Effects of Pulse-Modulated Microwave Radiation From Mobile Phones on the Sleep/Waking EEG and Psychomotor Vigilance

by

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ABSTRACT

This study employed multiple assessments, including sleep/resting waking EEG (visual scoring and power spectral analysis) and psychomotor vigilance task, to access effects of varying pulse-modulated microwaves (such as: 'talk', 'listen' and 'standby' mode signals) emitted from a standard mobile phone. The idea was prompted by a finding that the pulse modulation frequencies of mobile phone signals correspond to the frequencies of brain delta and alpha waves. Thereby it is possible the brain is able to recognize and respond to the low-frequency components of the mobile phone signals. Supporting evidence comes from repetitively reported EEG alpha and spindle effects of the 2, 8 and 217-Hz pulsed microwave exposure. Furthermore, brain imaging (EEG and PET) studies reveal 'low-frequency pulse-modulated waves' rather than the 'microwave frequency carrier waves' is the sine qua non for inducing these brain physiological effects [Huber et al., 2002, 2005; Regel et al., 2007a]. On the other hand, recent converging evidence, from molecular, behavioural and electrophysiological level, have shown that brain plasticity is a continuous process from waking to sleep and, sleep, a well-defined physiological condition, is 'shaped' by the waking experiences. The latter findings suggest certain sleep EEG features may characterize levels of cortical plasticity during wakefulness. The work presented in this thesis was inspired by these studies and aimed to understand how the real mobile phone signals with different low-frequency pulsing components [such as 'talk' (8, 217 Hz pulsed), 'listen' (2, 8, 217 Hz pulsed) and 'standby' mode (< 2 Hz pulsed)] change human brain electrical activities from waking to sleep. We approached this question based on EEG analysis in two domains: (1) EEG visual scoring; (2) EEG spectral analysis from relaxed waking to the deeper stages of non-NREM sleep. We also looked at the effects on the psychomotor vigilance performance. Results suggest 'talk' and 'listen/standby' modes have inverse effects on the distinctive thalamo-cortical oscillation modes and may thus impart inverse effects on their sleep structures. The implications of this study are of practical importance as it suggests the thalamo-cortical oscillations can be modulated by synchronizing rTMS/tDCS/DBS and sleep/waking EEG. This concept may be applied to modulate the brain oscillation modes for enhancing sleep-dependent brain plasticity or information processing.

KEYWORDS: sleep, electroencphalography (EEG); alpha activity; sleep spindles; psychomotor vigilance task (PVT); electromagnetic field (EMF); mobile phone; extremely low frequency (ELF); pulse modulation

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TABLE OF CONTENT

1 PREFACE

Worldwide, the introduction and technological advancement of mobile phones in the 1990's has rapidly fuelled increases in the numbers of subscribers. Over the last ten years, more than 2.1 billion users have registered mobile phone subscriptions [World Factbook, 2007]. Given such immense and fast growing usage, public anxiety and speculation for the health influences of electromagnetic fields (EMF, also referred to as electromagnetic radiation or waves, or radio waves) of mobile phone are spreading. As a response to this concern, the World Health Organization (WHO) established the International EMF Project [http://www.who.int/peh-emf/project/en/] in 1996 to assess the scientific evidence of possible health effects produced by non-ionizing EMF (in the frequency range from 0 to 300 GHz), and health effects related to short-term, high-level exposure to EMF at the range of radiofrequency (RF: > 10 MHz to 300 GHz) have been established and form the basis of two international exposure limit guidelines [ICNIRP, 1998; IEEE, 2002].

To date, these guidelines are designed to simply avoid health hazards related principally to excessive heating of tissue (> 1 °C of the global body temperature) due to RF energy absorption by the tissue's water, which may lead to health impacts once the temperature rise exceeds what the local thermoregulatory mechanism can cope with [IEGMP, 2000]. In the human body, the nervous system, especially the brain, is the most vulnerable area to such heating, having been identified in animal and in vitro studies to cause changes in the neuronal excitability, neurotransmitter function, innate and learned behaviours[for review see IEGMP, 2000].

Whilst the existing exposure guidelines are purely based on the thermal concept of RF EMF radiation protection, as yet a question for any standard is their sufficiency for safety aspects. This is because the mobile phone EMF has properties other than solely RF intensity, which could probably cause non-thermal biological effects. However, due to a lack of sound scientific advices, so far these properties are given limited account in most guidelines.

The study of this thesis was motivated in this context. Of specific interest is the non-thermal effects in connection with 'pulse modulation' properties of EMFs stemming from mobile phones. Nearly all new wireless access technologies make use of modulation, a pulsed transmitting mode of microwaves which introduce concomitant

extremely low-frequency (ELF: > 0 to 300 Hz) fields, but it is not until recently that human laboratory studies of mobile phone effects start to address this question. Nevertheless, effects of different modulation technologies are not confirmed yet – either restricted to a single study or there being variances concerning the power levels, modulation spectra, carrier frequencies et cetera in a number of studies.

The monograph builds and extends a review of the technical background of mobile phone signals, recent electrophysiological and neuro-metabolic findings in the field of bio-electromagnetic interaction and research gap (chapter 2). The focus is more limited on examining to what extent varying ELF pulse-modulated mobile phone signals, in terms of 'talk', 'listen' and 'standby' modes, can affect the electrical activity in the brain during sleep and waking, as well as the psychomotor function subsequent to a 30-min exposure. These three modes are the most typical mobile phone signals exposing to the human head but hitherto their brain effects are seldom studied together in the literature. The research described in this thesis looks into these effects using sleep/waking electroencephalogram (EEG, chapter 4, 5, 6) and psychomotor vigilance task (chapter 7). A generic description is given of methods employed in these studies (chapter 3). Final conclusions as well as some implications and future directions of the PhD work are discussed at the end of this thesis (chapter 8).

2 LITERATURE REVIEW

2.1 TECHNICAL BACKGROUNDS OF MOBILE PHONE EMF

To help match the real or simulated mobile phone EMFs studied in different laboratories, this section describes in a common basis the parameters of Global System for Mobile Communication (GSM, see section 2.1.1) in which the EMF in most studies has covered. They include: the spectrum and power output of the Carrier Wave (CW), the pulse modulation technologies of the CW and related pulse structure. The knowledge can be used as a comparison to setups used in different experiments to answer which aspect of GSM the effects may be attributed.

2.1.1 Global System for Mobile Communications (GSM)

GSM, the acronym for Global System for Mobile Communications, is an international, pan-European operating standard for the new generation of cellular mobile communication and mostly operates at 900 MHz and 1800 MHz. It replaced the first cellular system, the analogue TACS (Total Access Communication System), with digital processing, using phase modulation that results in only very small and essentially random changes in the amplitude of the CW. In the GSM system, each user requires a frequency channel of bandwidth 200 kHz so there is a maximum of 174 channels (175 minus one needed for technical reasons) within the 35 MHz bandwidth of the 900 MHz band and 374 channels within the 75 MHz width of the 1800 MHz band available for allocation to network operators. The channels are distributed across the cells in a way that allows neighbouring cells to operate at different frequencies to avoid interference [ref. chapter 4 in Stewart Report, 2000].

2.1.2 Carrier Wave (CW)

Mobile phones and their base stations sends and receives signals by the 'carrier wave (CW)', a continuous wave which consists of a sinusoidal oscillation at a single frequency located at the microwave spectrum [Foster et al., 2004]. The primary GSM 900 MHz handset emits in the band of 890-915 MHz ('uplink carrier frequency') and receives in the band of 935-960 MHz ('downlink carrier frequency'), while the extended GSM 900 MHz handset uses the 880-915 MHz band for transmission and the 925-960 MHz for reception [Wiart et al., 2000]. The GSM 1800 MHz handset transmits in the 1710-1785 MHz and receives in the 1805-1880 MHz. The microwave

power is mainly transmitted by the antenna together with circuit elements inside the handset. The antenna is usually a metal helix or a metal rod a few centimetres long extending from the top of the phone. Neither type is strongly directional, although more power is radiated in some directions than others. At points 2.2 cm from an antenna (the distance at which calculation were made), the maximum value of the electric field is calculated to be about 400 V/m for a 900 MHz phone and about 200 V/m for a 1800 MHz phone. The maximum magnetic field is calculated to be about 1 μT for both phones (Table 2. 1).

Table 2. 1 The Carrier Outputs from the GSM handset (at points 2.2 cm from an antenna).

Handset type	Maximum electric field	Maximum magnetic field	Maximum power	Maximum power intensity
GSM 900 MHz	400 V/m	1 μT	2 W	200 W / m^2
GSM 1800 MHz	200 V/m	1 μT	1 W	200 W / m^2

The maximum output power (peak value) of GSM handsets, by definition, is a normal tolerance of ± 2 dB and an extreme tolerance of ± 2.5 dB. In case of perfect matching, the maximum output power of GSM handset is equal to 2 W (30 dBm) ± 2.5 dB for GSM 900 MHz carrier and 1 W (15 dBm) ± 2.5 dB for GSM 1800 MHz carrier. For both 2 W, 900 MHz phones and 1 W, 1800 MHz phones, the maximum power intensity 2.2 cm from the antenna is roughly about 200 W/m^2 (this is about one-quarter of the intensity of the sun's radiation on a clear summer day, although the frequency of the emission from a phone is a million times smaller) (Table 2. 1).

