

Pulsed radio-frequency electromagnetic fields: dose-dependent effects on sleep, the sleep EEG and cognitive performance

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SUMMARY To establish a dose–response relationship between the strength of electromagnetic fields (EMF) and previously reported effects on the brain, we investigated the influence of EMF exposure by varying the signal intensity in three experimental sessions. The head of 15 healthy male subjects was unilaterally exposed for 30 min prior to sleep to a pulse-modulated EMF (GSM handset like signal) with a 10 g-averaged peak spatial specific absorption rate of (1) 0.2 W kg⁻¹, (2) 5 W kg⁻¹, or (3) sham exposed in a double-blind, crossover design. During exposure, subjects performed two series of three computerized cognitive tasks, each presented in a fixed order [simple reaction time task, two-choice reaction time task (CRT), 1-, 2-, 3-back task]. Immediately after exposure, night-time sleep was polysomnographically recorded for 8 h. Sleep architecture was not affected by EMF exposure. Analysis of the sleep electroencephalogram (EEG) revealed a dose-dependent increase of power in the spindle frequency range in non-REM sleep. Reaction speed decelerated with increasing field intensity in the 1-back task, while accuracy in the CRT and N-back task were not affected in a dose-dependent manner. In summary, this study reveals first indications of a dose–response relationship between EMF field intensity and its effects on brain physiology as demonstrated by changes in the sleep EEG and in cognitive performance.

KEYWORDS cellular phone, dose–response relationship, electroencephalogram

INTRODUCTION

There is increasing evidence that pulse-modulated radio frequency electromagnetic fields (RF EMF) such as those emitted by mobile phones affect brain physiology. The reported effects include changes in the electroencephalogram (EEG) and regional cerebral blood flow (rCBF), as well as changes in intracortical excitability and cognitive function (e.g. Aalto *et al.*, 2006; Borbély *et al.*, 1999; Curcio *et al.*, 2005; Ferreri *et al.*, 2006; Huber *et al.*, 2000, 2002, 2005; Koivisto *et al.*, 2000a,b). We recently found that pulse-modulation of the RF EMF is necessary to induce changes in the EEG in

waking and sleep (Huber *et al.*, 2002). Exposure to a continuous-wave signal was not eliciting a response. Furthermore, rCBF was only affected by a ‘handset-like’, but not by a ‘base station-like’ GSM signal (Global System for Mobile Communication, Huber *et al.*, 2005).

The specific absorption rate (SAR) is defined as the RF power absorbed per unit of mass of tissue. International limits for local exposures, i.e. peak spatial SAR averaged over any 10 g of tissue (psSAR_{10 g}), are 2 W kg⁻¹ for the general public and 10 W kg⁻¹ for occupational exposure (ICNIRP, 1998). In recent sleep studies, only a single dose was applied (Borbély, 1999; Huber, 2000, 2002, 2003, 2005; Loughran *et al.*, 2005; Wagner *et al.*, 1998). A dose–response relationship between field intensity and the magnitude of RF EMF-induced effects on human brain physiology has not yet been established. We addressed this issue by using a five times lower and a five times

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higher SAR than in our earlier experiments (1 W kg^{-1}). Based on previous studies (Huber *et al.*, 2002; Koivisto *et al.*, 2000a,b; Loughran *et al.*, 2005), we hypothesized that the sleep EEG and cognitive performance are affected in a dose-dependent manner by exposure to pulse-modulated GSM signal. The investigation of a potential dose-response relationship is important to estimate the critical level for possible adverse health effects of RF EMF.

METHODS

Subjects

Fifteen healthy young right-handed men [age range 20–26 years, mean age 22.4 ± 0.4 (\pm SEM)] participated in the study. They were recruited from the student population of the University of Zurich and the ETH Zurich and were remunerated for their participation. All subjects were non-smokers and reported to be in good health and free of sleep complaints. A screening night prior to the experiment served to exclude subjects with sleep apnea, nocturnal myoclonus and low sleep efficiency ($<80\%$). Handedness was verified with the Edinburgh Handedness Inventory (Oldfield, 1971). Thirteen of the subjects reported to own a cell phone and to use it <1 h per week (32.5 ± 2.3 min per week). They were instructed to abstain from caffeine and alcohol consumption at least 3 days prior to the study and to maintain a habitual sleep-wake schedule (8 h, 23:00–7:00 hours, ± 1 h with respect to bed and rising time). Compliance was verified by means of wrist-worn activity monitors and sleep logs. No mobile phone calls were allowed on the day of the experiment. Volunteers were informed that the field intensity in one of the conditions was above the exposure limit for the general population ($\text{psSAR}_{10 \text{ g}}$ of 2 W kg^{-1} , ICNIRP, 1998) but still below the limit for occupational exposure ($\text{psSAR}_{10 \text{ g}}$ of 10 W kg^{-1}). The subjects gave their written informed consent, and the local ethics committee for research on human subjects approved the study protocol.

