

Mobile Phone Emissions and Human Brain Excitability

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Objective: To test—via Transcranial Magnetic Stimulation (TMS)—the excitability of each brain hemisphere after ‘real’ or ‘sham’ exposure to the electromagnetic field (EMF) generated by a mobile phone operating in the Global System for Mobile Communication (GSM).

Methods: Fifteen male volunteers attended two experimental sessions, one week apart, in a cross-over, double-blind paradigm. In one session the signal was turned ON (EMF-on, real exposure), in the other it was turned OFF (EMF-off, sham exposure), for 45 minutes. Motor Evoked Potentials (MEPs) were recorded using a paired-pulse paradigm (testing intracortical excitability with 1 to 17 ms interstimulus intervals), both before and at different times after exposure to the EMF. Short Intracortical Inhibition (SICI) and Facilitation (ICF) curves were evaluated both on the exposed and non-exposed hemispheres. Tympanic temperature was collected during each session.

Results: The intracortical excitability curve becomes significantly modified during *real* exposure, with SICI being reduced and ICF enhanced in the *acutely* exposed brain hemisphere as compared to the contralateral, non-exposed hemisphere or to sham exposure. Tympanic temperature showed no significant main effect or interactions.

Interpretation: These results demonstrate that GSM-EMFs modify brain excitability. Possible implications and applications are discussed.

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As digital mobile phone technology is now used by more than 500 million people worldwide and is spreading, scientific interest in its potential impact on human health and performance has significantly increased in recent years.¹ Although the biological effects of electromagnetic fields (EMFs) on the overall body have been extensively studied over the past several decades, relatively few investigations have focused on more specific biological functions (namely, brain cortical excitability) under the influence of electromagnetic time-varying fields in frequency ranges relevant to mobile phone emissions applied directly to the human head. The literature contains a few sparse contributions using neurophysiological techniques. However, these studies either evaluate the effects on brain structures at some distance from the EMF source (brainstem, subcortical relays, visual pathways) or test the function of auditory relays reflecting contributions from both hemispheres,^{2–14} thereby diluting the unilateral effect of EMFs, which are applied mainly to one side of the head, or the studies address the effect of hyperthermia without considering EMF effects.^{15,16}

The signal generated by the Global System for Mobile Communication (GSM), the world’s most extensively used system, operates at frequencies around 900MHz and is also the most commonly studied signal in the area of biological effects.

To explain the interaction between EMFs and living organisms, researchers have proposed two kinds of mechanisms¹⁷: thermal and nonthermal. The thermal effects (correlated to radiation intensity) have been studied at great length, and safety guidelines have been produced and imposed by the International Authority to avoid adverse reactions.¹⁸ After GSM-EMF exposure of at least 25 to 30 minutes, temperature changes of about 0.1° C were evaluated empirically at the tympanic and brain levels, respectively^{19–21}; this temperature increase has been considered irrelevant for the functional and structural integrity of the brain and largely compensated by the thermo-stabilizing properties of the blood circulating in the head/brain.²²

In contrast, the nonthermal effects of EMFs so far have not been examined in depth,^{23,24} even if various mechanisms have been considered, such as the modu-

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lation of membrane ionic channels for Na^+ and K^+ ,²⁵ the alteration of Ca^{++} cell homeostasis,²⁶ the increase in cell excitability,²⁷ or the activation of cellular stress response.^{28,29} In this regard, both *in vitro*^{28,30,31} and *in vivo* experiments on animals^{32,33} and humans³⁴ have shown the biological effects after acute GSM 900 EMF exposure (from 30 minutes to 4 hours). These effects have been interpreted as secondary to a variety of cellular signal transduction pathways and to gene activation,³⁵ such as heat shock (see Cotgreave's³⁶ review).

