

Effect of a Single 30 min UMTS Mobile Phone-Like Exposure on the Thermal Pain Threshold of Young Healthy Volunteers

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One of the most frequently investigated effects of radiofrequency electromagnetic fields (RF EMFs) on the behavior of complex biological systems is pain sensitivity. Despite the growing body of evidence of EMF-induced changes in pain sensation, there is no currently accepted experimental protocol for such provocation studies for the healthy human population. In the present study, therefore, we tested the effects of third generation Universal Mobile Telecommunications System (UMTS) RF EMF exposure on the thermal pain threshold (TPT) measured on the surface of the fingers of 20 young adult volunteers. The protocol was initially validated with a topical capsaicin treatment. The exposure time was 30 min and the genuine (or sham) signal was applied to the head through a patch antenna, where RF EMF specific absorption rate (SAR) values were controlled and kept constant at a level of 1.75 W/kg. Data were obtained using randomized, placebo-controlled trials in a double-blind manner. Subjective pain ratings were tested blockwise on a visual analogue rating scale (VAS). Compared to the control and sham conditions, the results provide evidence for intact TPT but a reduced desensitization effect between repeated stimulations within the individual blocks of trials, observable only on the contralateral side for the genuine UMTS exposure. Subjective pain perception (VAS) data indicated marginally decreased overall pain ratings in the genuine exposure condition only. The present results provide pioneering information about human pain sensation in relation to RF EMF exposure and thus may contribute to cover the existing gap between safety research and applied biomedical science targeting the potential biological effects of environmental RF EMFs. *Bioelectromagnetics* 34:530–541, 2013. © 2013 Wiley Periodicals, Inc.

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INTRODUCTION

The potential physiological and behavioral consequences of exposure to electromagnetic fields (EMFs) have been receiving growing attention. The substantial interest is mainly driven by the fact that the stable and life-long effects of natural EMFs as well as the drastically increasing number of man-made EMF sources make EMF irradiation one of the most fundamental environmental exposure factors for any living organism. In general, research on the various types of EMFs has provided valuable insight into the everyday interaction of EMFs with physical, biological, and more specifically, behavioral measures.

One of the most frequently investigated effects of EMFs on the diverse behavioral functions of complex biological systems is pain sensitivity. According to Kavaliers and Ossenkopp [1985, 1993], repeated

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magnetic field (MF) exposure accompanied by extremely low frequency (ELF) EMFs induce analgesia in mice and land snails. In addition, a substantial body of animal studies dealing with acute exposure (30 min) to specific ELF MFs demonstrated consistent inhibitory effects on opioid-induced analgesia [Kavaliers et al., 1984; Kavaliers and Ossenkopp, 1987; Tysdale et al., 1991; Prato et al., 1995]. In a different study, Mathur [2008] demonstrated in peripubertal rats that the exposure to chronic (45 days), intermittent (2 h/day) and amplitude-modulated RF EMFs differentially affected the neuronal mechanisms involved in the processing of noxious stimuli. Especially, the emotional component of phasic pain was increased over a basal eualgesic state, while late responses to tonic pain stimuli were decreased.

As Del Seppia et al. [2007] summarized in their recent extensive review, a body of conclusive results have been provided by numerous researchers investigating the question of how electromagnetic radiation alters the physiological and behavioral aspects of pain sensitivity in animals. A remarkable conclusion emerging from those studies is that both static and pulsed MFs can elicit both hyperalgesic (i.e., decreased pain threshold) and hypoalgesic (i.e., increased pain threshold) effects, depending on the exposure conditions. In addition, the reversibility of these EMF-induced biological effects received support from both human and animal studies.

For example, for human volunteers in studies applying an oscillating EMF exposure for 2 h, both the behavioral reaction (as indices of perception) and physiological responses (e.g., cardiovascular indices, stress hormone levels) to pain stimuli suggested a decreased pain threshold during the genuine EMF exposure condition compared to the sham condition [Papi et al., 1995; Sartucci et al., 1997; Ghione et al., 2004]. In contrast, Shupak et al. [2004] found a beneficial analgesic effect to thermal pain stimuli in human participants exposed to pulsed MFs. Regarding millimeter waves, Radziewsky et al. [1999] reported a suppression of human pain sensation in a double-blind, crossover study. Similarly, in a randomized, placebo-controlled, double-blind study, Kovács-Bálint et al. [2011] reported that a positive thermal pain threshold (TPT) shift occurred in healthy human volunteers who were acutely exposed to inhomogeneous static MFs.

Despite the growing body of evidence about the EMF-induced changes in pain sensation, there is no coherent explanatory model about how the particular exposure parameters may affect the alteration between the hyperalgesic and hypoalgesic effects of EMFs. For a better understanding of such a relationship, there is

an ever-increasing need to investigate the different types of EMF exposures in well-controlled experiments with precise dosimetry of the signal. In the current study, conducted with healthy human participants, we aimed to investigate the potential changes in pain sensation induced by the effect of Universal Mobile Telecommunications System (UMTS) radio-frequency (RF) EMF exposure.

Mobile phone use has increased dramatically in recent years; therefore, the effects of electromagnetic exposure by various mobile technologies have received much research interest. More specifically, access to mobile networks is now available to 90% of the world population according to a survey by the International Telecommunication Union (ITU) [ITU, 2010]. UMTS was introduced as the third generation (3G) mobile phone system in the 2000s. Service providers are moving rapidly from 2G to 3G platforms in both developed and developing countries. In 2010, according to the European Information Technology Observatory (EITO), 143 countries were offering 3G services commercially, compared to 95 in 2007 [ITU, 2010], with an estimation of over one billion UMTS subscribers for the year 2011 [EITO, 2010].