Study design and exposure conditions

The experiments were performed in the sleep laboratory of the Institute of Pharmacology and Toxicology, University of Zurich. The study consisted of three sessions separated by

1-week intervals in a randomized double-blind crossover design. Each session consisted of an adaptation night and a subsequent experimental night. Only two participants could be exposed simultaneously. To run four subjects at a time, two groups were scheduled with sleep either from 22:40–6:40 hours or 23:20–7:20 hours. In the experimental night, subjects were exposed unilaterally (left hemisphere) for 30 min prior to sleep to either a pulse-modulated RF EMF or to a sham control condition. The time between exposure and lights off was 10 min. During exposure, subjects performed cognitive tasks while sitting in a chair. Their heads were positioned between two plates to ensure a well-defined position with respect to the planar antennas (Huber *et al.*, 2000, 2003). Pairs of subjects were exposed under the same condition. The two exposure conditions involved a pulse-modulated (PM) GSM-like handset signal (Huber *et al.*, 2005; 900 MHz carrier frequency, burst of 0.577 ms duration, multiframe averaged duty cycle 21%, modulation components of 2, 8, 217 and 1736 Hz and higher harmonics), which was applied at a $\text{psSAR}_{10 \text{ g}}$ of either 0.2 or 5 W kg^{-1} . The signal corresponded to a synthesized frame structure generating the components of discontinuous transmission (DTX) and non-DTX without temporal switching. The corresponding SAR levels induced in the brain are summarized in Table 1 (for details on signal and dosimetry see Huber *et al.*, 2003, 2005). All electrode leads were horizontally oriented to minimize interference with the RF EMF in the active exposure conditions.

Polysomnography

During the 8-h night-time sleep episodes the EEG (derivation C3A2), electromyogram (EMG), electrooculogram (EOG, differential recording) and electrocardiogram (ECG) were recorded by a polygraphic amplifier (PSA24; Braintronics Inc., Almere, the Netherlands), digitized, and transmitted via fiber-optic cables to a personal computer and stored with a resolution of 128 Hz (Rétey *et al.*, 2006).

Sleep stages were visually scored for 20-s epochs according to standard criteria (Rechtschaffen and Kales, 1968). EEG power spectra of consecutive 20-s epochs (FFT routine, Hanning window, averages of five 4-s epochs) were computed (Borbély *et al.*, 1999; Huber *et al.*, 2000, 2002) and visual and semi-automatic artifact removal was performed on a 20-s basis

Table 1 Computed specific absorption rate (SAR, W kg^{-1}) induced in brain tissue (grey matter, white matter, and thalamus) by exposure at a 10 g-averaged peak spatial SAR ($\text{psSAR}_{10 \text{ g}}$) of 5 and 0.2 W kg^{-1} . Provided are the 1 g-averaged peak spatial SAR ($\text{psSAR}_{1 \text{ g}}$), the averaged SAR (avg SAR, standard deviation in parenthesis) of the exposed hemisphere, estimations of the inter-subject variations (deviations from the mean value for individual subjects), and assessment of uncertainty (description of the confidence interval of the assessed mean SAR values). Note that the $\text{psSAR}_{10 \text{ g}}$ values have to be considered as a surrogate for the differentiation of the induced field levels in the brain and shall not be used to compare the exposures of different setups