Due to the close proximity of the mobile phone device to the head, the human brain is exposed to relatively high specific absorption rates (SARs) compared with the rest of the body.³⁷ This aspect was addressed previously by means of neurophysiological and radiological techniques to evaluate the *in vivo* effects of the GSM signal on both brain physiology and cognitive performance. Unfortunately, the resulting data are contradictory (see Hamblin and Wood's,¹ Hossmann and Hermann's,³⁷ and Cook and colleagues³⁸ reviews), and no concrete influence of GSM-EMF exposure on human brain functioning has been demonstrated to date. For instance, some authors who originally reported GSM-EMF effects on brain functioning were unable to replicate their original results in later experiments, conducted with "methodological improvements," including double-blind designs and/or multicenter testing (eg, see Wagner and colleagues,³⁹ Haarala and colleagues,^{40,41} and Krause and colleagues⁴²). These inconsistencies may have been due to a number of reasons, such as low and variable power output of the phones used, incomplete experimental designs, inappropriate statistical analysis, or as a main factor, the inadequacy of the techniques used to investigate brain functioning. To our knowledge, transcranial magnetic stimulation (TMS), which is currently one of the most effective and reproducible methods for directly addressing motor cortex physiology, has never been used for investigating brain functioning under GSM-EMF exposure. During normal mobile phone use, the aerial is near the head in the parietotemporal area, about 30 to 40mm from the scalp. TMS is known to provide a reliable measure of cortical excitability both in the motor target area and in its connections,^{43,44} such as the parietal and temporal ones. More importantly for the aim of this study, one should bear in mind that intracortical inhibitory/facilitatory (ICI/ICF) curves reflecting intracortical excitability of the motor cortex can be investigated reliably with paired-pulse TMS using a pair of *conditioning* and *test* stimuli separated by a programmable interval (ppTMS).⁴⁵ These measures are fairly symmetrical in the two hemispheres of healthy subjects and are highly reproducible in a test-retest paradigm in the same subject, as well as across different subjects, being little in-

fluenced by the experimental conditions.⁴⁵⁻⁴⁹ Therefore, TMS, specifically owing to the ppTMS paradigm, is particularly suitable for selectively testing the cortical excitability of each hemisphere after exposure to mobile phone emission.

Subjects and Methods

The experimental protocol was performed on healthy young male volunteers (15 subjects; age range, 20-36 years) to avoid the confounding effect of the cyclical ovarian hormonal impact on the motor cortex excitability of young women.⁵⁰ A written informed consent was obtained before the experiment, after approval by the local ethical committee. Subjects were instructed to abstain from caffeine, alcohol, and medication and to maintain their regular sleep-wake schedule on the 3 days before each experimental session. No mobile phone use was allowed on the day of the experiments. All subjects were right-handed (handedness score ≥ 0.70), as evaluated by the Handedness Questionnaire,⁵¹ and were in good health. In particular, none had ever suffered from epilepsy or had a family history of seizures. Moreover, repeated electroencephalogram examinations were performed to rule out any predisposition to seizures, as represented by spiky or paroxysmal focal or diffuse activity. The exclusion criteria established by international safety standards for TMS were followed.^{43,52}

To enhance ecological validity, we used a standard and commercially available mobile phone. It was set by a test card to transmit a typical GSM signal, working with a frequency of 902.40MHz, modulated at 217Hz, with a maximum power of 2W (equivalent to an average power of 0.25W). EMF exposure was measured beforehand by using a head phantom filled with semiliquid muscle equivalent material. As in the standards of compliance,⁵³ the SAR was evaluated inside the phantom by positioning a miniature field probe 1cm in depth over a grid of a few millimeters at the minimal distance from the shell containing the material, under the ear region. The phone was positioned in correspondence to the ear at a distance of 15mm and switched "on" at its maximum power. In this experimental condition, a maximum value of SAR equal to 0.5W/kg was measured (unpublished data).

In line with these simulated measurements, the mobile phone was always mounted to the left side of the subject's head by using a modified helmet that assured a constant distance of 15mm between phone and ear; that was done to avoid subjects having any heating or buzzing effects produced by the device.⁵⁴ An identical phone, but with no battery, was positioned on the right side of the head to balance the phone weight. Both phones were in the normal position for use over the ears in such a way that the microphone was oriented toward the corner of the mouth and the aerial near the head in the parietotemporal area, about 40mm from the scalp surface. To mimic conditions associated with normal use during exposure, we allowed the subjects to move around the experiment room and to chat with the experimenters.