Most of the previous studies, however, focused on the adverse effects of exposure to mobile phone EMFs. For example, a considerable number of studies dealt with the potential influences of mobile phones with the former Global System for Mobile Communications (GSM) technology on self-reported symptoms and sensations like headache, migraine, sleep disturbances, forgetfulness, and skin irritation in healthy and/or sensitive individuals [Koivisto et al., 2001; Balikci et al., 2005; Arnetz et al., 2007, 2009; Cinel et al., 2008; Hillert et al., 2008; Wiholm et al., 2009]. Findings from these studies do not consistently suggest an increased level of adverse subjective symptoms relating to mobile phone-induced EMF exposure.

As for the potential beneficial effects of GSM EMF exposure, a recent animal study found profound hypoalgesia in land snails (*Helix pomatia*) [Nittby et al., 2012]. After a 1900 MHz GSM exposure for 1 h, the snails were subjected to thermal pain stimulus (hot plate). The findings indicated a decreased sensitivity to thermal pain after GSM RF EMF exposure compared to the sham control situation in a within-subject design. In contrast to GSM technology, there are only a few studies applying the newer UMTS technology in investigating changes in either objective (physiological or cognitive) or subjective variables under RF EMF exposure. Studies addressing the possible biological effects of UMTS technology fo-

cused mainly on changes in subjective well-being, arousal, various physiological functions, and cognitive performance in healthy human participants and in participants with self-reported sensitivity to EMFs [Regel et al., 2006; Eltiti et al., 2007; Rubin et al., 2010; Augner et al., 2012]. However, to our knowledge, thermal pain sensitivity has not been investigated before in relation to RF EMFs, particularly for UMTS exposure of human participants in double-blind, placebo-controlled studies.

The burning and painful thermal sensation that is associated with capsaicin results from its chemical interaction with sensory neurons located in the skin [Tominaga and Julius, 2000; Willis, 2009]. Capsaicin-sensitive sensory neurons are known to be polymodal nociceptors, a significant part of C and A δ fiber nociceptors, which are typically involved in heat sensation. Capsaicin selectively excites these fibers. Following topical application of capsaicin, both nociceptor response thresholds and objective pain thresholds were shown to be lowered for heat application from 45 to 35 °C [Culp et al., 1989; LaMotte et al., 1992], indicating substantial chemical sensitization of capsaicin (and heat)-sensitive nerve endings. Thus, topical capsaicin treatment may be suitable for validating measurement protocols for heat-induced cutaneous pain.

The purpose of the present study was to investigate the potential effects of generic UMTS exposure on pain threshold perception in response to thermal stimuli in healthy human participants in a crossover, double-blind, placebo-controlled experimental arrangement. Before EMF exposure, the heat stimulation device (HSD) was validated in a separate protocol (positive control) where thermal pain was induced by topical capsaicin treatment.

Experiment 1: Pharmacological Validation of the Heat Stimulation Device by Measuring the Capsaicin-Induced Thermal Pain Threshold

Participants. Twenty students from the University of Pécs, Hungary (14 females, mean age 21.92 ± 2.8 years, range 18–30 years) were recruited from the department's volunteer database. All participants were right-handed by self-report. They were naïve with regard to the purpose of the experiment and reported normal, pain-free health conditions with no medication whatsoever. Participants were compensated by practical course credit for the time spent in the experiment. They were instructed that they could withdraw from the experiment at any time and this would not affect their compensation. All participants signed a written consent after the experiment was fully explained. The

work was conducted in accordance with the declaration of Helsinki and the experimental protocol was approved by the Ethical Committee of the University of Pécs.

Heat stimulation device. Heat stimuli were delivered by a computer-controlled device (HSD; designed by one of the authors, I.H.) equipped with a miniature piezoelectric heating pad (heating surface 5 mm $\times$ 5 mm), a 3D motion detector (accelerometer) and a precise digital temperature sensor (Metron Avionics, Pécs, Hungary). The sensor of the device was normally attached to the inner surface on the tip of the index finger. The mild noxious stimulus was the increasing surface temperature of the heating pad with adjustable temperature range and ramp rate. The temperature was increased from 35 °C at a rate of 5 °C/s. The heating phase was immediately interrupted and the device actively cooled down to the initial temperature level within 2 s if there was a quick movement of the stimulated finger (over 150 mg acceleration value). The pad temperature at the moment of the trial termination was logged in a PC microcomputer (100 Hz sampling rate) to assess the TPT. In the current study, the heating phase was interrupted by the participants' index finger movements or, in case of no movement, when the pad temperature reached 55 °C (cut-off temperature). The schematic arrangement of the TPT measurement is depicted in Figure 1A.

Procedure. Figure 2 schematizes the experimental procedure. Participants were asked to abstain from alcohol, caffeine, and peppery substances at least 6 h before the experiment. Each participant complied with these criteria by self-report. Both verbal and written instructions were used to inform the participants about the task. After participants signed the consent statement, they were comfortably seated in an air-conditioned room and the heat stimulation sensors were attached to the fingertips. Participants were instructed to move their stimulated finger at the moment when the heat sensation turns to an obvious pain sensation. Thus, their finger movement terminated the trial, and the heating pad temperature at the moment of the trial termination was considered to be the actual TPT. The participants received two practicing trials on both hands, which were followed by the five experimental blocks. In each block, both index fingers were stimulated randomly in three trials with 60 s inter-trial intervals. The first experimental block served as the control block, when no treatment was used. After the control block, a capsaicin solution (0.5 w/v% dissolved in 96% ethanol) was applied to the inner surface of the tip of the participant's index finger