These fields and intensities are emitted when the antenna is a long way from the head or the body. When the antenna is near the body, the radiation penetrates it but the fields inside are significantly less. For example, the largest maximum fields inside the head when its surface is 1.4 cm from the antenna are calculated to be about three times smaller than the values given above. Specific Absorption Rate (SAR) has been recognized as one of the most significant variables quantifying the EMF interaction with the human body. At frequencies greater than 100 kHz, SAR is defined as the rate at which EMF energy is absorbed per unit mass of biological tissue. Safety guidelines recommend limits for local exposures, i.e. peak spatial SAR average over any 10 g of tissue (psSAR10g) are 2 W/kg for the general public and 10 W/kg for occupational exposure [ICNIRP, 1998]. Recent progress in the computer technology has made it possible to use the finite-difference time-domain (FDTD) method to numerically calculate the electromagnetic interactions of a heterogeneous, realistic

head model with a realistic portable radio model. It has been shown that the characteristics of RF power absorption in the human head irradiated by EMF from a handset depend on mainly on the antenna type and direction [Watanabe et al., 1996].

Improvements in manufacturing techniques since the standards were set have substantially reduced the variations in performance and it appears very unlikely that any of the more recently produced mobile phones would approach the upper limits allowed by the standards. An important aim of the manufacturers is to achieve the greatest possible battery life, which requires the power to be as small as possible. Advice from the Mobile Manufacturers Forum (an international association of seven major manufacturers) notes that members of the Forum are not aware of any phones operating above the standard.

2.1.3 Pulse-Modulated Wave (PW)

The CW used for radiocommunication between the handset and the base station is a continuous wave at a single frequency. To enable it carry information (speech, music, computer data, etc), the waveform of the carrier is 'modulated' in either frequency ('frequency modulation') or amplitude ('amplitude modulation'). Pulse modulation, an extreme form of amplitude modulation, is produced by gating the CW on and off by several frequencies at once [Foster et al., 2004]. This generates pulses of RF energy, with which the pulse structure generates certain well-define frequencies and influences the emitted power of the GSM mobile phone signal.

2.1.3.1 Pulse Modulation Techniques and Pulse Structure of the GSM Signal

Time Division Multiple Access (TDMA)

In the GSM system, a pulse modulation technique called Time Division Multiple Access (TDMA) is used to allow each RF channel to support eight phone users for their speech communication. This is achieved by compressing each 4.6 ms chunk of information (defined as a TDMA 'Frame') to be transmitted into a pulse 577 μs long (called a 'Slot'). Therefore, the phone and the base station transmit for 577 μs in every 4.6 ms, which results in a repetition frequency of 217 Hz (= 1/4.6 ms) in their carrier output. The upper panel of Figure 2. 1 ('GSM Basic Signals' or 'Talk Mode') gives the basic timing structure of TDMA in a 'Super Frame', which by definition is a cycle of 4 multi-frames (= 104 frames = 4 × 26 frames; a multi-frame = 26 frames) and lasts for 478.4 ms (= 4 × 26 × 4.6 ms). Within each of these cycles, 24 frames

are dedicated Traffic Channels (TCH) for full speech while the 13th frame is the Slow Association Control Channel (SACCH) used to transmit signalling information about the transmission and the 26th frame ('Idle frame') is omitted for transmission. As a result, the repetition rate of both the 'SACCH' and the 'Idle' frame is at the lower frequency of 8.34 Hz [Pedersen, 1997; Wiart, et al., 2000; Stewart Report, 2000, chapter 4].

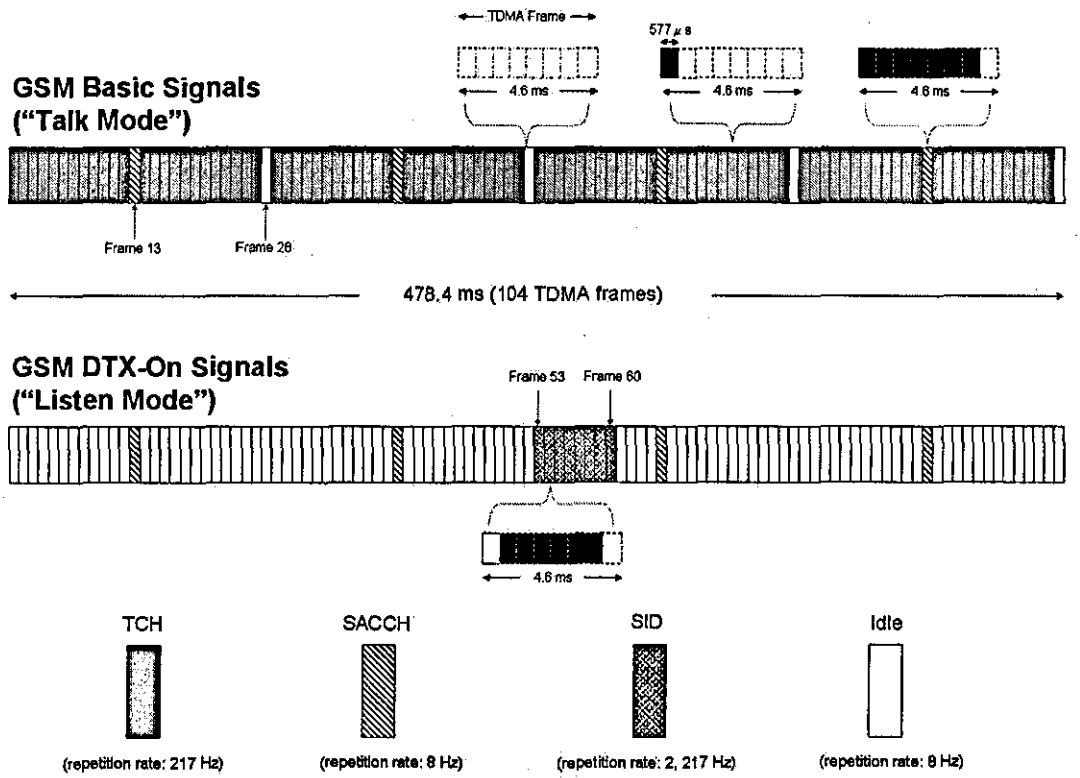

Figure 2. 1 Pulse Structure of GSM Signals (GSM Basic and DTX-On modes) of a super frame of 478.4 ms (= 104 TDMA frames). GSM basic signals are transmitted during the phone user is speaking ('talk mode'), whereas GSM DTX-On signals are transmitted when no speech is detected from the user ('listen mode'). A TDMA frame is defined as a set of eight slots. Inserts are a detailed TDMA timing structure within varying frames acting as the TCH, SACCH, SID or the Idle frame. TDMA: time division multiple access; DTX: discontinuous transmission; TCH: traffic channels; SACCH: slow association control channels; SID: silence descriptors.

Discontinuous Transmission (DTX)

Discontinuous Transmission (DTX) is another pulse modulation technique mainly used to save battery power. When the Voice Activity Detection (VAT) detects that the user stops speaking (either because this part is listening or because neither part is speaking), the DTX mode is entered with the background noise being sampled and transmitted, whereby the connection is still retained and the power is switched off. As shown in the lower panel of Figure 2. 1 ('GSM DTX-On Signals' or 'Listen Mode'), in case of full silence and when DTX is employed, not all TDMA frames are transmitted, except for the eight frames between 53 and 60 that should always be transmitted. These TDMA frames are called the Silence Descriptor (SID) speech frames, which transmit the evaluated comfortable noise parameters every 0.478 s (repetition frequency of about 2 Hz) [Wiart et al., 2000]. Compared with the DTX-Off ('talk mode') pulse structure, the GSM super frame with DTX-On ('listen mode') is only composed of the SACCH and SID frames. But both modes emit the SACCH and Idle frame every 0.12 s (= 25 × 4.6 ms, repetition frequency of about 8 Hz) respectively. This 8 Hz pulsing is a permanent ELF component either of talk-mode or of listen-mode EMF, which, unlike that at 217 Hz, is unaffected by call density (Table 2. 2).

The above paragraphs describe the GSM pulse modulation technologies employed when a mobile phone is used at talk and listen modes and their related pulse structures (and resulting pulsing frequencies). With regard to that of 'standby' mode (when the mobile phone is just switched-on, but not used), the phone emits RF signals of very low data rate and very infrequent (< 2 Hz) compared to an active call (talk mode). This is to allow the mobile phone service provider to direct a call (or accept one from the user's mobile phone) via the closest (best quality-connected) base station. Table 2. 2 summarizes the ELF components of the RF fields emitted from a GSM mobile phone at each mode.

Table 2. 2 ELF components of 'talk,' 'listen,' and 'standby' modes.