All subjects underwent two sessions, 1 week apart, according to a crossover, double-blind paradigm. In one session, the signal was turned "on" (EMF-on, real exposure), whereas in the other session, it was turned "off" (EMF-off, sham ex-

posure); the duration of exposure was 45 minutes in both cases. To avoid any possible uncontrolled effect due to the presence/absence of the mobiles, the subjects wore the helmet holding both phones in both sessions.

Motor-evoked potentials (MEPs) were recorded during motor cortex TMS via a paired-pulse paradigm (see later)^{45,55} before and immediately after exposure to the EMF (EMF-on or EMF-off), and also after a 1-hour interval, during which time the subject remained in the room quietly (Fig 1). MEPs were recorded after separate TMS of both hemispheres, always starting from the left one. Finally, tympanic temperature (Braun ThermoScan thermometer, Braun GmbH Kronberg, Germany) was measured before each of the three TMS recordings from both ears (see Fig 1).

Paired-Pulse Paradigm

The paired-pulse procedure was performed three times during each session according to standardized methods,^{45,55} with the subject wearing ear plugs and lying supine on a bed to facilitate complete muscular relaxation. Two magnetic stimulators were connected to a Bistim device (Magstim Company, Dyfed, United Kingdom) and to an eight-shaped coil with an inner diameter of 70mm for each wing, which was used for stimulation.⁵⁶ The center of the contact between the two circles of the eight-shaped coil was placed over the hand representation area, precisely on the designated hotspot, defined as the point from which stimuli at the minimal excitability threshold of TMS triggered MEPs of maximal amplitude and minimal latency in the target hand muscle. The hotspot position was marked on the scalp to facilitate an exact repositioning of the coil during the entire experiment. Then the resting motor threshold was identified according to international guidelines as the stimulator's output able to elicit reproducible MEPs (at least 50 μ V in amplitude) in about 50% of 10 to 20 consecutive stimuli.⁴³ Amplitudes of the "test" MEPs were measured between the two major and stable peaks of opposite polarity and compared with those of a series of "baseline," unconditioned (not preceded by the conditioning stimulus) MEPs. Muscle twitches from either hand triggered by TMS were recorded from the first dorsal interosseus muscle, via Ag/AgCl disks filled with conductive jelly in a belly/tendon montage. Skin/electrode resistances were less than 10KOhms. Signal recording was conducted using PHASIS equipment (Esaote Biomedica, Florence, Italy; 4 channels) via 1 to 2,000Hz filter setting and a poststimulus analysis time of 50 milliseconds with a 5KHz sampling rate. The stimulus intensity for the first *conditioning* pulse was set at 80% of the resting motor threshold. The second *test* pulse was given suprathreshold with an intensity of 120% of the resting motor threshold. Interstimulus intervals (ISIs) of 1, 3, and 5 milliseconds were selected to test short-interval intracortical inhibition (SICI).⁵⁷ Meanwhile, ISIs of 7, 9, 11, 13, 15, and 17 milliseconds were used to test Intracortical Facilitation (ICF). Up to a maximum of eight trials with paired TMS were recorded for each ISI during complete muscle relaxation, and the amplitude of the conditioned MEPs was expressed as the ratio of the control MEP elicited by the test stimulus alone.

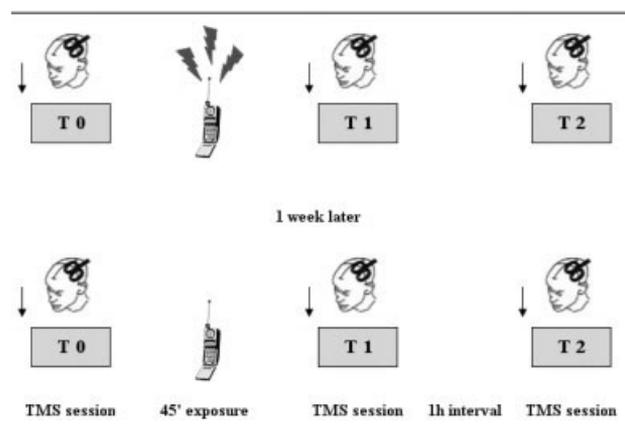


Fig 1. Schematic representation of the experimental design. Arrows indicate the timing of tympanic temperature measures. TMS = transcranial magnetic stimulation.