Tissue	$\text{psSAR}_{10 \text{ g}} = 0.2 \text{ W kg}^{-1}$		$\text{psSAR}_{10 \text{ g}} = 5 \text{ W kg}^{-1}$		Variations %	Uncertainty %
	$\text{psSAR}_{1 \text{ g}} (\text{W kg}^{-1})$	avg SAR (W kg^{-1})	$\text{psSAR}_{1 \text{ g}} (\text{W kg}^{-1})$	avg SAR (W kg^{-1})		
Grey matter	0.20	0.050 (0.039)	5.1	1.3 (0.96)	19	15
White matter	0.12	0.040 (0.027)	3.0	1.0 (0.66)	17	15
Thalamus	0.034	0.027 (0.0045)	0.84	0.68 (0.11)	29	15

(Huber *et al.*, 2000). The frequency resolution was 0.25 Hz, and frequencies up to 25 Hz were analyzed. Average power spectra (log-transformed values) of non-REM sleep, stage 2, slow wave sleep (SWS) and REM sleep were analyzed by means of linear mixed models (SAS 8.2; SAS Institute Inc., Cary, NC, USA) presuming an identical intraclass correlation for all subjects (option 'compound symmetry') and including the factors *Week* (1, 2, 3, to account for order effects) and *Condition* (sham, 0.2 W kg⁻¹, 5 W kg⁻¹). The factor *Condition* was modeled as a continuous variable. Statistical analyses revealed effects for the main factor *Condition* in the slow and fast spindle frequency range (overlapping significance or trend in non-REM sleep, stage 2, and SWS). Therefore, additional analyses were performed for power in the two bands (log-transformed values) of three consecutive intervals (thirds of the sleep episodes, i.e. from sleep onset until final awakening) by expanding the mixed model with the factor *Interval* (1, 2, 3) and the *Condition* × *Interval* interaction. In addition, a linear mixed model ANOVA was performed with sleep variables derived from visual scoring.

Cognitive tasks

Based on previous experiments, three tasks were used to assess cognitive performance. *Simple Reaction Time Task* (SRT, Koivisto *et al.*, 2000b): a '0' appeared on the computer screen until subjects pressed the corresponding button on a response box. A total of 42 targets per session was presented. Completion of the task took ~2 min. *2-Choice Reaction Time Task* (CRT, Koivisto *et al.*, 2000b; Preece *et al.*, 1998): a 'JA' (yes) or 'NEIN' (no) was shown and subjects had to press the 'J' and 'N' button, respectively. A total of 24 'yes' and 24 'no' targets per session was presented. Completion of the task took ~2 min. *N-Back Task* (1-, 2-, 3-back, Koivisto *et al.*, 2000a): single consonants were randomly presented on the screen. Subjects had to compare each current letter with each consonant presented 1-, 2- or 3-trials back and press 'J' for same letters and 'N' for different letters. 1-back, 2-back and 3-back consisted of 24 targets and 56 non-targets, respectively, preceded by a practice block including three targets and seven non-targets. Completion of the task took ~10 min. The tasks were implemented using e-PRIME (Psychology Software Tools Inc., Pittsburgh, PA, USA). All subjects completed a training session before the sleep recording of the adaptation night of the first week. On the experimental nights, subjects performed the tasks during exposure while sitting in the exposure setup. SRT, CRT and 1-, 2-, and 3-back tasks were performed twice in a fixed order, once during the first half and once during the second half of exposure (sessions 1 and 2). Subjects were instructed to respond as quickly and as accurately as possible to targets and non-targets by pressing the corresponding buttons on the response box.

Very short reaction times (< 50 ms) were excluded as well as outliers over all sessions according to a robust rejection

procedure (4 × median deviation, Hampel, 1985). Accuracy scores were not altered by this procedure. Residuals of speed [1/reaction time, (1/s); CRT and N-back, correct responses only] were checked for normal distribution and the values were analyzed by means of linear mixed models (see above). The model included the factors: *Week* (1, 2, 3), *Condition* (sham, 0.2 W kg⁻¹, 5 W kg⁻¹) and *Session* (first and second half of exposure), as well as interaction effects.

Accuracy (percentage of correct answers) in the CRT and the N-back task was statistically analyzed by non-parametric Wilcoxon-signed-rank tests. Comparisons of 0.2 W kg⁻¹ versus sham and 5 W kg⁻¹ versus sham were performed for (i) session 1, (ii) session 2 and (iii) the difference between the two sessions (Δ). Significance levels were adjusted for multiple testing (six tests) according to Bonferroni–Holm (Holm, 1979). For the cognitive outcomes, a multiple end-point adjustment was performed to control for multiple testing (Tukey *et al.*, 1985).