Transmission mode	ELF components
Talk	8, 217 Hz
Listen	2, 8, 217 Hz
Standby	< 2 Hz

2.1.3.2 Average Power

The 'maximum' transmitted RF power for a GSM mobile phone (as shown in Table 2. 1) is found by considering the power regulation by law and the power class of the phone. However, as regards to the 'average' power, additional factors should be considered when averaging the full power over a period of time. These factors include: the detailed TDMA timing structure, the time period for the averaging (e.g. over a frame period, a multiframe period or a whole call), if the DTX is active or not, and if the phone is a full- or half-rate phone [Pedersen, 1997].

As an example, the maximum average power for a full rate class 4 GSM 900 MHz phone with DTX-Off is 2W x (1/8) x (100/104) ≈ 240 mW. 1/8 is the one time slot out of 8 in a frame and 100/104 is the 100 frames in a super frame where the phone is transmitting. Based on the same rule, the average power emitted from the same phone with DTX-On in case of full-silence transmission during a super frame period is 2 W x (1/8) x (12/104) ≈ 28.8 mW, which DTX reduces the emitted power down to about 11% of the maximum level.

2.2 PREVIOUS STUDIES OF BIOLOGICAL EFFECTS OF MOBILE PHONE EMFS ON HUMAN BRAIN

Numerous studies have been published looking at different aspects of biological effects of mobile phone EMF exposure. These aspects include sleep/waking EEG, brain metabolism and excitability, as well as performance.

2.2.1 Effects on Sleep EEG

The evaluation of EMF effects on sleep EEG so far comprises an investigation of sleep architecture as well as EEG power spectrum. These studies will be reviewed below and listed in Table 2. 3.

Mann and Roschke [1996] were the first to focus on the effects of 900 MHz EMF (pulsed modulation at 217 Hz, and averaged power of 0.5 W/m^2) on human sleep EEG. The exposure was lasting for 8 hours during sleep at the vertex to a source located 40 cm from the head. EMF exposure showed hypnotic (as shown by a shortening of sleep onset latency) and REM sleep-suppressive effects (reduced duration and increased latency). EEG spectral analysis also showed a significant

increase of alpha band power (7.5-12.5 & 12.5-15 Hz). However, these results were not replicated in a subsequent study of the same group [Mann et al., 1998], which aimed to assess the effects of the GSM signal on the neuroendocrine system with a lower power output (0.2 W/m^2 rather than 0.5 W/m^2) in 24 subjects. Furthermore, even under more rigorous experimental conditions with an increased sample size (N = 24) and using a circular antenna (for generating more homogenous EMF distribution in the head), results of Mann and Roschke [1996] cannot be replicated by the same group [Wagner et al., 1998]. The lack of any significant effect was explained by the different type of antenna used (circular rather than liner/stick type), the different location (under the pillow rather than behind the bed head) or a lower power density (0.2 W/m^2 rather than 0.5 W/m^2). With an intention to assess dose-dependent power effects, the same group carried out another study using a sub-maximal power density (50 W/m^2 with a SAR value ≈ 2 W/kg) [Wagner et al., 2000]. Again, results did not show any significant change on the sleep structure and sleep EEG power spectrum.

Borbély et al. [1999] carried out an experiment using GSM 'base-station-like' signals, which share the same pulsing structure of handset signals (900 MHz modulated at 2, 8, 217/1736 Hz) but has higher a spectral power of pulsing frequency at 2, 8 Hz (duty cycle: 87.5 %). Power was set at 2.2 W and the SAR never exceeded 1 W/kg, calculated on 10 g of tissue. The signal was emitted by three antennas located behind the head at a distance of 30 cm from the subject's vertex. The subjects underwent intermittent exposure (15 min EMF on – 15 min EMF off) during the night-time sleep for two sessions (real or sham exposure) with a week interval, following a double blind paradigm. The EEG spectral analysis during the first episode of NREM sleep pointed to an early increase of power at the alpha and spindle frequency ranges (10.0-11.0 and 13.5-14.0 Hz).

The same research group [Huber et al., 2000] then evaluated the effect of the same signal with a shorter exposure duration (30 min), during a post-exposure nap in the morning (3-h nap starting at either 9:45 or 10:15 h, with prior night-time sleep being restricted to 4 h beginning at either 22:45 or 23:15 h). Following a double-blind protocol, subjects were exposed to the same signal as in the previous study [Borbély et al., 1999], with the head positioned between two planar antennas. EEG power at 9.75-11.25 and 12.5-13.25 Hz increased in both hemispheres, regardless of the side of exposure, during the first 30 min of NREM sleep. However, their later topographic analysis of the same data [Huber et al., 2003] showed that, even no sleep EEG spectral effect has been observed between or within the hemispheres irrespective of

exposure side; the sleep EEG power was higher in the left hemisphere for the 12.5-13.25 Hz and 9-13.5 Hz bands.

In 2002, Huber et al. reported an increase of S2 EEG sigma power at 12-14 Hz across all NREM cycles only after exposure to GSM 900 MHz carriers 'with' pulse modulation but 'not' after exposure to GSM 900 MHz carriers 'without' pulse modulation [Huber et al., 2002]. This study demonstrated for the first time a fundamental role of low-frequency pulse modulation on the sleep EEG effects.

Loughran et al. [2005] used a larger sample size (N = 50) to confirm a pulse-modulated EMF effect of enhanced EEG sigma (11.5-12.25 Hz) power in the first 30 min of NREM sleep (GSM 894.6 MHz pulsed at 217 Hz; average power density of 0.25 W; SAR = 0.11 W/kg over 10 g). No significant change in sleep structure except an unexpected decrease in REM sleep latency was found.

Regel et al. [2007b] were the first researchers to demonstrate the dose-response relationships between the field density and the magnitude of the EMF-induced sleep EEG effects. They compared the sleep EEG spectral results in 15 healthy male participants after unilaterally (left hemisphere) exposing pulse-modulated EMF (GSM 900 MHz, pulsing at 2, 8, 217/1736 Hz) for 30 min prior to sleep (8 h), which EMF specific absorption rate was of (1) 0.2 W/kg, (2) 5 W/kg, or (3) 0 W.kg (sham mode). Immediately after exposure, night-time sleep polysomnography was recorded for 8 h. They found sleep architecture was not affected by the EMF exposure. The sleep EEG power spectral analysis, however, revealed a dose-dependent increase of power in the spindle frequency range during NREM sleep. In particular, the spectral power in the fast spindle frequency range (13.5-13.75 Hz) increased by 7.7 % after exposure at 0.2 W/kg, 10% after exposure at 1 W/kg [reported by Huber et al., 2002] and 13.6 % after exposure at 5 W/kg. Furthermore, such spindle effects were long lasting, as the increase was at a similar level throughout the sleep episode, but not adapting to the change of spindle activities in the course of sleep as reported by their previous study [Huber et al., 2002].

From Regel et al's finding of dose-dependent sleep EEG effects [2007b], it shall be expected that the lower SAR dose present at the non-exposed hemisphere is not sufficient to induce the cortical spindle effects. However, previous research by Huber et al. [2002, 2003] reported bi- as well as unilateral exposure of the cortex caused sleep EEG spindle power changes in both hemispheres. A possible explanation for

the occurrence of EEG spindle effects on the non-exposed hemisphere is that the the spindle generating system – either the thalamo-cortical loop or the thalamus itself – was stimulated directly by the EMF.

To conclude, the most consistent reported effects of GSM handset-like EMFs on the sleep EEG are an increase of alpha and sigma EEG power during the initial sleep. In particular, the EEG power at 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; Regel et al., 2007b]. Sleep EEG effects are only found with the pulse-modulated EMFs and show a dose-response relationship with the field intensity (SAR strengths). The possible mechanism for the observed sleep spindle effects of pulse-modulated EMFs may be due to stimulation on the thalamo-cortical loop.

Table 2. 3 Summary of ELF-modulated EMF effects on the sleep EEG.

Study	Ss	Exposure features	Key findings
Mann & Roschke [1996]	12 M	GSM 900 MHz modulated at 217 Hz; power = 0.05 mW/cm^2; 8-h nocturnal sleep exposure at vertex in a distance of 40 cm from the antenna; SAR not reported	During exposure: ↓ sleep latency; a trend of REM sleep reduction (onset latency ↑ & duration ↓); ↑ NREM sleep EEG alpha power (at 7.5-12.5 Hz and 12.5-15 Hz)
Mann et al. [1998]	24 M	Replication of [Mann & Roschke, 1996] but with a lower power (0.02 mW/cm^2)	No significant alternation of EEG; trend to reduction of REM sleep duration and percentage
Wagner et al., [1998]	24 M	Replication of [Mann & Roschke, 1996]) but with a circular antenna (to generate a more homogeneous exposure), 40 cm below the pillow	No significant effects on the sleep EEG visually-scored structure and spectrum
Wagner et al. [2000]	20 M	Replication of [Wagner et al., 1998]) but with a stronger power density (50 mW/cm^2), SAR ≈ 2 W/kg over 10 g	No significant effects on the sleep EEG visually-scored structure and spectrum
Borbély et al. [1999]	24 M	GSM 900 MHz modulated at 2, 8, 217/1736 Hz ('base-station-like' signals): duty cycle: 87.5 %; SAR = 1 W/kg over 10 g; intermittent (15 min on – 15 min off) exposure during nocturnal sleep at vertex in the distance of 30 cm from the antenna	During exposure: ↓ WASO; EEG alpha (10-11 Hz) & ↑ sigma (13.5-14 Hz) power during the initial part of sleep but then subsided
Huber et al. [2000]	16 M	Replication of Borbély et al. [1999], but changed to lateral exposures [Left & Right hemisphere] before a 3-h diurnal sleep (with prior nocturnal sleep restricted to 4h) for 30 min	Post-exposure: ↑ the first 30-min NREM sleep EEG power at alpha (9.75-11.25 Hz) and sigma bins (12.5-13.25 Hz)
Huber et al. [2003]	16 M	Re-analysis of data from Huber et al. [2000]: GSM 900 MHz modulated at 2, 8, 217/1736 Hz	Post exposure: hemispheric effect (Left ↑ > Right ↑) in the sleep EEG 9-13.5 Hz, which is irrespective to