Data Analysis

STATISTICAL PROCEDURES. Statistical evaluation was conducted by a professional biostatistician with great expertise in TMS (P.P.). Because both single- and double-pulse MEP amplitudes were approximately log-normally distributed, a log transformation was applied before any statistical procedure, allowing for the attainment of a relevant reduction of outliers, a better approximation to gaussianity, and a higher homoscedasticity. For each subject and experimental condition, the ratio between each log-transformed MEP to paired pulses and the mean of log-transformed MEPs to single pulses (with the intensity of the *test* one) was calculated. The distribution of these ratios was analyzed further, because ratios are usually not suitable for treatment by means of general linear models, such as analysis of variance (ANOVA). However, the coefficients of variation of ratios in each cell of the experimental design was low (mean 8%, median 6%) and tended to increase after applying common transformations (log, logit, power, arcsin). No evidence of other serious violations of ANOVA assumptions was found, and simple ratios were therefore the main dependent variable in the statistical analysis.

The complete experimental design consisted of the following factors: ISI (9 levels: 1, 3, 5, 7, 9, 11, 13, 15, 17), STIM (type of EMF exposure, 2 levels: sham, real), SIDE (side of TMS stimulation, 2 levels: right, left), TIME (time of TMS stimulation, 3 levels: T0 = baseline, T1 = immediately after, T2 = after 1 hour). Therefore, the experimental design defined a data matrix of $9 \times 2 \times 2 \times 3 = 108$ cells. For an individual cell, a maximum of 8 MEPs were recorded for each of the 15 subjects. To take into account the within-subject correlation, we entered "Subject" as an additional factor. More precisely, Subject was entered as a random-effects factor. As known, this approach is more conservative than a fixed-effects design and is geared toward making inferences about average characteristics of the population (from which our sample of subjects could be assumed to be drawn).

Because this design involved four experimental factors (plus the random-effects factor of Subject), a multiway ANOVA was used to identify the significance of each source of variation (main and interactive terms).⁵⁸ The

working hypothesis of an effect across time (T1 and T2 vs T0) of real EMF (vs sham) on excitability of the ipsilateral (vs contralateral) motor cortex can be formalized statistically by the interaction TIME*STIM*SIDE. Therefore, this triple interaction became the effect of main interest. Because this effect could vary according to ISI levels, four-way TIME*STIM*SIDE*ISI was also evaluated carefully. In addition, to specifically test whether excitability changes were different in the inhibitory versus facilitatory ranges, we derived a new factor (SICI-ICF) (with 2 levels: 1 = SICI, obtained by averaging 1–3 milliseconds; and 2 = ICF, obtained by averaging 9–13-millisecond ISIs) and entered in the above ANOVA model, replacing ISI with SICI-ICF (TIME*STIM*SIDE*SICI-ICF).

Finally, with respect to tympanic temperature, a factorial ANOVA STIM (type of EMF exposure, two levels: sham, real), SIDE (side of TMS stimulation, two levels: right, left), TIME (time of TMS stimulation, three levels: T0 = baseline, T1 = immediately after, T2 = after 1 hour) was conducted.

Throughout the statistical analysis, p less than 0.05 was considered statistically significant. However, for each effect of interest, exact p values and 95% confidence intervals (CIs) were reported to provide more information on effect sizes.

Results

Resting Motor Threshold

Three-way ANOVA (TIME, STIM, SIDE) indicated that resting motor thresholds were not affected by experimental conditions, remaining quite stable during the recording session. In fact, the threshold means ranged between 50.4 and 52.6% of the maximal stimulator's output in the conditions with lowest and highest values.

