM: 6.89) compared to Pre (mean: 432.78, SEM: 5.75) block. The early AUC significantly decreased ($F(1,15) = 17.56$, $p < 0.001$, $\eta^2 = 0.54$) in the Post (mean: 1132 μV^2, SEM: 114.83) compared to Pre block (mean: 1449.7 μV^2, SEM: 139.42), in each Treatment condition. Overall, treatment main effects were found on the FAL ($F(3,45) = 4.865$, $p < 0.006$, $\eta^2 = 0.24$) or late AUC ($F(3,45) = 5.62$, $p < 0.003$, $\eta^2 = 0.27$). Tukey HSD post hoc test revealed significant differences on the FAL between Caffeine and Control ($p < 0.02$) and between Combined and Control ($p < 0.021$). Post hoc test of the late AUC showed that both Caffeine and Combined treatments significantly decreased the area compared to Control or UMTS treatments. Tukey HSD test did not show differences between the Caffeine and Combined Treatment in any P300 measures. These results were further supported by the analyses of the summative model.

The analysis of Laterality showed significant main effect on the early P300 AUC [$F(1,15) = 16.38$, $p = 0.001$, $\eta^2 = 0.522$], which was caused by the larger responses in the left side relative to right. However no Laterality × Treatment interactions were found.

4.2.2. Exposure block

In the first analysis, ANOVA of target P300 during the whole exposure yielded significant treatment effect both on P300 FAL [$F(6,54) = 3.165$, $p < 0.032$, $\eta^2 = 0.15$] and late AUC [$F(3,54) = 3.65$, $p < 0.018$, $\eta^2 = 0.169$]. Although the main effect of the P300 FAL did not survive the Tukey HSD post hoc test, the post hoc analysis of the late AUC showed significant differences ($p < 0.048$) between Control (mean: 2267.31 μV^2, SEM: 215.08) and Caffeine (mean: 1908.42 μV^2, SEM: 196.14) treatments. Furthermore, marginally significant differences ($p = 0.0863$) were found between Control and Combined (mean: 1942.83 μV^2, SEM: 190.28) treatments (Fig. 6). Tukey HSD test revealed no significant differences between Caffeine and Combined treatments in any P300 measures. Furthermore, the analysis of the summative model showed no significant differences between the summed individual and the simultaneous data on all measures of the P300

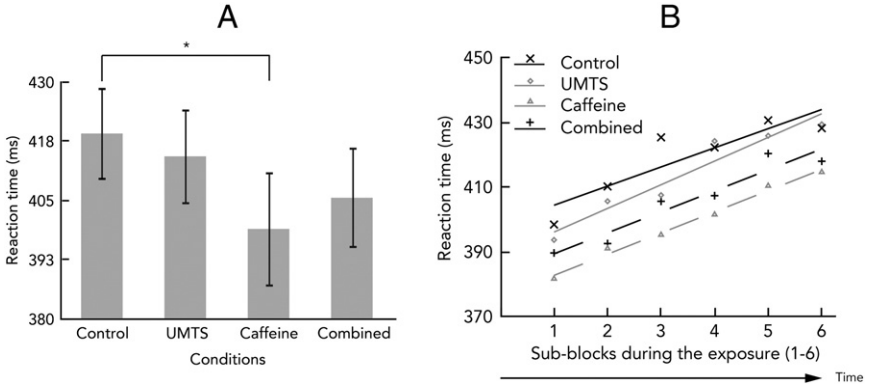

Fig. 5. A: Results for reaction time after the target onset during the exposure block. Significant difference was found between Caffeine and Control treatments ($p < 0.05$). B: Serial changes in the mean reaction time (RT) during the exposure (Exp) block. The Exp block was divided into six equal sub-blocks in each treatment which contained max. 20 target stimuli. We found significant Pearson's correlation between sub-blocks during the Exp block and RT in each treatment (Control: $R^2 = 0.79$, $p = 0.017$; UMTS: $R^2 = 0.93$, $p = 0.02$; Caffeine: $R^2 = 0.98$, $p < 0.001$; Combined: $R^2 = 0.92$, $p = 0.002$).