		('base-station-like' signals), duty cycle of 87.5 %; SAR = 1 W/kg over 10 g; 30-min lateral exposures [Left & Right hemisphere] before a 3-h diurnal sleep (with prior nocturnal sleep restricted to 4h)	exposure site
Huber et al., [2002]	16 M	GSM 900 MHz unmodulated (CW) and pulse modulated (PW) at 2, 8, 217/1736 Hz with a duty cycle of 12.5 %; SAR = 1 W/kg over 10 g; 30-min exposure at the left hemisphere before nocturnal sleep	Post-exposure: ↑ S2 EEG sigma (12-14 Hz) power during the first cycle of night time sleep, only with PW
Loughran et al. [2005]	27 M, 23 F	GSM 894.6 MHz modulated at 217 Hz, peak power of 2W (average 0.25 W); peak SAR = 0.29 W/kg (average SAR = 11 W/kg) over 10 g, 30-min exposure at the right hemisphere before nocturnal sleep	Post-exposure: ↓ REM sleep latency; ↑ sleep EEG sigma (11.5-12.25 Hz) power during the initial part of sleep
Regel et al. [2007b]	15 M	GSM 900 MHz modulated at 2, 8, 217/1736 Hz ('handset-like' signals), duty cycle of 21 %, which was applied at a SAR of 0.2, 5 or 0 W/kg (sham control, nil-signal condition) over 10 g; 30-min exposure at the left hemisphere prior to an 8-h nocturnal sleep EEG recording. During exposure, series of cognitive tasks (simple reaction time, continuous reaction time, 1-back, 2-back, 3-back) were performed twice,	Post-exposure: a dose-response relationship was occurred between SAR and (i) S2 EEG power in the fast spindle frequency range (13.5-13.75 Hz) during S2; (ii) all-night spectral in the slow spindle frequency range (10.75-11.25 Hz)

Ss, Subjects; M: male; F: female; WASO: waking after sleep onset

2.2.2 Effects on Resting Waking EEG

The evaluation of effects on resting waking EEG to date mostly based on power spectral analysis, although there are some studies applying non-linear analytic methods of the EEG [e.g. Perentos et al.,2007]. Here we reviewed these studies, and summarized their exposure features and findings in Table 2. 4.

Reiser et al. [1995] were the first to carry out an experiment which aimed to observe the effects of a GSM signal on the waking EEG. The phone was operated at 902.4 MHz pulsing at 217 Hz, with the power being emitted 0.25 W at the distance of 40 cm from the subject's head. Each participant was recorded 15 min for the baseline EEG (nil-signal condition), then exposed to GSM signals for 30 min, followed by another 15-min post-exposure waking EEG recording. Compared to baseline, the post-exposure waking EEG power spectra showed an increased power across a broad frequency band including delta (1.25-4.5 Hz), alpha and beta frequencies (9.75-35 Hz).

Roschke & Mann [1997] assessed the effect of a short-term exposure (3.5 min) on 34 subjects with an exposure similar to the settings of Reiser et al. Both real and sham EEG recordings lasted 10 min with an interval of 30 min in between. The EEG spectral power analyses showed no changes either with regard to the electromagnetic field (real vs. sham) or the hemisphere considered.

Huber et al. [2002] compared the post-exposure effects of GSM 900 MHz signal unmodulated (CW) and modulated (PW, at 2, 8, 217/1736 Hz) on the resting EEG before stage 2 sleep onset (therefore, data included waking and Stage 1 sleep EEG). The participants received a 30-min exposure to the left hemisphere. Results are similar to their sleep (stage 2) EEG spectral findings that only after exposure to GSM 900 MHz carriers 'with' pulse modulation but NOT after exposure to GSM 900 MHz carriers 'without' pulse modulation showed EEG power changes from sham mode (as indicated by an increase power at alpha frequency range, peak at 10 Hz).

Huber et al. [2003] reported an extended analysis of their data published in 2000 [Huber et al., 2000], focusing on effects on the resting waking EEG spectral changes (with eye closed). Surprisingly, they found that the resting waking EEG power (EEG derivation: C3-A2) during exposure was decreased at both alpha (10.5-11 Hz) and beta (18.75-19.5 Hz) bands. This finding was reverse to their previous resting waking EEG findings, which they reported an increase power in the 11-11.25 Hz range in the EEG spectrum of waking prior to sleep onset [Huber et al.,2002]. The authors proposed the difference might be due to that the waking EEG is more susceptible to artefacts and the presence of sleep may be a prerequisite to reliably detect EMF effects in the EEG (as Borbély et al.'s experiment [1999] revealed that a short exposure duration of 15 min is sufficient for enhancing power in the sleep EEG. [see Fig. 3 in Huber et al., 2003]) .

Croft et al. [2002] assessed whether exposure to the active mobile phone signal (GSM 900 MHz modulated at 217 Hz; time averaged power emission was 0.3-0.4 W) affected EEG activities as a function of exposure time. The phase-locked EEG responses to auditory stimuli (3 min) followed by the resting waking EEG recording (2 min, with eyes opened) were acquired during exposure to the posterior midline brain region, repeated four times. Results from resting waking EEG power spectral analysis demonstrated an increased of alpha (8-12 Hz) power and a decrease of delta (1-4 Hz) power over the right hemisphere. It should be noted that the authors proposed these

resting EEG findings could corroborate their findings of phase-lock EEG responses (see table 2.4). Specifically, the right hemisphere resting delta decrease correlated inversely and strongly with activation[1], and their findings of enhancement of the phase-locked gamma response correlated directly with activation as well.

D'Costa et al. [2003] conducted a single-blind experiment in ten participants to examine the resting waking EEG effects during exposure to two kinds of pulse-modulated GSM 900 MHz handset signals: 217 Hz pulsed and 1-32 Hz pulsed (standby mode). During exposure, they found the 217 Hz pulsed signals reduced the resting alpha power (with eyes closed) from frontal (9-Hz bin), central (7- and 9-Hz bins) to occipital region (7-9 Hz bins), with the effect being stronger at the irradiated area (occipital region). The standby mode, however, induced a different resting alpha effect in the frontal region, where the resting waking EEG power at 12-Hz bin was enhanced during exposure.

Curcio et al. [2005] were the first to notice that the mobile phone's resting alpha effect 'during' and 'post' exposure may be variable in topographical regions and frequency bins. They conducted high EEG frequency resolution analyses (i.e. Hz-by-Hz) on the resting waking EEG recordings (sitting position with eyes closed) from five unipolar EEG channels (Fz-A1, Cz-A1, Pz-A1, T3-A2, T4-A1). Two groups of participants (N=10 per group) receiving equal amount of EMF/control exposure (45 min, at the left ear) were had their resting waking EEG measured at different times: the last 7 min during exposure (Group 1) and the 7 min immediately after the cessation of exposure (Group 2). Each participant had to come to the lab for three times for three exposure conditions (Baseline, EMF-on and EMF-off), with each condition being separated at least for 2 days. The EMF signal was GSM 902.4 MHz pulsing at 217 Hz emitted at full power. A mixed design of analysis of variance [Group (during exposure, post-exposure) x Condition (Baseline, EMF-on, EMF-off) x Frequency (1, 2, ..., 24 Hz)] were carried out on resting EEG power values recorded from each derivation. Results demonstrated that, 'during' and 'post' exposure, GSM signals increases the resting waking EEG power at the 9-10 Hz bins at the central (EEG derivation: Cz) and temporal (EEG derivation: T3) region. However, over the parietal lead (EEG

[1] The authors used the AD-ACL [Thaya, 1967] test, which consists of 20 words that describe mood or feelings, to measure the psychological state of the participants. Participants rate the degree to which these adjectives describe their mood at that particular point in time on a 4-point liker-scale. Items relate to the adjectives 'calm', 'excited', 'tired', 'tense', and average to form an 'activation' scale (low scores represent high activation levels). 'Activation' level is measured by a difference of scores between 'in condition' and 'pre-experiment'.

derivation: Pz), the resting waking EEG power at 11 Hz was higher 'during' exposure than 'post' exposure.