Single-Pulse Transcranial Magnetic Stimulation

It is known that test-MEP amplitude can effect the amount of SICI/ICF.⁵⁷ However, MEP amplitude did not show any dependence on the experimental condi-

tions, being nonsignificant regarding main effects and for the interactive terms of the three-way ANOVA (STIM, TIME, SIDE), with p always greater than 0.05. The Table reports the means and standard deviations of single-pulse MEP amplitudes for each cell of the experimental design.

Double-Pulse Transcranial Magnetic Stimulation

Inhibition-facilitation curves for each of the six combinations of Time and Hemisphere are illustrated in Figure 2, where the characteristic relationship between ISI and MEP ratios are shown, together with the statistical tests for the difference between real and sham exposure (main effect of STIM) and for the dependence of this difference on ISI (interaction STIM*ISI). The “real” exposure raised the curve with respect to the sham condition only at T1 and T2 in the exposed left hemisphere [$F(1,14.0) = 9.746$, $p = 0.007$, and $F(1,14.0) = 5.642$, $p = 0.032$, respectively]. At T1, the lack of a significant STIM*ISI interaction was due to a nonsignificant difference between the increase of ICF and the decrease of SICI. In contrast, at T2, a significant STIM*ISI interaction was found in the left hemisphere [$F(8,112.9) = 2.073$; $p = 0.044$], suggesting that the EMF effect was not homogeneous across ISI, and planned comparisons indicated a significant effect only at facilitatory ISI, whereas no difference between real and sham EMF was found at each inhibitory ISI. On first glance, this could indicate that the increased excitability is more lasting for facilitatory than inhibitory ISI.

However, these first findings stem from the six patterns of Figure 2, considered separately from each other, like six different snapshots. Therefore, further analyses were performed to (1) use the nonexposed right hemisphere as control for the exposed left hemi-

Table. Means and Standard Deviations of Single-Pulse Motor-Evoked Potential Amplitudes (Original Scale, Logarithmic Scale, and Retransformed to Original Scale) for Each Cell of the Experimental Design (Pooled Subjects)

Experimental Conditions	T0			T1			T2		
	Original (μ V)	Log-Transformed	Retransformed (μ V)	Original (μ V)	Log-Transformed	Retransformed (μ V)	Original (μ V)	Log-Transformed	Retransformed (μ V)
Sham EMF									
Right hemisphere									
Mean	589	5.86	352	737	6.21	497	912	6.32	554
SD	618	1.09	367	682	0.93	479	959	1.04	565
Left hemisphere									
Mean	675	5.96	389	906	6.37	583	864	6.30	542
SD	909	1.06	400	885	0.98	576	924	1.01	545
Real EMF									
Right hemisphere									
Mean	945	6.41	607	1007	6.51	672	1180	6.51	673
SD	1064	0.94	590	965	0.93	648	1215	1.14	718
Left hemisphere									
Mean	843	6.37	582	802	6.29	539	1062	6.54	692
SD	694	0.94	562	826	0.88	506	938	1.01	697

To obtain the standard deviation (SD) of the retransformed data, the following formula was applied: $SD_y = \sqrt{[(dy/dx)_{x=E(x)}^2 * \text{var}(x)]}$ was applied.