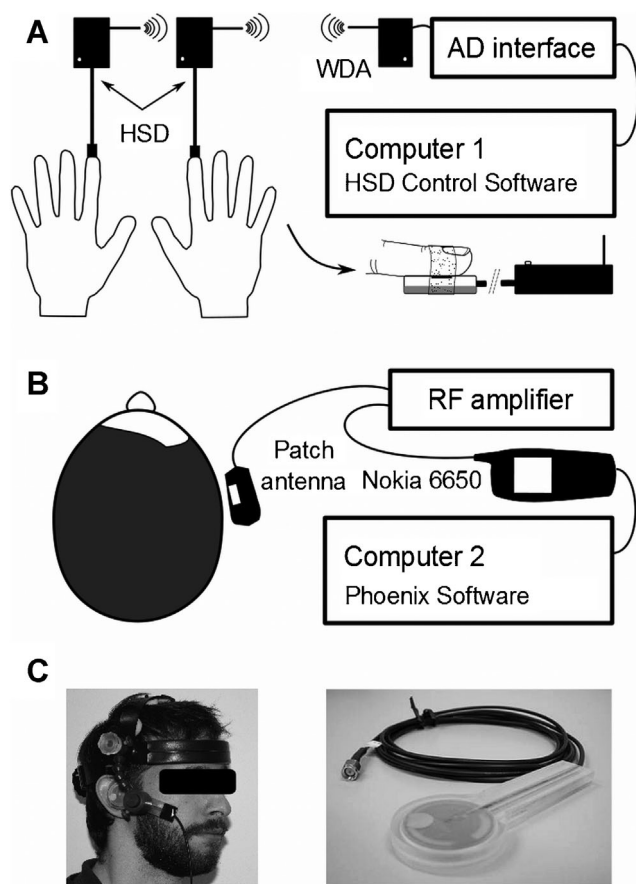


Fig. 1. Schematic representation of the experimental arrangements. **A:** Thermal pain threshold (TPT) was measured by a computer-controlled heat stimulation device (HSD) equipped with a miniature piezoelectric heating pad, 3D motion detector (accelerometer) and precise digital temperature sensor. **B:** EMF exposure device was based on a dual-band patch antenna attached to a UMTS mobile phone connected by a serial cable to a personal computer and controlled by software. **C:** Patch antenna (right) was mounted next to the right ear, mimicking the normal use of mobile phones (left) as previously reported by the volunteers.

(either the left or right index finger in a counter-balanced order across participants) on an area of about 1 cm × 1 cm. For the sham condition, the other index finger was treated with ethyl alcohol on an area of

similar size. The TPT was measured in four consecutive blocks of trials: immediately after the treatment (Block A), and with a delay of 30 (Block B), 60 (Block C), and 90 min (Block D). Each participant performed a total of 30 trials in one experimental session (2 fingers × 3 trials × 5 blocks).

Results. TPT data (in °C) were recorded for each trial and for each participant, and were analyzed by repeated measures of ANOVA (*rANOVA*) using the ϵ -adjustment procedure [Quintana and Maxwell, 1994] and paired-sample *t*-test, respectively. In addition, Bonferroni adjustments were performed for the follow-up analysis of the significant main effects and interactions. Figure 3 shows the average threshold data as a function of the blocks.

To analyze the TPT data, we performed separate analyses for the treatment blocks (Blocks A, B, C, D) and the control block. First, for the control block, the average TPT data for each trial were analyzed by *rANOVA* with factors of index finger (two levels: left vs. right index finger) and Trial (three levels). This yielded a significant main effect of Trial ($F(2,36) = 26.75, P < 0.001$) with a significant linear trend ($F(1,18) = 29.08, P < 0.001$), indicating that participants showed a linear increase in their TPT in three consecutive trials of the control block. This linear increment in TPT values might rely on the effect of desensitization to the repeated stimulation.

The data of the treatment blocks were also analyzed by a *rANOVA*. The three-way factorial design comprised, as independent variables, treatment (two levels: capsaicin, sham), block (four levels: A, B, C, D), and trial (three levels). The main effects of treatment and trial reached significance (treatment: $F(1,18) = 8.45, P < 0.01$; trial: $F(2,36) = 417.11, P < 0.001$). Although TPT values again increased linearly as a function of trial in each block, the participants still showed significantly lower TPTs in each trial of the capsaicin condition compared to the sham condition. As post hoc

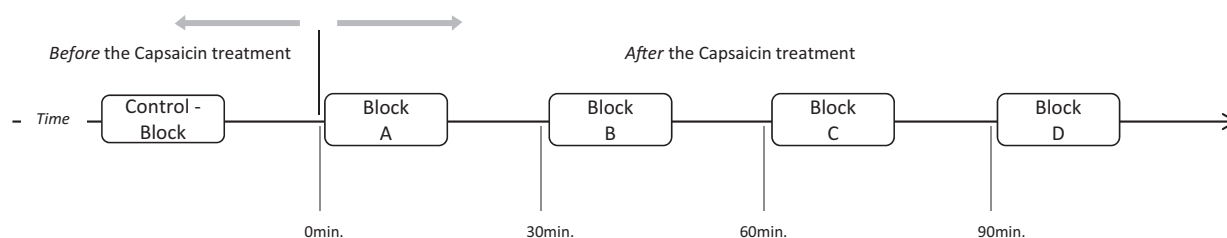


Fig. 2. Schematic diagram of the protocol of Experiment 1. Schedule of the experimental session consisted of one control block and four treatment blocks (A, B, C, D). In each block, both index fingers were stimulated randomly in three trials with a 60 s inter-trial intervals. "0 min" indicates the moment of capsaicin treatment.