Regel et al. [2007a] provided additional waking EEG evidence to corroborate their prior findings of pulsed EMF effects [Huber et al., 2002], as they found only PW (GSM 900 MHz modulated at 2, 8, 217 Hz, peak SAR = 1 W/kg), not CW (un-modulated GSM 900 MHz), affects alpha activities in the resting waking EEG (eyes closed, sitting position). Furthermore, they found resting alpha activity (in the range of 8-12 Hz) was significantly increased 30 min after the end of PW exposure, but not immediately after, or 60 min after exposure (which, in contrast, showed a reduced resting waking EEG power at 12-Hz bin), indicating that the effect appeared and disappeared within this time window.

In order to verify the widely-reported EEG alpha enhancement after or during mobile phone exposure [e.g. Huber et al., 2002; Croft et al., 2002; Curcio et al., 2005], Croft et al. [2008] employed a methodologically rigorous experiment to examine the resting waking EEG effects [i.e. a large sample size (N = 120), a stronger exposure level (30-min exposure and the mobile phone was set to transmit at the maximum power that a standard mobile phone is permitted to operate), a standard 'resting' EEG protocol (sitting position, with eyes opened), a double-blind and crossover design with sham control and the exposure site (left or right hemisphere) being counterbalanced between subjects]. They conducted power spectral analysis of resting waking EEG acquired 'during' exposure (90-s recording repeated four times during exposure) and 'after' cessation of exposure (10-min recording). Their main result, an overall alpha (8-12 Hz) power enhancement 'during' mobile phone exposure (relative to sham), confirmed previous reports. In particular, they found this effect larger at ipsilateral than contralateral sites over posterior regions (posterior ipsilateral effect). However, post-exposure, no overall change to alpha power was observed (relative to sham) regardless of the posterior ipsilateral effect being maintained during this period. In addition, the increase in the resting alpha as a function of exposure duration as reported in their previous study [Croft et al., 2002] could not be replicated in this study.

In view that the pulse-modulated EMF exposure distribution employed by previous research [Huber et al., 2002] are not typical of normal GSM handset usage (deep brain areas were overexposed due to usage of the 'patch' antenna), Perentos et al. [2007] tried to replicate the modulation-linked post-exposure resting waking EEG alpha effects with an exposure source more closely resembling that of a real GSM

handset (GSM 900 MHz, pulse modulation at 2, 8, 217/1736 Hz, peak power: 2 W, peak SAR = 1.56 W/kg over 10 g of tissue, 'monopole' antenna) and with a shorter exposure duration (15 min), which was just sufficient to allow for a cumulative effect to take place [Reiser et al., 1995]. With their experimental setup and exposure procedure, they could not replicate the previous reported alpha effects; neither could they relate effects to the non-linear features of the resting waking EEG using the Approximate Entropy (ApEn) method of analysis.

Hinrikus et al. have reported a series of experiments aimed to figure out the microwave (450 MHz) effects at different modulation frequencies on the resting waking EEG [modulation frequency at 7 Hz: Hinrikus et al., 2004; 7, 14 and 21 Hz: Hinrikus et al., 2008]. They found the GSM microwave modulated at 14 and 21 Hz enhanced resting waking EEG alpha (8-13 Hz) and lower beta (15-20 Hz) power (in the case of GSM signals with 14 and 21 Hz modulation) and higher beta (22-38 Hz) power (only in the case of GSM signals with 21 Hz modulation) [Hinrikus et al., 2008]. At the lower modulation frequency of 7 Hz, a minor alpha enhancement occurred but it was not statistically significant [Hinrikus et al., 2004; 2008]. Their findings of pulse modulation frequency-dependent EEG effects have prompted this research group to propose an interesting hypothesis: the resting waking EEG power enhancement occur at the frequency bands that are *close to* or *lower* than the modulation frequency of the EMF [Hinrikus et al., 2008]. In other words, the effect of an external stimulus on brain oscillations is stronger if the frequency of the stimulus is higher or close to the physiological frequency of brain rhythms. Accordingly, the absence of microwave effects at 7 Hz modulation might be due to the lack of brain oscillation modes at theta or lower frequency range during exposure. This may be true considering their experimental control of participants' brain states during resting waking EEG recording (i.e. excluding drowsy participants before or during the experiment; conducting experiment before mid-day when participant's sleepiness is at the lowest level – as theta oscillation is correlated to sleepiness). However, the lack of observable effects may also be due to their usage of broad (and fixed)-band spectrum analyses – which could not detect some specific sub-band effects or other effects that occurred at frequency bands out of their observation ranges.

In sum, present findings of pulse-modulated EMF effects on the resting waking EEG are inconsistent and somewhat controversial. Most evidence indicate enhancing resting waking alpha activities, which effects have been reported to occur 'during' [i.e. Croft et al., 2002; Curcio et al., 2007; Croft et al., 2008; Hinrikus et al., 2008] as well

as 'post' exposure [i.e. Huber et al., 2002; Regel et al., 2007a; Reiser et al., 1995; Curcio et al., 2005, Croft et al., 2007]. Other studies, nevertheless, reported changes in the direction of alpha power decreasing [i.e. Huber et al., 2003, during exposure] or no change in the resting waking EEG spectrum [i.e. Roschke & Mann, 1997; Perentos et al., 2007]. Both studies of Regel et al. [2007a] and Hinrikus et al. [2008] found resting EEG alpha effects only occur with GSM microwave being pulse modulated, but not with the microwave alone, suggesting the EEG effects may depend on the modulation frequency rather on the microwave. Furthermore, according to Hinrikus et al.'s study [2008], the effect of an external stimulus on brain oscillations is stronger if the on-off stimulation cycles of the stimulus is *higher* and *close to* the physiological frequency of brain rhythms.

Table 2. 4 Summary of ELF-modulated EMF effects on the resting waking EEG.

Study	Ss	Exposure features	Key findings
Reiser et al. [1995]	18 M, 18 F	GSM 902.4 MHz modulated at 217 Hz, power emission was set at 8 W but the actual power was 0.25 W at 40 cm of distance from occipital region; SAR not reported, 15-min exposure	Post-exposure: ↑ EEG 1.25-4.5 Hz & 9.75-35 Hz power
Roschke & Mann [1997]	34 M	GSM 900 MHz modulated at 217 Hz, power emission was set at 0.05 mW/cm^2 at 40 cm of distance from occipital region; SAR not reported, 3.5-min exposure	Post-exposure: no EEG spectral change from sham mode; no interhemispheric EEG spectral difference
Huber et al. [2002]	16 M	GSM 900 MHz unmodulated (CW) and pulse modulated (PW) at 2, 8, 217/1736 Hz with a duty cycle of 12.5 %; SAR = 1 W/kg over 10 g; 30-min exposure at the left hemisphere before nocturnal sleep	Post exposure: ↑ EEG alpha (peak at 10 Hz) power during resting waking prior sleep onset; only with PW
Huber et al. [2003]	16 M	Re-analysis of data from Huber et al. [2000]: GSM 900 MHz modulated at 2, 8, 217/1736 Hz ('base-station-like' signals), duty cycle of 87.5 %; SAR = 1 W/kg over 10 g; 30-min lateral exposures [Left & Right hemisphere] before a 3-h diurnal sleep (with prior nocturnal sleep restricted to 4h)	During exposure: ↓ resting waking EEG power at 10.5-11 Hz and 18.75-19.5 Hz (with eye closed).
Croft et al. [2002]	16 M, 8 F	GSM 900 MHz modulated at 217 Hz, time averaged power emission was 0.3-0.4 W, SAR not reported, 4 cycles of 20-min posterior midline exposure during which an auditory discrimination task and a resting waking EEG recording (with eye opened) were executed.	During exposure (with auditory discrimination task): three exposure-related EEG activities were changed as 'a function of exposure time': (1) ↑ phase-locked EEG 30-45 Hz power at midline frontal and lateral posterior sites; (3) ↓ early phase-locked EEG 12-30 Hz power globally; (3) ↓ normal

			response decrement over time in the EEG 4-8 Hz power. During exposure (with rest, eyes opened): (1) ↑ resting waking EEG power at 8-12 Hz (as a function of exposure duration); (2) ↓ waking EEG 1-4 Hz power at the right hemisphere (not exposure duration-dependent).
D'Costa et al. [2003]	5 M, 5 F	GSM 900 MHz handset signals modulated at either 217 Hz or 1-32 Hz (standby mode), time averaged power emission was 0.25 W (peak power of 2 W), SAR not reported. Two trials (217 Hz pulsed or 1-32 Hz pulsed) were conducted at the same participants on different days. Each trial was consisted by ten 5-min exposure sessions (5 'active' and 5 'sham' exposure) and nine 10-15 min break intervals. The resting waking EEG was acquired during exposure session with sitting position, eyes closed. The handset was placed horizontally behind the subject's head with the antenna positioned 2 cm away from the occipital region. Exposure order of 'active' and 'sham' mode recordings was randomized and blind to participants.	During exposure: 217 Hz-pulsed signals: ↓ frontal power at 9-Hz bin, ↓ central power at 7 and 9-Hz bins, ↓ occipital power at 7-9 Hz bins; 1-32 Hz pulsed signals: ↑ frontal power at 12-Hz bin
Curcio et al. [2005]	10 M, 10 F	GSM 902.40 MHz modulated at 217 Hz, time averaged power emission was 0.25 W (peak power of 2 W), maximum SAR = 0.5 W/kg (10 g averaged). 45-min exposure at the left-ear standard phone position (with the phone-ear distance = 1.5 cm). Five males and Five females (Group 1) were measured resting waking EEG (7 min) after cessation of exposure. Another five males and five females (Group 2) were measured resting waking EEG in the last 7 min of exposure. Resting waking EEG were acquired with sitting position with eyes closed	During exposure & Post-exposure: ↑ central (Cz) and temporal (T3) EEG power at 9-10 Hz, but the parietal (Pz) EEG power at 11 Hz was larger during exposure than after exposure
Regel et al. [2007a]	24 M	GSM 900 MHz unmodulated (CW) and pulse modulated (PW) at 2, 8, 217/1736 Hz with a duty cycle of 12.5 %; SAR = 1 W/kg over 10 g; 30-min exposure at the left hemisphere during which series of cognitive tasks (simple reaction time, continuous reaction time, 1-back, 2-back, 3-back) were performed twice; the waking EEG	Post exposure (with PW): (i) no EEG spectral change was observed immediately after exposure; (ii) ↑ central EEG power at 10.5-11 Hz 30-min after exposure; (iii) ↓ EEG 12-Hz power 60-min after exposure