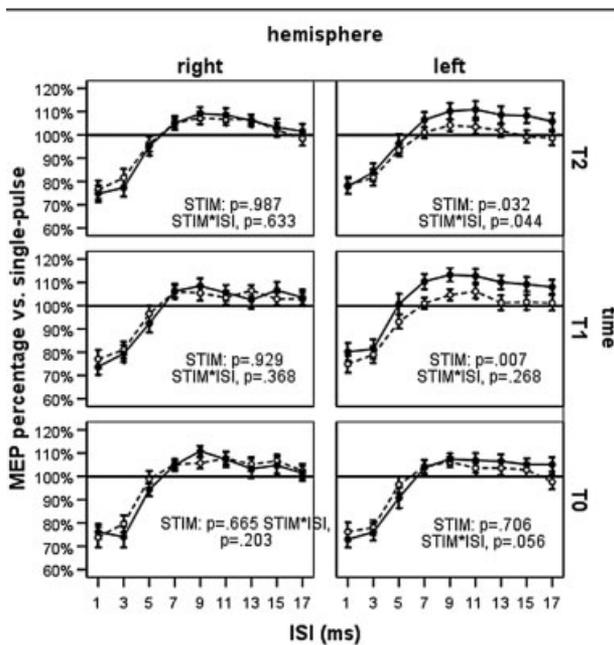


Fig 2. Inhibition-facilitation curves for each combination of the experimental design. Rows represent time (from bottom: baseline, soon after exposure, 1 hour after exposure). Columns represent hemisphere (right, left) and type of stimulation (continuous line indicates real; dashed line indicates sham). Error bars correspond to 95% confidence intervals after pooling subjects together. MEP = motor-evoked potential; ISI = inter-stimulus interval.

sphere, and (2) to evaluate changes occurring across the time course of the study.

First, when both hemispheres were considered, at T1, the real versus sham excitability changes resulted significantly different in the two hemispheres [STIM*SIDE interaction: $F(1,14) = 7.133$; $p = 0.018$]. This finding endorsed the specificity of an excitability increase in the exposed left hemisphere. About T2, STIM*SIDE interaction did not reach the significance threshold [$F(1,14) = 2.904$; $p = 0.110$]; thus, the excitability increase in the exposed left hemisphere was not strengthened by the comparison with the nonexposed hemisphere. In addition, at T2, the interhemispheric difference after sham exposure was significant ($p = 0.022$); thus, the larger excitability after real exposure of the left hemisphere could be accounted for by the lower (and probably accidental) inhibition-facilitation curve after sham exposure.

Second, to specifically test the “increased excitability,” the analysis should not be limited to each time (T0, T1, T2) separately, but rather should be extended on the changes across time (T0-T1-T2). Therefore, the ANOVA model used in the first analysis above was enriched by adding TIME as factor. The four-way TIME*STIM*SIDE*ISI interaction (testing the homogeneity of the ISI effect across the

different TIME*STIM*SIDE interactions) was non-significant [$F(16, 224.4) = 0.854$; $p = 0.623$], allowing ISI collapse. Instead, the triple interaction TIME*STIM*SIDE approached the conventional p value threshold of 0.05 [$F(2, 28.1) = 2.925$; $p = 0.070$]. As evident in Figure 3, no EMF effect was found in the nonexposed right hemisphere, whereas a clear change of excitability occurred in the exposed left hemisphere, namely, at T1. It appears notable that the 95% CIs for the right hemisphere and for the sham EMF in the left hemisphere were significantly below the reference line at 100%. This simply indicates that, when averaging the ISIs, the weight of the inhibitory effects (mainly due to ISI between 1 and 3) was larger than the weight of the facilitatory effects (mainly due to ISI between 7 and 13). In the left (exposed) hemisphere, the 95% CI at T1 was significantly above the reference line, indicating an inversion of the weights of inhibitory and facilitatory ISIs. When comparing with the sham EMF, the computation of the marginal means showed that the net excitatory effect of real EMF in the left hemisphere was clearly significant ($p < 0.001$) and resulted equal to 7.6% (95% CI: 6.2–9.0%). This effect diminished at T2, still remaining statistically valid (5.3%; 95% CI: 4.1–6.5%).

The latter analysis, controlling for both the nonexposed hemisphere (right) and the preexposure condition (T0) strongly reduced the differential effect of ISI, as shown in Figure 2 and in the first analysis. To better verify a potentially different effect on SICI and ICF, we reran the analysis replacing the factor ISI (9 levels)