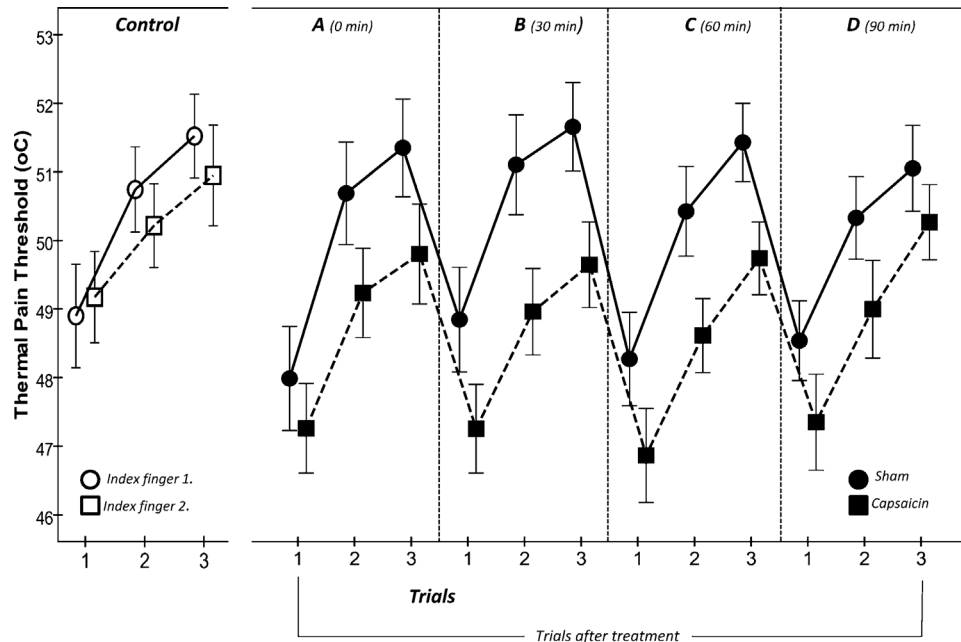


Fig. 3. Results of Experiment 1. The mean thermal-pain threshold (in °C) was measured in 19 individuals as a function of blocks of trials (A, B, C, D) for two treatment conditions (capsaicin and sham). Error bars represent the standard error of the mean.

analyses revealed, the capsaicin and sham conditions, with lower TPT values for the capsaicin condition, were significantly different in Blocks B ($t(18) = 2.99$, $P < 0.05$) and C ($t(18) = 3.11$, $P < 0.01$), but did not differ in Blocks A ($t(18) = 2.11$, not significant (n.s.)) and D ($t(18) = 1.71$, n.s.). These results clearly indicate that capsaicin treatment significantly lowers the TPT in the present measurement protocol. This conclusion was further supported by analyzing the differences between the control block and treatment blocks. More specifically, paired-sample t -tests revealed a non-significant difference between the control block (average TPT data) and any of the sham condition blocks. In contrast, TPT data of the capsaicin condition were found to be significantly lower compared to the control in Blocks A ($t(18) = 2.82$, $P < 0.05$), B ($t(18) = 3.33$, $P < 0.05$), and C ($t(18) = 4.29$, $P < 0.001$), and marginally but significantly lower in Block D ($t(18) = 2.57$, $P = 0.07$).

Taken together, the present results, in line with the vast evidence of literature data, strongly suggest that topical application of capsaicin as a positive control protocol is appropriate in an experimental arrangement concerning the induction of heat-related pain sensation in a TPT protocol. The TPT protocol, in turn, can be used for testing possible adverse effects of EMF exposure on heat-related nociception.

Experiment 2: Effect of UMTS EMF Exposure on the Thermal Pain Threshold

Participants. A new group of 22 under- and post-graduate students (10 females, aged between 20 and 29 years with a mean of 22 years, $SD = 2.65$) from the University of Pécs participated in this experiment. All participants were right handed by self-report. They were naïve with regard to the purpose of the experiment and reported normal, pain-free health conditions with no recent history of medication. All participants received course credit for their participation and provided a written consent.

UMTS exposure device. The UMTS RF exposure system was previously developed and successfully used in our laboratories in conjunction with the EMF NEAR project [Stefanics et al., 2008; Parazzini et al., 2010; Trunk et al., 2013]. The schematic arrangement of the UMTS exposure is depicted in Figure 1B.

The exposure device was based on a single-sided, round, dual-band patch antenna (Model M30EXO-0250-XX, Reinheimer Elektronik, Wittenberg, Germany) with the resonant surface and ground plane on the same side. This antenna arrangement provided sufficiently enhanced local exposure at the ear region (Fig. 1C, right). The 31 mm diameter, 0.5 mm thick patch antenna was encapsulated in a

40 mm diameter, 7 mm thick transparent plastic capsule with styrofoam isolation. The antenna was tuned with a waveguide resistor resonator and capacitors (SMD realization). Reflection measurements demonstrated that the capsule did not have any significant effect on the antenna's reflection parameters or effectiveness. Three configurations were measured: (1) patch antenna in free space, (2) patch antenna in free space with capsule, and (3) patch antenna with capsule close to the head. The measured reflection coefficient (S_{11}) values for the three conditions were -23 , -23.3 , and -25 dB, respectively. The non-metallic side of the antenna was designated to be the application side. The covering case on this side was 1 mm thick. The signal source of the patch antenna was a UMTS mobile phone (Nokia 6650, Nokia, Espoo, Finland), operating with a constant power level out of the normal service power control scheme. The phone was connected by a serial cable to a personal computer and was controlled by Phoenix Service software (Version 2005/44_4_120, Nokia). The service software was used in test mode and provided a stable and adjustable constant level of output power from -13 to $+21$ dBm (with 1 dB increments). The system generated a specific RF signal cocktail in order to model the operation of a real UMTS (3G) mobile phone handset. The system was therefore set to Wideband Code Division Multiple Access (WCDMA) mode operating at the 1947 MHz carrier frequency (which corresponds to the operating frequency of UMTS mobile phones in Europe) with a wideband 5 MHz modulation of the RF carrier signal [Ndoumbè Mbonjo Mbonjo et al., 2004]. The instability of the output power of the Nokia 6650 was less than 2% in variation ($\sigma < 2\%$) measured via the external connector (Online Supplementary Material, Fig. S1). The cable attenuation level between the phone and amplifier was found to be 0.4 dB at 1947 MHz.