		(sitting position, with eyes closed) were recorded immediately after (0 min), and 30 min and 60 min after exposure.	
Croft et al. [2008]	46 M, 74 F	GSM 895 MHz modulated at 16 and 217 Hz, time averaged power emission was 0.25 W (peak power of 2 W), a maximum SAR over the temporal lobe was 0.110 W/kg (10 g average); 30-min left or right hemisphere exposure (counterbalanced between subjects), resting waking EEG during exposure (90-s x 4) and after the exposure cessation (10 min) was recorded and analyzed (eye opened, sitting position)	During exposure: ↑ overall resting waking EEG 8-12 Hz power (more pronounced ipsilateral to exposure source, particularly at the posterior site, but the 'exposure duration-dependent alpha enhancement' as reported in their previous study: Croft et al., 2002) was not replicated. Post exposure: ↑ resting waking EEG 8-12 Hz power comparing with sham control but not overall effects; however, the posterior ipsilateral effects was maintained during this period
Perentos et al. [2007]	6 M, 6 F	Similar to the signals used by Huber et al. [2000], the only difference was the signal transmission in this study was via monopole antenna rather than the patch antenna used by Huber et al.: GSM 900 MHz unmodulated (CW) and pulse modulated (PW) at 2, 8, 217/1736 Hz with a duty cycle of 12.5 %; SAR = 1.56 W/kg over 10 g. Each recording session comprised sham, PW, and CW EMF conditions, in each of which the 15-min EMF exposure (single blind, left-ear) was preceded and succeeded by 7.5-min resting waking EEG recording (sitting position with eyes closed).	Post-exposure: No changes to EEG alpha power and non-linear features (using Approximate Entropy method) for either PW or CW exposure.
Hinrikus et al. [2004]	11 M, 9 F	GSM 450 MHz modulated at 7 Hz, duty cycle: 50%, field power density at the skin: 0.16 mW/cm^2, SAR: 0.35 W/kg. The experimental protocol consisted of a short-term photic (16 Hz on-off, duration 20s) and then ten-cycles of EMF/sham exposure (1-min on and 1-min off). Participants were blind to the exposure signals, lying in relaxed waking, eyes closed, ears blocked with their EEG being recorded continuously during the experiment. Left-side exposure.	During exposure (with rest): showing trend of ↑ EEG 8-13 Hz power in all EEG channels (Fp1, Fp2, P3, P4, T3, T4, O1, O2), with changes more noticeable in the frontal regions
Hinrikus et al. [2008]	4 M, 9 F	GSM 450 MHz modulated at fixed frequencies of either 7 or 14 or 21 Hz, duty cycle: 50%, field power density at the skin: 0.16 mW/cm^2, SAR: 0.35 W/kg. The experimental protocol consisted of two five-cycle	During exposure (with rest): pulse modulation frequency-dependent effects, as shown by: (i) ↑ EEG alpha (8-13 Hz) and lower beta (15-20 Hz) power (with 14 and 21 Hz-pulsing EMF exposure);

		(1-min on and 1-min off) series of EMF exposures at fixed modulation frequencies preceded by sham exposure (power-off condition), Participants were blind to the exposure signals, lying in relaxed waking, eyes closed, ears blocked with their EEG being recorded continuously during the experiment. Left-side exposure.	(ii) ↑ EEG higher beta (22-38 Hz) power (only with 21 Hz-pulsing EMF exposure); (iii) no EEG effect with 7 Hz-pulsing EMFs (The effect calculation was based on the relative percentage change of the EEG power between the exposure and resting segments averaged over 10 cycles of exposure, 8 electrodes and 13 subjects.)

Ss, Subjects; M: male; F: female

2.2.3 Effects on Brain Metabolism and Excitability

Only few studies have used functional neuroimaging to assess the effects of EMF with direct measures of brain metabolism or cortical excitability. Table 2. 5 summarizes their experimental characteristics and main findings.

Huber et al. [2002] were the first to explore the possible effects of GSM handset-like signals on the waking regional cerebral blood flow (rCBF). The positron emission tomography (PET) scanning was started 10 min after the end of the 30-min EMF exposure to the left side of the head, during which the participants were instructed to slowly count silently from one to 60 to ensure similar cognitive activity during all conditions and to avoid spurious activation [Gusnard & Raichle, 2001]. The exposure signal was GSM 900 MHz, pulse modulated at 2, 8, 217/1736 Hz, with a SAR level on 10 g of tissue of 1 W/kg. Their data showed that, compared with the sham condition, pulse-modulated EMF exposure induced diffuse changes in rCBF significantly larger in the dorsolateral prefrontal cortex than the localized antennae region of the mobile phone. The diffuse changes of rCBF in the cortex adds considerable support to the supposition that the EMF exposure may modify the thalamo-cortical loops known to be involved in generation of sleep spindles [Contreras et al., 1996 a, b; Steriade et al., 1993 b, c]. This mechanism might also account for enhancement of the EEG alpha activity seen in waking, as alpha generating mechanisms involve both thalamic and non-thalamic sources [Lopes da Silva, 1991].

In order to substantiate their prior findings of 'pulse modulation-dependent effects on the waking and sleep EEG' in which the analysis was restricted to the comparison between handset and sham (nil) exposure [Huber et al., 2002], the same research

group investigated the effect of a 'base-station-like' (bstat) signal on local rCBF and compared it with a 'handset-like' (handset) signal [Huber et al., 2005]. Physically, both of their 'handset' and 'bstat' signals share the same ELF pulse modulation components (2, 8, 217/1736 Hz) as well as the SAR strength and distribution in the tissue (1 W/kg over 10-g of tissue). But they are different in their ELF spectral amplitude (up to two orders of magnitude in the 'handset' signal compared with the 'bstat' signal) and crest factors [four times higher for the 'handset' signal (= 4.8) compared with the bstat signal (= 1.2)]. The authors hypothesized that, if only the 'handset' signal (with its stronger ELF components), but not the 'bstat' signal, affects rCBF, the supposition that 'any biological effects of mobile phone exposure are likely non-thermal and are instead related to the ELF components of the modulation scheme of the mobile phone.' Indeed, the experimental results of comparing two signals on the post-exposure regional cerebral metabolism supported this hypothesis that ELF pulse modulation is the necessity and sufficiency for GSM mobile phone signals to influence brain physiology. Similarly to their previous findings of pulse-modulation effect on the rCBF (handset vs. sham, [Huber et al., 2002]), the authors observed an increase in cerebral metabolism on the left dorsolateral prefrontal cortex in proximity to the exposure head side (handset vs. bstat).

Aalto et al. [2006] conducted a double-blind, counterbalanced within-subject experiment on 12 healthy individuals performing a working memory task (1-back task) during 14 PET scans. The phone (GSM 902 MHz with 217 Hz pulsation, mean power of 0.25 W, averaged SAR over 10 g of tissue revealed a 0.743 W/kg with peak value of 1.51 W/kg) was active or in sham mode during the first or second half of the scans. The statistical analysis showed a decrease in rCBF during the active exposure condition in the left fusiform gyrus in correspondence to the antenna, while an increase was observed bilaterally in the medial and superior frontal gyri. These results were not comparable to Huber et al.'s findings [2002, 2005] as this study measured 'immediate effects' rather than the 'after effects.' Furthermore, these imaging were collected during exposure with the participants engaging in the cognitive task, thereby it was hard to tell if the effects were pure EMF effects.