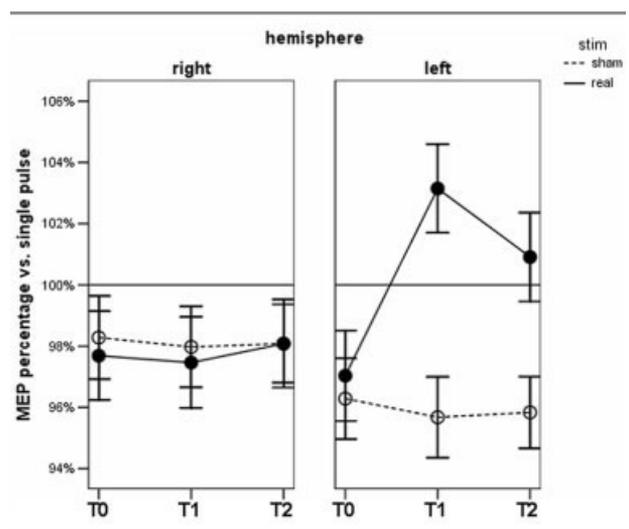


Fig 3. Time course of the double/single-pulse ratio in the two hemispheres (the left was exposed to electromagnetic field), after averaging across different interstimulus intervals (ISIs). Error bars correspond to 95% confidence intervals after pooling subjects together. MEP = motor-evoked potential. Continuous line indicates real; dashed line indicates sham.

with a new factor, namely, SICI-ICF, with 2 levels: 1 = SICI, obtained by averaging 1- to 5-millisecond ISIs, and 2 = ICF, obtained by averaging 9- to 13-millisecond ISI. Again, the TIME*STIM*SIDE*SICI-ICF interaction result was not significant [$F(2,28.1) = 0.286$; $p = 0.754$]. Even when analysis was limited to the exposed left hemisphere and to the two contrasts T1-T0 and T2-T0, no evidence of a different real or sham effect on SICI and ICF was found [$F(1,14.1) = 0.635$, $p = 0.439$ for T1-T0; $F(1,14.0) = 0.009$, $p = 0.927$ for T2-T0]. Therefore, the null hypothesis of a homogeneous increase of excitability for SICI and ICF could not be ruled out. These findings were not modified when ICF also included ISI = 15 and ISI = 17.

Finally, because ISI = 1 and ISI = 3 to 5 have been suggested to have different biological meaning,⁵⁹ we tested the following: (1) whether the average of the ratios at 3 and 5 milliseconds modulates the effect; in fact, this was not the case because the SICI-ICF*TIME*SIDE*STIM interaction was again not significant [$F(2,28.1) = 0.067$, $p = 0.936$]; and (2) whether there was any statistical difference between the MEP ratio at ISI = 3 to 5 milliseconds and the ratio at ISI = 1 millisecond; again, no significant effect was found [$F(2,28.3) = 0.319$; $p = 0.730$].

An important point to be addressed is the homogeneity of such an effect across subjects. When analyzed separately, the data from each subject showed an excitability change due to real EMF versus sham in the left hemisphere in 12 of 15 subjects. *Tympanic temperature* showed no significant main effect or interactions ($p > 0.14$).

Discussion

This study has shown definitively an effect of cellular phone emissions on the excitability of the motor cortex adjacent to the EMF source. We still do not know whether this effect is neutral or potentially dangerous or beneficial to cortical and brain functioning, but we firmly believe that, starting from this observation, more research is needed both in healthy people and in specific groups of subjects suffering from neurological diseases in which cortical excitability is affected (eg, epilepsy).

It might appear somewhat paradoxical that a strong magnetic field, for TMS, has been used to assess the effects of a weak EMF emitted by a mobile phone. However, it should be considered that the physical properties of a short-lived (<1 millisecond) magnetic stimulus, such as the one emitted from the coil for TMS, cannot be compared with a continuous flow of EMFs such as the ones emitted from a cellular phone. Moreover, to our knowledge, there are no other techniques able to reliably and noninvasively measure intracortical excitability. Furthermore, it is worth recalling that the amount of TMS delivered to the two

hemispheres was identical, whereas the exposure to EMFs was asymmetrical (real to the left, sham to the right).