If not otherwise indicated, only significant effects are reported.

RESULTS

Sleep and sleep EEG

Spectral analysis of the sleep EEG in non-REM sleep, stage 2 and SWS revealed a dose-dependent increase of power in the slow (10.75–11.25 Hz) and fast spindle frequency range (13.5–13.75 Hz) after exposure to pulse-modulated RF EMF (Fig. 1). In addition, during SWS a dose-dependent effect was present in the theta/ low alpha range. The temporal evolution of the effect in the slow and fast spindle frequency range during non-REM sleep was analyzed for thirds of the sleep episode (Fig. 2). Statistical analysis revealed a significant *Condition* effect ($F_{1,119} = 4.93$, $P < 0.03$; *Week*: $F_{2,119} = 5.50$, $P < 0.006$) for the fast spindle range only. The effect was not limited to a specific time interval but present in all three intervals (Fig. 2; *Condition* × *Interval*: $F_{2,119} = 0.01$, n.s.). *Post hoc* analyses comparing each exposure condition with the sham condition separately revealed that only the 5 W kg⁻¹ condition differed from the sham control condition (*Condition*: $F_{1,74} = 4.56$, $P < 0.04$; *Condition* × *Interval*: $F_{2,74} = 0.03$, n.s.; *Week*: $F_{2,75.3} = 4.64$, $P < 0.02$).

No effects on REM sleep EEG spectra were observed. Sleep architecture was not affected by RF EMF exposure (Table 2). Sleep latency (interval from lights off to stage 2 sleep) was slightly prolonged with increasing field intensity (*Condition*: $F_{1,75} = 3.80$, $P < 0.06$, Table 2). No other dose–response related effects were observed. In particular, waking after sleep onset (WASO) and movement time were not altered due to exposure. This also holds when thirds of the sleep episodes were analyzed (WASO + MT averaged over conditions; interval 1: 4.1 min; interval 2: 4.1 min; interval 3: 6.3 min; linear mixed model ANOVA: *Condition*: $F_{1,120} = 0.03$, n.s.; *Interval*: $F_{2,120} = 3.95$, $P < 0.03$, *Condition* × *Interval*: $F_{2,120} = 0.06$, n.s.).