Instead of using EEG or PET techniques to indirectly measure phone effects on the neuronal excitability, the most recent study has started using transcranial magnetic stimulation (TMS) for direct assessment [Ferreri et al., 2006]. Fifteen males underwent two sessions (real and sham), one week apart, in a cross-over, double-blind paradigm. In both sessions, the exposure lasted 45 min and the cortical

excitability was assessed before (baseline, T0), immediately after exposure (T1), and after a 1-h interval (T2). It was shown that intracortical excitability was significantly modified after real exposure to a GSM signal (GSM 902.40 MHz pulsing at 217 Hz, averaged power of 0.25 W and maximum SAR of 0.5 W/kg), in the direction of a greater cortical excitability. In fact, short intracortical inhibition was reduced while intracortical facilitation appeared enhanced. These effects are clear in the acutely exposed human cerebral hemisphere as compared to the non-exposed contralateral hemisphere or to sham exposure. Moreover, these phenomena are transient, as shown by EEG studies [e.g., Croft et al., 2002; Huber et al., 2002; Curcio et al., 2005] since the baseline condition is almost completely regained 1 h after the end of exposure.

In short, these studies seem to support the possibility of an EMF-induced effect of increased cerebral metabolism and excitability in the directly exposed brain areas. Nevertheless, these cortical electromagnetic phenomena with a rapid recovery of baseline brain activity are transient and reversible. At present, no study seems to verify the existence of long-term effects.

Table 2. 5 Summary of ELF-modulated EMF Effects on brain metabolism and excitability.

Study	Ss	Exposure features	Key findings
Huber et al. [2002]	13 M	GSM 900 MHz pulse modulated (PW) at 2, 8, 217/1736 Hz with a duty cycle of 12.5 %; SAR = 1 W/kg over 10 g; 30-min exposure at the left hemisphere before nocturnal sleep	Post exposure: ↑ waking rCBF on the left dorsolateral prefrontal cortex (exposed side)
Huber et al. [2005]	16 M	GSM 900 MHz 'handset' and 'bstat' signals, both share the same (i) ELF spectral components (2, 8, 217/1736 Hz); (ii) strength and distribution of the time-averaged SAR in the tissue (1 W/kg over 10 g), but are different in their (a) duty cycle ('handset' signals: 12.5 %, 'bstat' signals:87.5 %); (b) crest factor ('handset' signals: 4.8; 'bstat' signals: 1.2); (c) spectral amplitude of ELF components (up to two orders of magnitude in the 'handset' signals compared with the 'bstat' signals). 30-min exposure at the left hemisphere.	Post exposure: ↑ waking rCBF on the left dorsolateral prefrontal cortex (exposed side), and the effect was only with 'handset' signals.
Aalto et al. [2006]	12 M	GSM 902 MHz pulsing at 217 Hz; average power = 0.25 W; averaged SAR in the tissue over 10 g = 0.743 W/kg with peak SAR = 1.51 W/kg	During exposure: ↓ waking rCBF in the left fusiform gyrus (exposed side); ↑ waking rCBF in the bilateral medial and superior frontal gyri.

Ferreri et al. [2006]	15 M	GSM 902.40 MHz pulsing at 217 Hz, average power = 0.25 W, maximum SAR = 0.5 W/kg	Post exposure:↑ cortical excitability in the exposure hemisphere (as revealed by ↑ of intracortical facilitation and ↓ of intracortical inhibition) as compared to the non-exposure hemisphere or to sham exposure. Such effect is transient as baseline conditions are partially regained 1 h after the end of exposure.

Ss, Subjects; M: male; F: female

2.2.4 Effects on Performance

Up to date, the majority of studies seeking to assess the central nervous system (CNS) effects of mobile phone upon cognitive performance rely on neuropsychological assessment instruments as dependent measures. They measured several cognitive constructs such as 'working memory,' 'long-term memory,' 'attention,' 'executive function' and 'motor dexterity.' In this section, we look into effects on performance by reviewing some important papers published since 2000 and categorizing the reported findings according to the neurocognitive function of relevant tasks used in these papers (Table 2. 6). The methodology of each paper reviewed is outlined in Table 2. 7.

Compared with the studies examining EEG response to mobile phone exposure, evidence suggest neurocognitive performance does not seem to be consistently affected and studies frequently failed to corroborate previous findings with improvement in the methodology. For example, Haarala et al. [2003a] used the same mobile phone parameters and cognitive tasks with a larger sample size, more tests and a double-blind condition but failed to replicated their earlier study [Koivisto et al., 2000a], which reported a significant decrease in reaction time in the sustained attention test over the experimental time in the EMF-exposed group compared to control. Likewise, with a methodological improvement (by increasing sample size and implementing a double-blind design), this research group [Haarala et al., 2004b] could not replicate their previous findings of facilitator EMF effects upon n-back working memory task [Koivisto et al., 2000b].

Why this might be the case is unclear. It is possible that EEG effects are superfluous and result in no behavioural changes. It is equally possible that the behavioural measures were not sensitive enough to detect changes in cognitive function. This is particularly relevant given the number of EMF-induced EEG effects observed over the

parietal/occipital regions, while many of the behavioural tests employed in the studies measures mainly the frontal or temporal lobe function. Alternatively, in several studies, statistical power may have been insufficient to reliably detect EMF-induced alternation as EMF effect sizes are generally small [Whittington & Podd, 1996]. Coupled with this statistical issue is the selection of performance tests that may be sensitive, that is, not adequate at discriminating subtle effects [Cook et al., 2006, see discussion]. Many of the performance tasks utilized in these studies are designed to discriminate between neurologically normal and abnormal subjects. Considering the subtle EMF effect size, it is quite possible to obtain a non-significant result in the study employing a very robust performance measure with inadequate statistical power.

Furthermore, the equivocal findings may also be due to the large differences found across studies with respect to the induced field strength distribution, exposure signal and study design. This point is important as evidenced by researches on the dose-dependent effects of field intensity [Regel et al., 2007b]. However, again, cognitive performance did not seem to be consistently affected.

Table 2. 6 Summary of ELF-modulated EMF Effects on performance measures.

Ability	Task	Studies	Results
Working memory[2]	Visual short-term memory	Lass et al. [2000]	↓ (error variance increased)
	Short-term recall of spatial and semantic memory	Smythe & Costall [2003]	↑ (fewer spatial errors in male subjects comparing between active and inactive condition)
	Visual working memory	Haarala et al. [2003b]	No effect (↓ rCBF in bilateral auditory cortex but no rCBF changes in the area of maximum EMF)
	N-back task	Haarala et al. [2004]	No effect
	N-back task	Regel et al. [2007a]	↓ reaction speed (in both 2- and 3-back tasks), ↑ accuracy (only in the 3-back)
	N-back task	Regel et al. [2007b]	↓ reaction speed (tended to decelerate during GSM exposure in a dose-dependent manner, reaching significance in the 1-back task), No dose-response relationship was found for accuracy
Long-term memory[3]	Long-term recall	Smythe & Costall [2003]	No effect
Attention +	Digit span	Edelstyn &	↑ (processing speed increased)

[2] Working memory: the ability of keeping an amount of information 'in mind' in a few seconds [Baddeley, 1992] and identify and replay back that information if enquired

[3] Long-term memory: recall learned information at a much later time period > 10 min onwards

working memory[4]	forwards/backwards	Oldershaw [2002]	
	Spatial span forwards/backwards	Edelstyn & Oldershaw [2002]	↑ (processing speed increased)
	Auditory discrimination	Croft et al. [2002]	No effect in reaction time (but the early phase-locked EEG response was changed: attenuating the normal decrement over time in the 4-8 Hz band, decreasing 12-30 Hz power globally and as a function, increasing midline frontal and lateral posterior EEG power at 30-45 Hz band)
	Auditory discrimination (order threshold)	Maier et al. [2004]	↓
Attention + motor speed[5]	Trail making test	Lass et al. [2002]	↓ (error variance increased)
	Trail making test	Lee et al. [2003]	No effect
	Simple/Choice/10 choice reaction time	Haarala et al. [2003a]	No effect
	Simple/choice reaction time	Curcio et al. [2004]	↑ (processing speed increased)
	Visual search	Curcio et al. [2004]	↑ (processing speed increased)
	Simple/choice reaction time	Regel et al. [2007a]	No effect
	Simple/choice reaction time	Regel et al. [2007b]	No effect (but reaction speed tended to decelerate with increasing field intensity)
	Simple reaction time	Curcio et al. [2008]	No effect
Focused / Sustained attention[6]	Symbol digit modalities	Lass et al. [2002]	↓ (error variance increased)
	Verification vigilance	Haarala et al. [2003a]	No effect
	Sustained attention to response	Lee et al. [2003]	↑ (processing speed increased)
	Auditory and visual oddball task	Hamblin et al. [2006]	No effect for reaction time or any auditory or visual event-related potential component
	Simple/choice reaction time	Regel et al. [2007a,b] and Curio et al. [2004, 2008]	(see above)
Executive function	Verbal fluency	Edelstyn & Oldershaw [2002]	No effect
	Serial subtraction	Edelstyn & Oldershaw [2002]	No effect
	Subtraction task	Haarala et al. [2003a]	No effect

[4] Attention + Memory: highlights ability to closely concentrate on a task while also requiring the need to keep information in mind simultaneously (such as tasks of forward and backward digit/spatial span, time estimation, visual and auditory discrimination, auditory-verbal learning)
[5] Attention + Motor speed: requires concentration on a target stimulus with emphasis on reaction speed to the target
[6] Sustained/focused attention: highlighted by intense concentration for an extended period on a single entity with competing stimuli or distraction