The signal of the mobile phone was amplified by a constant RF power amplifier and the signal was fed to the patch antenna. The output power of the amplifier, measured at the antenna input cable, was 29.6 ± 1 dBm. Double-blind experimental conditions were ensured by a two-position switch (A or B) located on the front panel of the RF amplifier: one position was associated with genuine exposure, and the other with sham exposure. The investigator was not aware of the actual exposure condition, apart from the status of the switch (A or B). All participants were exposed to UMTS EMFs with both switch positions (genuine and sham exposure conditions).

The patch antenna was mounted on a plastic headset in a position mimicking the normal use of a mobile phone (Fig. 1C, left). To estimate the level of

RF exposure in the brain, measurements of the absorbed RF power in the head (the specific absorption rate, SAR, in W/kg) were performed in a Specific Anthropomorphic Mannequin (SAM) phantom filled with standard brain tissue-equivalent liquid (HSL1950, Schmid and Partner Engineering, Zurich, Switzerland). In these measurements, a 3D step motor robot system (3-Axis Positioning Table, Arrick Robotics, Tyler, TX), and an internal E-field probe (ER3DV4R, Schmid and Partner Engineering) was connected to an EASY4 four-channel exposure acquisition system (Schmid and Partner Engineering) and a non-metallic positioning system. The sensitivity of the system in the brain tissue-equivalent phantom was 0.005 W/kg. The uncertainty of SAR measurements according to the European Committee for Electrotechnical Standardization (CENELEC) standard EN 62209-1 is 1.12 dB [CENELEC, 2006]. These measurements revealed that the SAR pattern generated by the patch antenna was localized close to the area of the antenna surface and was highly concentrated there. The total uncertainty of the exposure system was ± 2.8 dB, including the uncertainty of positioning the antenna at the subject's head. Quantitatively, the maximum SAR in the brain tissue-equivalent liquid was 1.75 and 0.73 W/kg averaged over 1 and 10 g liquid, respectively, at a depth of 2 cm from the shell surface of the phantom, which roughly corresponded to the position of the inner ear region. The estimated SAR levels at the skin of the pinna were 3.75 W/kg. This estimation was based on numerical extension of the SAR measurements in the CENELEC standardized head phantom [CENELEC, 2006]. The averaged SAR over 10 g in the brain tissue-equivalent liquid phantom was below 2 W/kg in any position within the phantom, meeting the limit of public exposure to RF radiation in the European Union (EU) Recommendation (Brussels, Belgium) [EU, 1999]. The participants were asked about their general thermal perception in each session. A question regarding any possible heating effect felt around the ear was included in the questionnaire. All subjects reportedly did not experience substantial thermal sensation from the antenna.

Protocol. Figure 4 schematizes the procedure of Experiment 2. The protocol was similar to that used in the first experiment. A double-blind, counterbalanced design was employed to test the effect of UMTS exposure on the TPT. The new participants were asked to perform the same TPT task as in Experiment 1, but now capsaicin treatment was replaced by UMTS exposure. Participants performed the task in two experimental sessions—UMTS and sham exposure sessions—with 1 week apart. The order of the UMTS

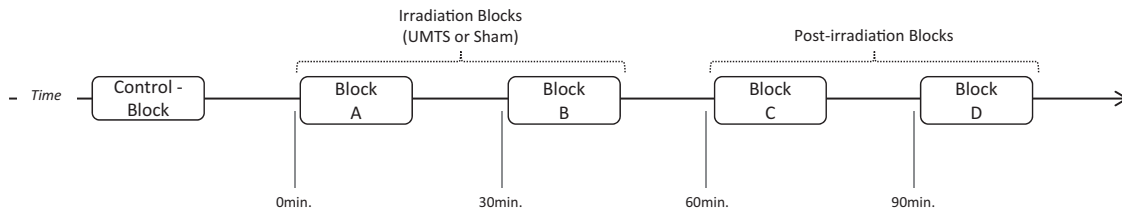


Fig. 4. Schematic diagram of the protocol of Experiment 2. In two exposure sessions (UMTS and sham), there were five blocks of trials (control block, A, B, C, D). The participants index fingers received heat stimulation. Prior to the exposure sessions, participants performed a block of control trials. After the control block, the participants head was exposed to UMTS or sham irradiation for 30 min. The TPT was recorded in one block of trials at the beginning (Block A) and end (Block B) of the irradiation period. Participants also received two blocks of trials 60 min (Block C) and 90 min (Block D) after irradiation.

and sham sessions was counterbalanced across participants and gender. There were five blocks of trials in each session. In each block, the participants' two index fingers received heat stimulation randomly in six trials (three trials $\times$ two fingers). Two practicing trials were given for both fingers. The participants performed a block of control trials 30 min prior to the exposure sessions. After the control block, the participant's head was exposed to either UMTS or sham irradiation for a duration of 30 min in the normal mobile phone use position on the right side. The participant's TPT was recorded in one block of trials at the beginning (Block A) and in another block at the end (Block B) of the irradiation period. In addition, the participants received two blocks of trials with a delay of 60 (Block C) and 90 min (Block D) after the irradiation. Thus, each participant performed a total of 60 trials in the two separate experimental sessions: (3 trials $\times$ 2 index fingers $\times$ 5 blocks $\times$ 2 sessions).