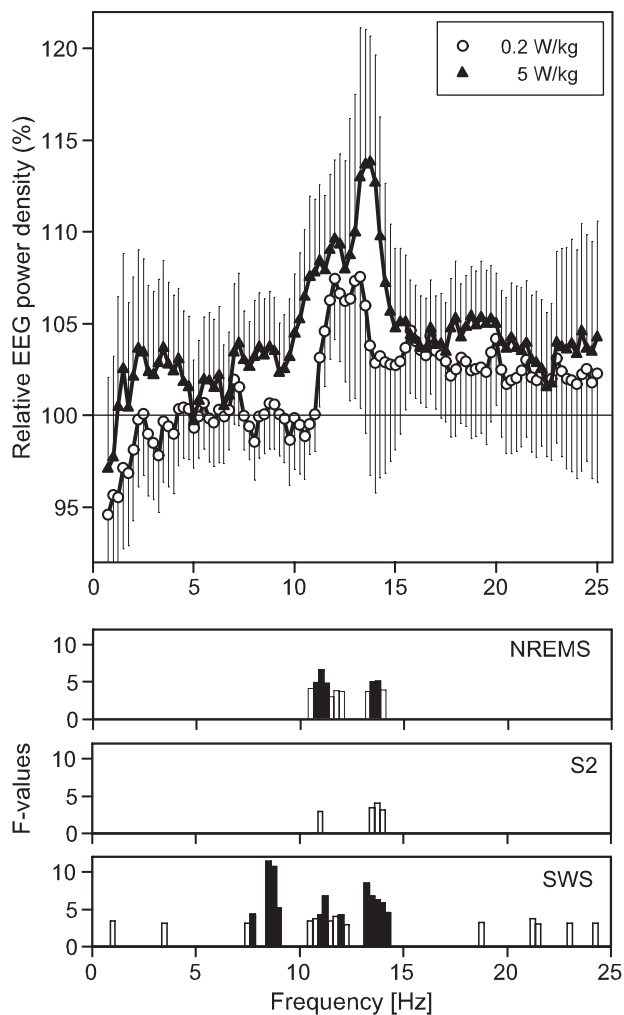


Figure 1. Dose-dependent effect of RF EMF exposure on EEG power spectra in non-REM sleep (derivation C3A2). Relative EEG power density spectra (mean \pm SEM for 0.25 Hz bins; $n = 15$; 100% = sham) are illustrated. Three conditions were applied: sham, 0.2 and 5 W kg⁻¹ RF EMF exposure (10 g-averaged peak spatial SAR). *F*-values (trend: $P < 0.1$, open bars; significance: $P < 0.05$, black bars) of the analysis with linear mixed model ANOVA factor *Condition* are illustrated for non-REM sleep (NREMS), stage 2 (S2) and slow wave sleep (SWS). After artifact removal, on average 269.9 min of non-REM sleep contributed to the data (range: 82.9–87.4% of 20-s epochs, linear mixed model ANOVA: *Condition*: $F_{1,30} > 0.84$, n.s.). Due to electrode problems at the end of some nights, spectra were restricted to the minimal common length across conditions (three subjects).

Cognitive tasks

All subjects completed the tasks during the 30-min exposure interval. In the course of the experiment, subjects became faster in the N-back task (1-, 2-, 3-back, *Week*: $F_{2,75} \geq 15.75$, $P < 0.0001$). No changes in speed over the experimental period were observed in the SRT and the CRT.

Speed significantly decreased with increasing field intensity in the 1-back task and tended to decrease in the 2-back task and the CRT (Fig. 3). No RF EMF induced effect on speed

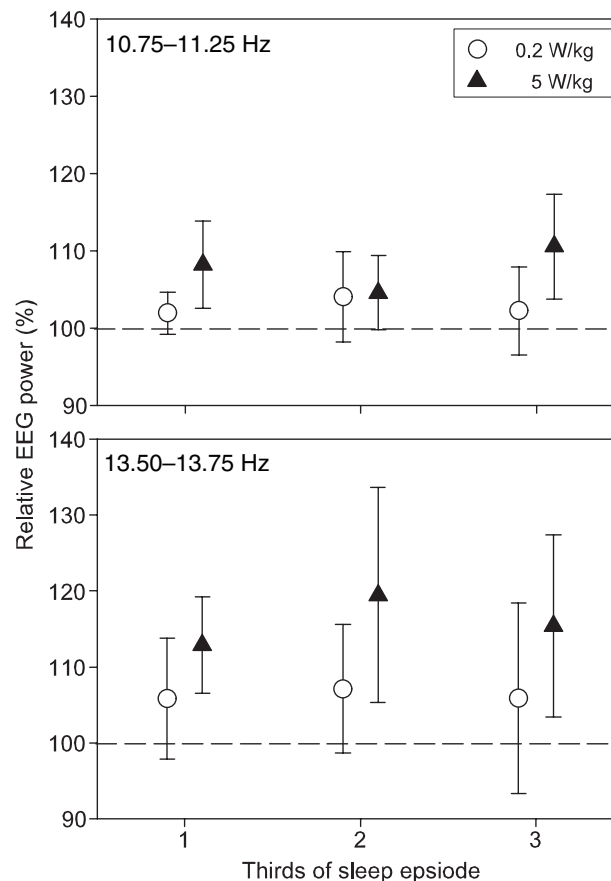


Figure 2. Temporal evolution of the effect of RF EMF exposure on spectral power in the slow (10.75–11.25 Hz) and fast spindle frequency range (13.5–13.75 Hz) in non-REM sleep. Thirds of sleep episode are indicated. Three conditions were applied: sham, 0.2 and 5 W kg⁻¹ RF EMF exposure (10 g-averaged peak spatial SAR). Relative EEG power (mean \pm SEM; sham = 100%) in the fast spindle frequency range (13.5–13.75 Hz) was increased in a dose-dependent manner in the three intervals ($n = 15$; linear mixed model ANOVA, factor *Condition*: $F_{1,119} = 4.39$, $P < 0.03$; *Condition* \times *Interval* interaction: $F_{2,119} = 0.01$, n.s.). On average 113.1 min (interval 1), 90.2 min (interval 2), and 71.7 min (interval 3) of non-REM sleep contributed to the data (linear mixed model ANOVA: *Condition*: $F_{1,120} = 3.02$, $P < 0.09$, *Interval*: $F_{2,120} = 50.68$, $P < 0.0001$, *Condition* \times *Interval*: $F_{2,120} = 0.14$, n.s.). After artifact removal, on average 83.8% of non-REM sleep contributed to the data (all factors and interaction n.s.).