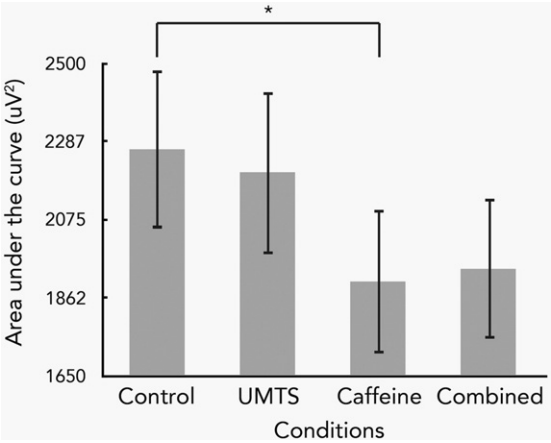

Fig. 6. Results for the late area under the curve (AUC) analysis of the P300 ERP component from 400 ms to 700 ms after the target onset during the Exposure (Exp) block. Significant mean difference was found between Caffeine and Control treatments ($p < 0.05$).

suggesting no interaction of caffeine and UMTS. Similar to the Pre vs. Post analysis in the Exposure block we also found significant main effect of Laterality on the early P300 AUC [$F(1,15) = 18.11$, $p < 0.001$, $\eta^2 = 0.501$], which was caused by larger responses in the left side compared to right. The analysis showed no Laterality × Treatment interactions.

The analysis of the segmented Exp. block showed significant sub-block effect on the P300 FAL [$F(5,80) = 12.54$, $p < 0.001$, $\eta^2 = 0.44$]. Post-hoc test revealed that P300 FAL significantly increased from the second to the last (6th) sub-block compared to the first one. This sub-block effect on the P300 FAL was further confirmed by Pearson's correlation (Control: $R = 0.89$, $p = 0.02$; UMTS: $R = 0.95$, $p < 0.01$; Caffeine: $R = 0.79$, $p = 0.06$; $R = 0.85$, $p = 0.03$). Furthermore, significant treatment effect was found on late AUC [$F(3,48) = 6.32$, $p = 0.001$, $\eta^2 = 0.28$]. Post hoc Tukey HSD revealed that the late AUC decreased in either Caffeine (mean: 2092.92 μV^2, SEM: 200.8) or Combined (mean: 2053.88 μV^2, SEM: 198.22) treatments compared to Control (mean: 2437.24 μV^2, SEM: 226.72). Overall, Tukey HSD post hoc test on the FAL ($p = 0.93$) or AUC ($p = 0.97$) showed no significant differences between UMTS and Control treatments. Neither the Tukey HSD post-hoc test nor the analyses of the summative model of the P300 measures showed significant differences between the Caffeine and Combined treatments in each sub-block.

Single-trial analysis yielded significant main effect of Treatment on the late AUC from trial 68 to trial 76 at the beginning of the Exp block (Fig. 7). Although in these single-trials we found significant Caffeine effect compared to Control or UMTS, the analyses did not show any significant differences between Caffeine and Combined treatments. Furthermore, the additive analyses of the single-trials showed no interaction between Caffeine and Combined treatments.

5. Discussion

To date, the possible combined or interactive effects between caffeine and MP EMFs on human brain physiology have not been systematically investigated. However, independent lines of evidence indicate that both caffeine and MP EMFs may affect the functioning of neuronal Ca^{2+} channels (Fredholm et al., 1999; Stavroulakis, 2003). Therefore, in the current study, we investigated the possible combined action of simultaneous caffeine and UMTS MP exposure on human RT and ERPs in a visual target detection (oddball) task. In addition, caffeine exposure also served as a widely accepted pharmacological control to validate results of the present study (positive control treatment).

To test the possible combined effects or interaction of caffeine and UMTS MP exposure we applied a full factorial experimental design. We adopted an additive model (Giard and Peronnet, 1999; Molholm et al., 2002; Boll and Berti, 2009) to test the interaction of caffeine and UMTS MP exposure. Furthermore, as no ERP studies so far have investigated possible MP induced effects on the single-trial level, we applied a 'single trial ERP analysis' as it is a sensitive way to test for possible acute, transient exposure effects.