Over the past several decades, a range of mechanisms has been suggested to explain how EMFs may interact with biological systems.²⁶ In in vivo exposure studies, it was demonstrated that EMFs from GSM mobile phones are mainly absorbed by extracerebral tissues including hairy skin, cranial muscles, and skull, and the real amount of power reaching the brain neurons was greatly attenuated by such an absorption process. Previous reports also demonstrated that 700MHz of continuous EMF can increase the level of neuronal excitability.²⁷

In this study, findings with TMS in investigating the effects of GSM 900 EMF exposure on brain physiology are reported for the first time. It is shown that intracortical excitability is significantly modified, short intracortical inhibition is reduced, and facilitation is enhanced in an *acutely* exposed human cerebral hemisphere compared with the nonexposed contralateral hemisphere or sham exposure. It is also shown that these effects are transient; that is, the baseline conditions being partially regained 1 hour after the end of exposure. It is known that test-MEP amplitude can effect the amount of SICI/ICF⁵⁷; thus, it is noteworthy that significant spontaneous modifications of brain excitability, as pointed out by test-MEP and/or resting threshold symmetric changes, were not found at different times of the experimental session. However, significant asymmetric modifications of the interhemispheric SICI/ICF slopes were identified.

Based on the time course of cortical inhibition and facilitation and on results of pharmacological manipulations during ppTMS, several authors have suggested that SICI is mediated by GABA_A receptors,⁶⁰ whereas ICF is mediated by glutamatergic *N*-methyl-D-aspartate (NMDA) receptors,⁶¹ and that the balance between SICI and ICF is altered in several neurological conditions showing abnormal cortical excitability.⁵⁷ Therefore, the monohemispheric hyperexcitability we found might depend on decreased GABA_A-mediated inhibition or increased NMDA-mediated excitatory activity,^{61,62} or both. Such a disruption in neurotransmitter balance leading to hyperexcitability may also be associated⁶³ with the monohemispheric increase of regional cerebral blood flow as actually observed via neurometabolic measurements during GSM mobile phone utilization.^{64,65}

Although the literature is not homogeneous in this respect,⁶⁶ there is evidence indicating that acute (1–4 hours)³⁴ and chronic GSM 900 EMF exposure (ranging from 30 minutes to 1 hour for 7–10 days)^{67–71} may slightly modify the cellular oxidative status. Neurotransmitters, namely, GABA and glutamate, are *acutely and reversibly* affected by situations inducing

neuronal hyperexcitability. For instance, oxidative stress⁷²⁻⁷⁴ can interact with receptors and ion transportation proteins either directly by changing receptor activity and ionic homeostasis or indirectly by altering ligand-receptor interactions and ion transportation. Oxidative stress also reduces the release of GABA and the activity of GABA_A receptors at presynaptic and postsynaptic sites,^{72,75} impairs redox-sensitive glutamate uptake in membrane transport systems of neurons and astrocytes,⁷⁶⁻⁷⁸ and selectively increases NMDA transmission, activating normally silent NMDA receptors and Ca⁺⁺ influx, possibly via phosphorylation by means of reactive oxygen species-dependent tyrosine kinase.⁷⁹ Recently, it was observed that both animal and human cells can respond to acute GSM 900 EMF exposure by changing transiently the expression levels and/or the phosphorylation pattern of a certain number of proteins,⁸⁰ such as heat shock proteins (see Cotgreave's³⁶ review), which are involved in the protection from oxidative stress and cell apoptosis.^{29,32,81} Neuronal hyperexcitability is considered to play a role in promoting cortical plasticity, either of the adaptive or maladaptive kind, with opposite effects on functional recovery, both in healthy people and in neurological diseases.⁸²⁻⁸⁵ Modifications of cortical excitability as shown in this report should therefore be regarded with interest because it is theoretically possible that exposure to GSM-type EMFs may provide a new, noninvasive method for modifying brain functioning.⁶⁴ Meanwhile, it should be argued that long-lasting and repeated exposure to EMFs linked with intense use of cellular phones in daily life might be harmful or beneficial in brain-diseased subjects. Further studies are needed to better circumstantiate these conditions and to provide safe rules for the use of this increasingly more widespread device.

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