was found in the SRT and the 3-back task. Speed did not differ between first and second half of exposure (*Condition* \times *Session*: $F_{1,75} \leq 1.99$, n.s.). In addition, accuracy was not affected in a dose-dependent manner in any of the tasks applied. In the first session of the 2-back task (first half of exposure) statistical analysis revealed a difference between accuracy scores in the 0.2 W kg⁻¹ condition compared with the sham control condition ($P < 0.003$), but not in the 5 W kg⁻¹ condition ($P < 0.4$). Subjects performed worst during the sham condition (93% correct responses) and best during the 0.2 W kg⁻¹ condition (96%) with performance during 5 W kg⁻¹ in between (95%). The reported *P*-values remained below the significance level of $P = 0.01$ after adjusting for multiple

Table 2 Sleep variables derived from visual scoring of the three experimental conditions: sham condition, pulse-modulated RF EMF with a 10 g-averaged peak spatial SAR of 0.2 and 5 W kg⁻¹. All-night means in min (SEM in parenthesis; *n* = 15). Sleep latency: Interval from lights off to stage 2 sleep. REM sleep latency: Interval from sleep onset (stage 2) to the first occurrence of REM sleep. Slow-wave sleep: NREM sleep stages 3 and 4

	Sham	SAR 0.2 W kg ⁻¹	SAR 5 W kg ⁻¹
Time in bed	479.2 (0.5)	479.9 (0.0)	479.9 (0.0)
Total sleep time	449.2 (2.9)	445.0 (4.5)	444.5 (3.6)
Sleep latency	16.9 (2.9)	19.4 (2.4)	20.7 (2.8)
REM sleep latency	65.8 (4.9)	67.3 (4.9)	71.8 (5.9)
Waking after sleep onset	3.8 (1.2)	5.2 (2.6)	3.6 (0.9)
Stage 2	270.6 (9.2)	268.5 (7.2)	267.3 (7.7)
Slow wave sleep	59.4 (6.0)	60.4 (5.5)	58.0 (5.7)
REM sleep	92.1 (4.2)	83.1 (5.2)	87.7 (3.5)
Movement time	9.3 (0.8)	9.6 (0.7)	9.9 (1.2)

end-points ($\alpha = 0.05$, number of tests = 18, overall correlation among cognitive outcomes = 0.44, Tukey *et al.*, 1985).

DISCUSSION

Our data point to a dose-dependent effect of pulsed RF EMF on non-REM sleep and cognitive performance in humans. Sleep EEG recordings in a controlled environment constitute a reliable method to study the effects of RF EMF exposure. Sleep is an endogenous, self-sustained cerebral process. Moreover, the sleep EEG is well characterized such that even minor physiological or pharmacological effects can be reliably recognized (e.g. Borbély *et al.*, 1983; Landolt *et al.*, 2004). With respect to GSM RF EMF, consistent evidence accumulates that pulse-modulated RF EMF exposure affects the non-REM sleep EEG in the alpha and sigma range (present study, Borbély *et al.*, 1999; Huber *et al.*, 2000, 2002, 2003; Loughran *et al.*, 2005). In agreement with the results of Huber *et al.* (2002), we observed an increase of power after handset-like RF EMF exposure (see Huber *et al.*, 2005 for signal characteristics) in the fast spindle frequency range. In addition, our data also provide evidence for a dose-response relationship: spectral power in the fast spindle frequency range (stage 2)

increased by 7.7% after RF EMF exposure at a psSAR_{10 g} of 0.2 W kg⁻¹, 10% after exposure at 1 W kg⁻¹ (Huber *et al.*, 2002), and 13.6% after exposure at 5 W kg⁻¹. Whereas; however, the increase was at a similar level throughout the sleep episode in our study (Fig. 2), Huber *et al.* (2002) reported an increase of the effect in the course of sleep that paralleled the increase of spindle activity. These long-lasting changes in the non-REM sleep EEG provide further evidence for a non-thermal effect of RF EMF up to 5 W kg⁻¹ in humans as a thermal effect is not likely to last for several hours after termination of exposure.