5.1. Reaction time

In the present study we found no effects of UMTS exposure on RT to visual targets in an oddball paradigm. The present negative findings of the UMTS MP exposure on RT are consistent with prior investigations (Schmid et al., 2005; Regel et al., 2006; Riddervold et al., 2008; Unterlechner et al., 2008). These findings indicate no alternation of cognitive performance under UMTS MP exposure. In line with previous results (Lorist and Tops, 2003; Tieges et al., 2004, 2006; Barry et al., 2007; Kenemans et al., 2010), apparent caffeine-induced effects were found. Caffeine treatment significantly decreased RT relative to control treatments. Thus the present results from a choice reaction time task corroborate prior results showing that caffeine facilitates behavioral responses to visual target stimuli. However, in contrast to our present results, some studies (Deslandes et al., 2004, 2005; Montenegro et al., 2005) found no improvement in reaction time after caffeine intake. Although in these studies similar visual tasks were used, a fix high dose of caffeine (400 mg) was given to the volunteers irrespective of their body weight. In our study volunteers received 138–410 mg caffeine depending on their actual body weight (3 mg/kg). According to (Deslandes et al., 2005), one possible explanation of the discrepancy is that the optimal performance is expected at intermediate caffeine levels whereas in the study by (Deslandes et al., 2005) some participants might have received too low or too high doses. This is also in line with the well-known relationship between arousal and performance (Yerkes and Dodson, 1908) which describes suboptimal performance during too low and too high arousal levels. Although we found that caffeine improved RT, the analysis of the summative model showed that the UMTS exposure did not influence caffeine effects on RT suggesting no combined or synergistic underlying processes.

5.2. Event related potentials

We investigated the possible effects of caffeine, UMTS MP exposure and their combination on different indices of the P300 component, such as latency, amplitude, FAL and AUC.

In the Pre vs. Post analysis we found that the P300 FAL shortened and the late AUC decreased in the caffeine and combined treatment compared to control. These results confirm prior reports (Lorist and Tops, 2003; Deslandes et al., 2004, 2005; Montenegro et al., 2005; Barry et al., 2007) that caffeine affects neural correlates of information processing such as stimulus detection indexed by P300.

In the exposure block we used three different analyses to test for possible treatment effects. First, the effects were analyzed over the whole exposure block. Here, significant caffeine-induced effects were found on the FAL. Second, when the exposure block was divided into 6 sub-blocks, significant caffeine effects were found on the late AUC. Third, the single-trial analysis showed that caffeine significantly shortened the FAL compared to the control treatment. Taken together, although we observed clear effects of caffeine on the P300 response, none of the different P300 indices showed any reliable difference between caffeine and combined treatments, indicating that the effects observed in the combined treatment condition were primarily caused by the caffeine itself.

It is well known that caffeine increases memory function and improves performance of the attentional system (Lynch, 2004; Lorist and Tops, 2003). Our result of late P300 AUC decrease after caffeine intake are in accordance with studies that reported beneficial effects of caffeine on information processing indexed by P300 (Lorist and Tops, 2003).