In addition, after each block of trials, participants were asked to mark how painful the stimulation was using a visual analogue rating scale (VAS). The scale was a 10 cm long line on a printed sheet, where "no pain" was printed on the left side, and "worst possible pain" on the right. The participants' responses were later measured from left to right and the subjective pain rating was expressed in mm.

RESULTS

Control Block

To analyze the effects of UMTS irradiation on TPT, separate *r*ANOVAs were performed with average TPT data for the control block, the irradiation blocks (Blocks A and B), and the post-irradiation blocks (Blocks C and D). For the control block, the ANOVA with factors "device" (2 levels: UMTS control and sham control) and "trial" (3 levels: three within-block trials) yielded a significant main effect

only for the factor of trial ($F(2,42) = 117.13$, $P < 0.001$), indicating that TPT increased in the three consecutive trials of the control block. This finding is in line with the pattern of results found in Experiment 1 and suggests an increased desensitization to thermal pain across the trials. Figure 5 depicts mean TPT data in initial control, irradiation, and post-irradiation blocks.

Irradiation Blocks

For the irradiation block, we also tested whether the side of the thermal pain induction (contralateral or ipsilateral side, relative to the side of UMTS exposure) had any differential effect on TPT. Therefore, a four-way factorial ANOVA was performed with the factors "induction side" (two levels: contra/ipsilateral), "device" (two levels: sham and UMTS), "block" (two levels: Blocks A and B), and "trial" (three levels). Of the main effects, only the factor of trial was found to be significant ($F(2,42) = 138.24$, $P < 0.001$).

The analyses of interactions revealed, first, a significant two-way interaction of block $\times$ trial ($F(2,42) = 4.84$, $P < 0.05$); the participants' TPT showed a stronger increase as a function of trials in Block A compared to Block B. Second, a marginally significant result was found for the device $\times$ trial interaction, indicating a slightly stronger desensitization to thermal pain across trials for the UMTS condition compared to the sham condition ($F(2,42) = 3.01$, $P = 0.09$). In addition, a significant three-way interaction of induction side $\times$ device $\times$ trial was found, suggesting that the side of UMTS irradiation relative to the side of thermal pain induction might have a differential effect on the device $\times$ trial interaction ($F(2,42) = 4.46$, $P < 0.05$). More specifically, results of separate ANOVAs for the contra- and ipsilateral conditions suggest that when the irradiation fell contralateral to the thermal pain induction side, the UMTS irradiation induced a stronger desensitization to thermal pain compared to the sham condition

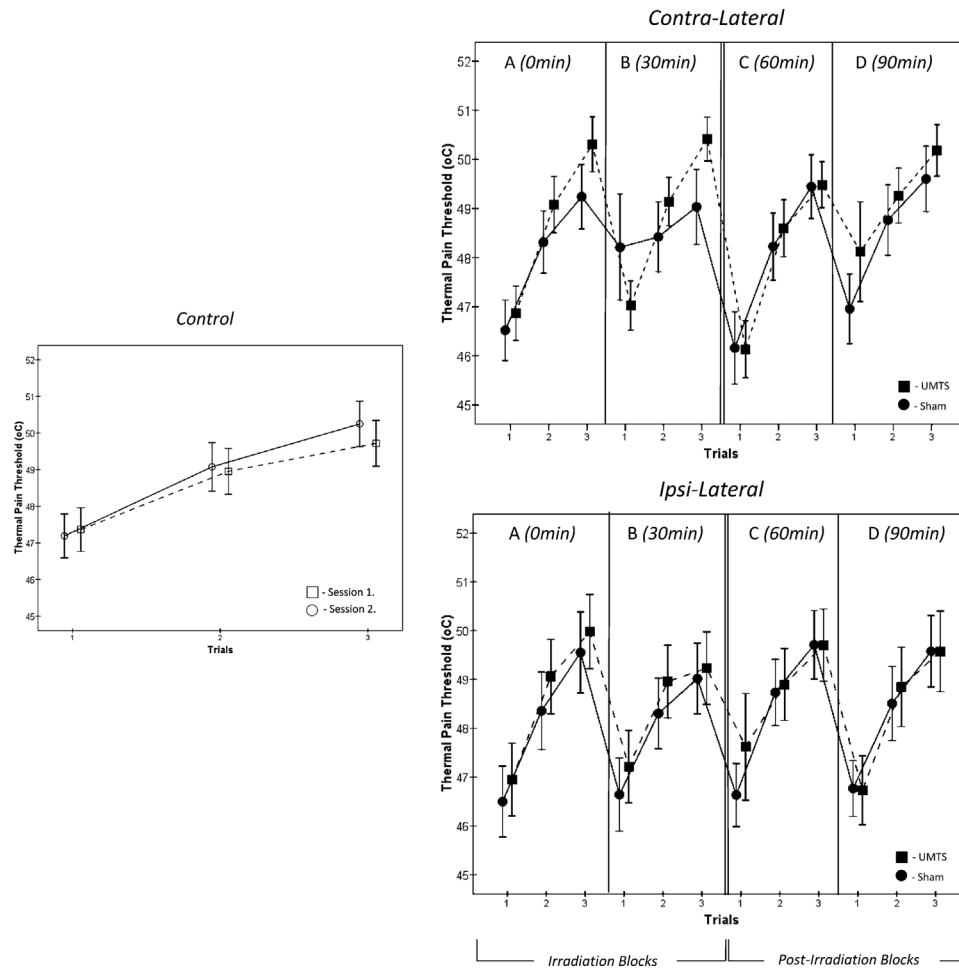


Fig. 5. Results of Experiment 2. Mean thermal-pain threshold (in °C) was measured in 22 individuals in five blocks of trials (control block, A, B, C, D). The side of thermal pain induction was either contra- or ipsilateral to the side of UMTS exposure. Results are presented separately for the ipsi- and contralateral induction sides. Error bars represent the standard error of the mean.