In addition to the fast spindle range also frequencies in the slow spindle range were affected in a dose-dependent manner by RF EMF exposure (Fig. 1). The effect, however, was only observed in the all-night spectra but not over time. This may be due to the small sample size and high inter-individual variation. More likely, the fast spindle frequency range seems to be the frequency range most sensitive to GSM exposure (Borbély *et al.*, 1999; Huber *et al.*, 2000, 2002; Loughran *et al.*, 2005).

Interestingly, bi- as well as unilateral exposure of the cortex caused changes in the sleep EEG of both hemispheres (Huber *et al.*, 2000, 2003). Because the effect did not depend on the side of exposure, we had previously hypothesized that the lower dose present at the non-exposed hemisphere may have been sufficient for a maximal effect. This interpretation, however, is not supported by our present findings of a dose-dependent effect. Therefore, the thalamus, which is critically involved in sleep spindle generation, may be a sensitive structure to RF EMF (Huber *et al.*, 2003).

In three of five cognitive tasks, speed tended to decrease during GSM exposure in a dose-dependent manner, reaching significance in the 1-back task. No dose-response relationship was found for accuracy. Surprisingly, subjects performed best in the 2-back task in the first half of the 0.2 W kg⁻¹ exposure condition. This is in contrast to our previous finding where accuracy increased during exposure to a pulse-modulated, but not to a 900 MHz continuous-wave exposure at 1 W kg⁻¹ in the 3-back task (Regel *et al.*, 2007). Thus, cognitive performance does not seem to be consistently affected and recent studies frequently failed to corroborate previous findings

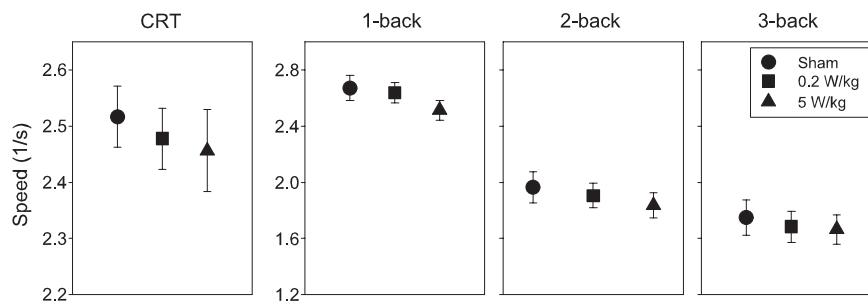


Figure 3. Dose-dependent effect of RF EMF exposure on speed (1/reaction time, mean \pm SEM; *n* = 15) in the CRT (2-Choice Reaction Time Task) and N-Back Task (1-, 2-, 3-back). Three conditions were applied: sham (●), 0.2 W kg⁻¹ (■) and 5 W kg⁻¹ (▲) RF EMF exposure (10 g-averaged peak spatial SAR). CRT: $F_{1,75} = 3.12$, $P < 0.09$; 1-back: $F_{1,75} = 9.32$, $P < 0.004$; 2-back: $F_{1,75} = 3.54$, $P < 0.07$; 3-back: $F_{1,75} = 0.87$, $P < 0.4$; factor *Condition*, linear mixed model ANOVA.

(Haarala *et al.*, 2003, 2004; Krause *et al.*, 2004; Preece *et al.*, 2005). Such inconsistencies may be due to the lack of standardized and validated cognitive tasks to assess effects of RF radiation, as well as to the large differences found across studies with respect to the induced field strength distribution, exposure signal and study design (for a discussion see Regel *et al.*, 2006). Alternatively, in several studies including our own, statistical power may have been insufficient to reliably detect RF EMF induced changes on cognitive functioning. Cognitive performance may be influenced by a variety of factors (e.g. motivation, distraction, boredom, etc.) and a sufficiently high sample size might be needed to compensate for the high intra- and inter-individual variability.

In conclusion, evidence is increasing that RF EMF exposure prior to sleep alters brain activity. Our results suggest a dose-response relationship between GSM exposure and its effects on the non-REM sleep EEG and cognitive performance. Furthermore, the long-lasting changes in the non-REM sleep EEG provide additional support for a non-thermal biological effect of RF EMF exposure.

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