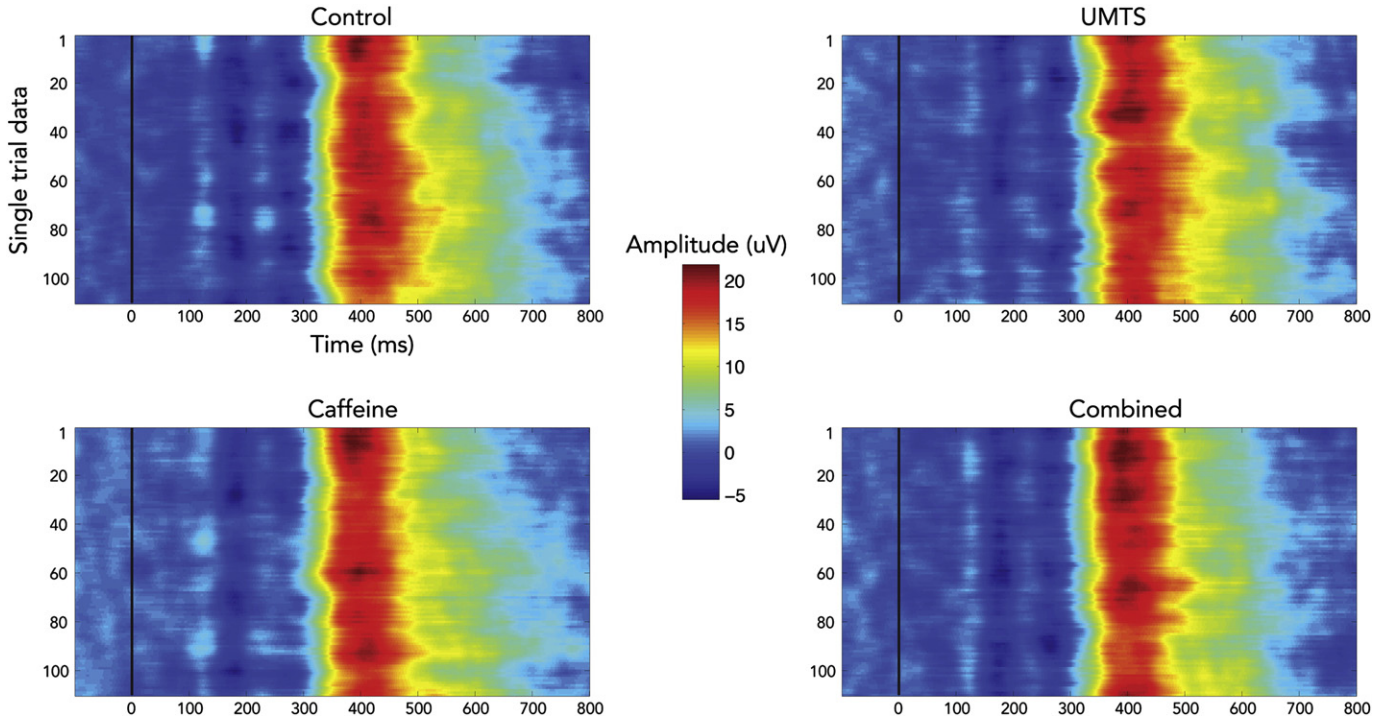

Fig. 7. Event related potentials of single trial data selected from Pz electrode from 17 subjects in the exposure (Exp) block. Here, each horizontal line corresponds to a single target (deviant) trial. Trials are sorted according to their occurrence during the experimental session. Data were smoothed using a window of 10 trials. (Note that the Exp. block started from trial 21.) The first (mean from trial 21 to trial 30) and the second (mean from trial 22 to trial 31) single trial data in the 250-400 and 300 - 700 ms time-windows were used for P300 FAL analysis. We found that caffeine significantly decreased the P300 FAL of the first single trial compared to Control. Black lines at the zero position in each treatment indicate the onset of the target stimuli.

Although to date only three studies have investigated the potential effects of (3G) UMTS MP exposure on the P300 ERP component (Kleinlogel et al., 2008a; Stefanics et al., 2008; Trunk et al., 2013) the results are consistently showing no effects. The present results correspond with previous findings showing no measurable effects of the newer (3G) UMTS mobile communication standard exposure on human cognition (Schmid et al., 2005; Unterlechner et al., 2008) or brain electric responses (Kleinlogel et al., 2008b; Stefanics et al., 2008; Trunk et al., 2013) indexed by the amplitude or latency measures of the P300 ERP component.

Previous studies reported possible combined effects of caffeine and other energy drink ingredients such as glucose and taurine (Kennedy and Scholey, 2004; Scholey and Kennedy, 2004; Adan and Serra-Grabulosa, 2010; Giles et al., 2012) or alcohol (Azcona et al., 1995; Hirvonen et al., 2000; Martin and Garfield, 2006). Although these findings showed combined effects of the applied chemicals on human cognition, in the present study we found no evidence of such measurable interaction between caffeine and the UMTS EMF exposure. The lack of combined effects in the present study is corroborated by the lack of significant EMF effects in the UMTS only treatment condition. The possible explanation for the lack of UMTS and caffeine-UMTS synergistic interaction effects might be due to the low level of the applied field or the ineffective modulation type of the UMTS signal to reach the threshold for biological effects (Juutilainen et al., 2011). Although the present results are in line with previous EEG studies where the UMTS MP signal was applied (Kleinlogel et al., 2008a, 2008b; Stefanics et al., 2008; Trunk et al., 2013) we cannot entirely rule out that general MP exposure alone or in combination with caffeine does not affect human cognitive performance. It has been evidenced that other MP signal types (e.g., the GSM modulated signal) were reported to alter brain physiology both in sleep (Borbély et al., 1999; Regel et al., 2007b; Schmid et al., 2012) and awake conditions (Regel et al., 2007a; Perentos et al., 2013). Therefore we suggest that further studies should choose validated pharmacological stimulating agents serving as positive controls and use them to test possible combined interaction of emerging newer EMF energy sources such as Wireless Fidelity (WiFi), Terrestrial Trunked Radio (TETRA) or Long Term Evolution (LTE) using various different frequency modulation and carrier frequencies.

Authors' contributions

A.T., G.S. and I.H. designed research; A.T. and N.Z. performed EEG experiments; I.B. and A.F. performed HPLC analyses; G.T. designed exposure system and performed dosimetry; A.T. analyzed data; A.T., G.S. and I.H. wrote the paper. All authors read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.pbb.2014.07.011.

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