(device $\times$ trial interaction for the contralateral induction side: $F(2,42) = 4.3$, $P < 0.05$). No similar difference between the UMTS and sham conditions was found for the ipsilateral induction side. To elaborate on the source of the significant device $\times$ trial interaction on the contralateral induction side, additional ANOVAs were performed. Both for the UMTS and sham condition, we again found an increasing TPT as a function of trials, with a larger effect size for the UMTS condition (sham condition: $F(2,42) = 59.85$, $P < 0.05$, $\mu_p^2 = 0.22$; UMTS condition: $F(2,42) = 147.57$, $P < 0.001$, $\mu_p^2 = 0.87$). The difference in the TPT between the UMTS and sham conditions showed a significant increase ($F(2,42) = 4.3$, $P < 0.05$) with a significant linear trend ($F(1,21) = 5.4$, $P < 0.05$) across the trials, suggesting a stronger increase in desensitization under UMTS irradiation. Finally, over the two induction sides, the average

TPT values of Blocks A and B were compared with the control block by an ANOVA. The results again indicate a desensitization process across trials (main effect of trials: $F(2,42) = 169.85$, $P < 0.001$), with a stronger effect under UMTS irradiation (block $\times$ device $\times$ trial interaction: $F(2,42) = 5.8$, $P < 0.05$).

Post-Irradiation Blocks

Another four-way factorial ANOVA with the same factors was performed for the post-irradiation blocks (Blocks C and D). Only the factor of trial had a significant main effect ($F(2,42) = 118.76$, $P < 0.001$), again suggesting an increased desensitization across the trials. None of the interactions, however, were found to be significant with the factor of device. In addition, no differences were found between the control block and the post-irradiation blocks.

Subjective Pain Ratings

Subjective pain ratings, similar to the TPT analysis, were analyzed by *r*ANOVAs with the factors “device” (two levels: sham and UMTS) and “block” (two levels: Blocks A and B, or Blocks C and D). In addition, a paired-sample *t*-test was performed to compare subjective pain ratings in the two sessions of the control block. Subjective pain rating data from three of the 22 participants were excluded from analyses because their ratings were highly irresponsive in respect to the instructions (e.g., they indicated no pain, or just an extremely low level of pain near cut-off temperatures). Descriptive statistics of the subjective pain ratings are shown in Table 1. The detailed results of the subjective pain rating analyses are summarized below.

The two device conditions of the control block of sham control and UMTS control were not found to be different in subjective pain ratings. The analysis of the irradiation blocks (Blocks A and B) revealed a significant interaction between the factors of device and blocks ($F(1,18) = 6.16$, $P < 0.05$). As the ANOVAs for the sham and UMTS conditions suggested, the main source of the interaction derived from the difference between the sham and UMTS conditions in the change of subjective pain ratings from Block A to Block B. More specifically, while there was a marginally significant increase in subjective pain ratings from Block A to Block B for the sham condition ($F(1,18) = 4.2$, $P = 0.055$; 15 of the 19 participants), no similar change was revealed for the UMTS condition (only 6 of the 19 participants showed such an increase).

In addition, compared to the pre-exposure control block (control), results of Bonferroni-corrected paired-sample *t*-tests indicated that the subjective pain ratings in the second irradiation block (Block B) of the sham condition were significantly higher than those measured in the control ($t(18) = -3.28$, $P < 0.01$). In contrast, for the UMTS condition no difference was obtained between the control block and the second

irradiation block (Block B). This finding suggests that compared to the pre-exposure control, participants showed an increased sensitivity to thermal pain across the two exposure blocks in the sham condition, but not in the UMTS condition.

The analysis of the post-irradiation blocks yielded a significant main effect of block ($F(1,18) = 5.17$, $P < 0.05$), as well as a significant interaction of device $\times$ block ($F(1,18) = 5.67$, $P < 0.05$). The post hoc analyses showed that subjective pain ratings under UMTS irradiation significantly increased from Block C to Block D ($F(1,18) = 10.01$, $P < 0.01$). In contrast, no such a change was obtained for the sham condition. Compared to the control blocks, none of the post-irradiation blocks were found to be significantly different.

In sum, the above findings suggest that subjective pain became stronger by the second irradiation block for the sham trials. In contrast, the trials under UMTS exposure were not accompanied with an increased sensitization to thermal pain.

DISCUSSION

In the current study, we tested the possible acute effects of a 30 min generic RF EMF exposure emitted by the new generation of commercially available 3G UMTS mobile phones on the human TPT in a capsaicin-validated protocol. Experimental data were obtained using randomized, placebo-controlled trials in a double-blind manner with a precisely tested and controlled dosimetry for the UMTS EMF exposure. Although the present exposure did not robustly interfere with human TPT values, it caused a measurable desensitization effect through acutely (blockwise) increasing TPT thresholds on the contralateral side of exposure. In parallel, subjective pain, according to VAS ratings, became stronger in the second irradiation block (i.e., by the end of the irradiation phase) for the sham condition (but not for UMTS), indicating that the overall subjective sensitization to repeated thermal

TABLE 1. Means (and Standard Deviations) of Subjective Pain Ratings Assessed Using the Visual Analogue Rating Scale (VAS) for Each Block in Experiment 2

Control blocks		Irradiation blocks				Post-irradiation blocks			
		Block A (0 min)		Block B (30 min)		Block C (60 min)		Block D (90 min)	
Sham control	UMTS control	Sham	UMTS	Sham	UMTS	Sham	UMTS	Sham	UMTS
39.86 (16.65)	41.76 (16.69)	42.89 (14.92)	42.55 (18.55)	45.42 (15.93)	40.78 (17.95)	43.42 (18.12)	40.34 (17.07)	44.06 (19.9)	45.81 (17.95)

N = 19.

stimulation was attenuated in the genuine exposure. Possible physiological mechanisms behind the observed “desensitization” effect are briefly discussed below.

Validation of the Thermal Pain Threshold Measurement Protocol

The experimental TPT protocol was validated with a topical capsaicin treatment. Capsaicin can result in acute pain and potent acute hyperalgesia in humans when applied topically to the skin surface or injected into the skin [Szolcsányi, 1977; Carpenter and Lynn, 1981; LaMotte et al., 1992]. The involvement of capsaicin-sensitive sensory nerve endings in static MF-evoked anti-nociceptive effects has also been recently demonstrated in animal studies using mice [Sándor et al., 2007]. In the present protocol, capsaicin exerted an immediate and lasting decrease of the TPT in human participants, indicating the development of acute thermal pain sensitization. Contrary to this, the slope of the blockwise thermal desensitization to repetitive stimulation did not change compared to TPT in the sham condition, indicating that although topical capsaicin treatment effectively lowers TPT, it does not directly interfere with the brief desensitization elicited by repeated heat stimulation trials within an experimental block.

Taken together, the present validation results, in line with the vast evidence of literature data, strongly suggest that topical application of capsaicin as a positive control protocol is appropriate in an experimental arrangement to induce heat-related pain in a TPT paradigm.

Possible Mechanisms of UMTS-Induced Desensitization Effects

The mild alteration in pain intensity may have been derived from the attenuating influence of RF EMFs on objective pain discrimination, which manifested as a reduced sensitization to repetitive stimulation on the contralateral side of exposure. As shown by results of the VAS ratings, this mild desensitization effect was accompanied by a reduced overall subjective unpleasantness of the heat stimuli in the UMTS but not in the sham condition. These effects were not observable before the exposure, only developed during genuine but not sham exposure, and recovered about 60 min post-exposure.

Widespread psychophysical research evidence combined with functional magnetic resonance imaging (fMRI) showed that after unilateral tactile stimulation of the body, contralateral activation can be observed in the primary somatosensory cortex (S1), which is accompanied by a more complex and often

bilateral activation in the secondary somatosensory cortices (S2) [Coghill et al., 1994, 2001]. On the contrary, the parallel sub-system, which conveys thermal and noxious information and is located in the anterolateral (spinothalamic) pathway, is not as highly lateralized, showing bilateral interconnections already at the level of the spinal cord and subsequent relay structures of the central nervous system (CNS). Recent fMRI studies showed that noxious stimuli (including heat) applied unilaterally in healthy volunteers may produce reliable contralateral activation only in the S1, while most of the pain-relevant, higher-order cortical structures such as the S2, or more particularly the posterior insula, anterior cingulate cortex, and posterior parietal cortex, also show bilateral activation to such stimuli [Talbot et al., 1991; Frot and Mauguier, 2003]. A recently published meta-analysis of 140 neuroimaging studies provided activation-likelihood estimates (ALE) for hemispheric dominance in pain processing and showed the importance of the right hemisphere, with the strongest ALE peaks and clusters found in the right insular cortex and anterior cingulate cortex [Duerden and Albanese, 2013], which have been previously shown as bilaterally active, secondary pain processing areas often termed as the cortical representations of the “suffering” component of pain.

The presently described acute desensitization effects of genuine UMTS exposure were small in appearance, suggesting that either the rapidly responding pain detection system of the S1 may not be susceptible to the UMTS exposure, or the effects of exposure may have been compensated by the bilateral nature of the cortical representation of pain. This latter is thought to subserve the obvious evolutionary purpose of survival of the individual [Coghill et al., 1994]. However, the acute (within-block) desensitization to repeated applications of mild noxious thermal stimuli may have been represented elsewhere (e.g., in the S2, which is primarily denoted to pain intensity discrimination and is usually activated contralaterally to the stimulation side).

Intensity discrimination is mainly a neocortical function that is primarily represented in sensory brain areas located in the vicinity of the source of the UMTS signal. As it is accepted that the brain tissue susceptible absorbs the energy of the signal [Gandhi, 2002], in line with previous investigations [Eulitz et al., 1998], it is reasonable to suppose that the behavioral effects that are attributed to non-thermal RF EMF exposure may be caused by subtle perturbations in neural oscillations, resulting in a decreasing internal signal-to-noise ratio and thus less accurate information processing.

In VAS ratings, the affective (“suffering”) components of pain were reflected, which are known to be encoded in the reportedly right hemisphere-dominant secondary somatosensory (pain) areas such as the anterior cingulate cortex or posterior insula. Their involvement may account for the observed reduced overall affective pain perception during the irradiation blocks in the genuine UMTS but not in the sham exposure sessions.

In conclusion, the present study is the first to demonstrate that mobile phone-like UMTS EMF exposure may induce an acute, mild pain desensitization shift in healthy human participants. Already published subjective symptoms in human studies are mostly based only on self-reported pain sensation, and do not unequivocally occur as being related to RF radiation in double-blind conditions. Aside from sporadically observed effects on health, the therapeutic use of pulsed EMFs for whole-body exposure in pain relief cannot be recommended without more scientific evidence from high quality medical trials in the future. In a systematic review, Hug and Rösli [2012] collected randomized, sham-controlled, double-blind human studies to assess the possible therapeutic effects of low frequency pulsed EMFs and concluded that the evidence for the therapeutic effects of whole-body pulsed EMF exposure is currently insufficient due to the small number of studies and heterogeneity of the findings.

The present data, therefore, may fill the existing gap between biomedical and safety EMF research and may open new avenues for the optimization of EMF parameters, even for possible therapeutic clinical applications involving pain.

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