	Arithmetic descending subtraction task	Curcio et al. [2004]	No effect
Motor dexterity	Sequential motor tapping task	Curcio et al. [2008]	No effect

Table 2. 7 Outline of methodology of the reviewed studies

Results	Studies	Ss	Exposure features
Immediate effect	Lass et al. [2000]	63 M, 37 F (between-subject design)	GSM 450 MHz pulsing at 7 Hz; SAR = 0.0095 W/kg; 10-20 min exposure over the right hemisphere
	Smythe & Cotstall [2003]	33 M, 29 F (between-subject design: no phone, inactive phone and active phone)	GSM 1800 MHz; SAR = 0.79 W/kg; 15-min exposure over the left hemisphere;
	Croft et al. [2002]	16 M, 8 F	GSM 900 MHz modulated at 217 Hz, time averaged power emission was 0.3-0.4 W, SAR not reported, 4 cycles of 20-min posterior midline exposure
	Lee et al. [2003]	N = 78 (between-subject design: no phone, inactive phone and active phone)	GSM 1900 MHz pulsing at 217 Hz; SAR = 0.0095 W/kg; < 60 min exposure over the right hemisphere
	Regel et al. [2007a]	24 M	GSM 900 MHz modulated at 2, 8, 217/1736 Hz with a duty cycle of 12.5 %; SAR = 1 W/kg over 10 g; 30-min exposure at the left hemisphere during which series of cognitive tasks (simple reaction time, continuous reaction time, 1-back, 2-back, 3-back) were performed twice
	Regel et al. [2007b]	15 M	GSM 900 MHz modulated at 2, 8, 217/1736 Hz, duty cycle of 21 %, which was applied at a SAR of 0.2, 5 or 0 W/kg (sham control, nil-signal condition) over 10 g; 30-min exposure at the left hemisphere prior to an 8-h nocturnal sleep EEG recording. During exposure, series of cognitive tasks (simple reaction time, continuous reaction time, 1-back, 2-back, 3-back) were performed twice,
	Curcio et al. [2008]	12 M, 12 F	GSM 902 MHz, pulsing at 8.34 and 217 Hz; < 45 min exposure over the left hemisphere
	Hamblin et al. [2006]	46 M, 74 F	GSM 895 MHz modulated at 16 and 217 Hz, time averaged power emission was 0.25 W (peak power of 2 W), a maximum SAR over the temporal lobe was 0.110 W/kg (10 g average); 30-min left or right hemisphere exposure (counterbalanced between subjects)
Delayed effects	Edelstyn & Oldershaw [2002]	N = 38 (between-subject design: no phone, inactive phone and active phone)	GSM 900 MHz; 30 min exposure
	Maier et al. [2004]	N = 11	GSM 902 MHz, pulsing at 217 Hz; 50-min exposure over the left hemisphere
	Curcio et al. [2004]	10 M, 10 F	GSM 902.4 MHz pulsing at 217 Hz; average power = 0.25 W; a maximum SAR = 0.5 W/kg; 45 min exposure over the left hemisphere
No effect	Haarala et al. [2003a]	32 M, 32 F	GSM 902 MHz pulsing at 217 Hz; peak power = 0.25 W; 30-min exposure over the left hemisphere

	Haarala et al. [2003b]	N=14	GSM 902 MHz pulsing at 217 Hz; peak power = 0.25 W; 30-min exposure over the left hemisphere
	Haarala et al. [2004]	32 M, 32 F	GSM 902 MHz pulsing at 217 Hz; peak power = 0.25 W; 65-min exposure over the left hemisphere

Ss, Subjects; M: male; F: female

2.2.5 Factors that Contribute to Inconsistencies between Studies

2.2.5.1 Exposure Conditions: Duration, Monitoring Periods, Statistical Methods

On the afore-mentioned review, though neurophysiological effects seemed to be more consistent than neurocognitive effects, available neurophysiological effects are highly variable. Part of the variance between studies arises due to the variable experimental conditions. These include exposure duration (or dosage), post-exposure monitoring periods and statistical analysis methods. Indeed, studies reporting a similar resting waking EEG alpha effect [e.g., Huber et al., 2002; Croft et al., 2008; Curcio et al., 2005] were common in some methodologies, such as accurate dosimetry, the extended duration of exposure and the duration of EEG recordings. On the contrary, resting waking EEG studies showing no alpha effects have tended to employ smaller exposure duration [e.g., Roschke & Mann,1997, exposure period < 3.5 min]. Significant effects of both EMF exposure duration and EEG recording duration have been discussed comprehensively by Croft et al. [2002].

Another important factor contributing to incongruent results is the modulation characteristics. Of particular importance are the variations in SAR distributions inside the brain tissue (due to the microwave power density and the type of antenna used to transmit the microwave) and the ELF spectral contents (due to the type of modulation employed). These two factors are discussed in the following two sections.

2.2.5.2 Variation in SAR Distributions

Regel et al [2007b] measuring possible dose-response SAR effects on the sleep EEG, by varying the SAR intensity of simulated GSM 900 MHz mobile phone signals (with low-frequency pulse modulation at 2, 8, 217 Hz), have demonstrated a 'dose-dependent' SAR effect on the alpha band activity. Given the close relationship between the SAR intensity and EEG effects, this study implies the variable SAR distribution in the brain is critical for inducing variable EEG findings. The variation of

brain SAR distribution is mainly contributed by two factors: microwave power density and the antenna types. As most studies of real or simulated GSM mobile phone signals have identical microwave power density, the brain SAR variation shall be contributed by other factors that affect differential microwave transmission. One of the possible factors is the usage of different antennas.

Huber et al. [2003] indicated that the 'patch antenna' used by in their prior study Huber et al. [2002] (and later by Regel et al. [2007a, b]) resulted in a SAR variation within the exposed hemisphere of approximately 12.5 dB (between the exposed surface and the farthest side to the exposed hemisphere), with some areas deep in the brain exposed to SARs of at least -5 dB. However, it has been shown that the variation of SAR in the head due to exposure from a 'monopole antenna' (employed by real GSM handsets) operating at 900 MHz is much greater, reaching 24 dB [Li et al., 2000]. Thus a more homogeneous exposure is produced under the patch antenna relative to the localised nature of the exposure resulting from a monopole antenna. In particular, some parts of the mid-brain (such as the thalamus) may be exposed to SARs by a factor of up to 80 dB under the patch antennas. As this brain region could possibly be more vulnerable to external stressors such as RF, it is speculated that the homogeneity of the patch antenna exposure may result in over-exposure of this brain region (which is thought to be the pacemaker of EEG rhythms), and thereby produces an enhanced (and protracted) effect in those studies using this type of antenna. Perentos et al.'s study [2007] has provided further experimental evidence to verify this possibility as they failed to replicate the post-exposure EEG alpha power increase as described in previous research with an exposure source (dipole antenna) more closely resembling that of a real GSM handset.

2.2.5.3 ELF Spectral Contents

Huber et al. [2002] and Regel et al. [2007a] tested the importance of ELF pulse modulation by comparing post-exposure EEG effects between PM EMF (pulse-modulated at frequencies of 2, 8, 217 Hz) and CW EMF exposure. Results showed only PM EMF but not CW EMF exposure induced EEG effects. This study implies 'ELF pulse modulation' is a pre-requisite of EMF to induce brain physiological changes. Their later study [Huber et al., 2005] comparing regional cerebral blood flow (rCBF) effects of 'handset-like' and 'base-station-like' pulse-modulated signals (both share the same ELF pulse modulation frequencies at 2, 8, 217 Hz, but the 'handset-like' signal has stronger spectral power of the 2 and 8 Hz pulsing) substantiated this

notion as evidenced by (i) both signals altered the post-exposure waking rCBF; (ii) the signal with stronger ELF spectral power (i.e., the 'handset-like' signal) demonstrated a stronger change.

The mechanisms behind the observed pulse modulation-dependent effects of EMF are still unknown. But there are several candidate mechanisms have been proposed (see discussion in Croft et al. [2008]), such as:

(i) Calcium efflux through microwave stimulation of the outer layer of neurons [Bawin et al., 1975; Blackman et al., 1979; Adey, 1981];
(ii) Thermal increases of less than 1 °C that may affect the brain in subtle way (for review, see Adair and Black [2003]);
(iii) Increases in permeability of the blood–brain barrier (for review, see D'Andrea et al. [2003]), and
(iv) Increases in neural excitability, which is a hypothesis put forward by Freude et al. [1998] and has recently been experimentally supported by Ferreri et al. [2006].

However, some researcher posit that microwaves cannot cause any EEG effect alone as they cannot induce regular change in the movement of ions due to their small cross-section of absorption (the wavelength of the microwave is much larger than the dimensions of a cell) as well as their inertial properties and viscosity of the liquid medium [Adair, 2002]. On the other hand, as being noted in the current WHO Research Agenda for Radio Frequency Fields [2006] and in a recent review by Challis [2005], 'neural interference' may also be a viable mechanism for the EEG effects of EMF. Since the ELF components of the phone emissions are within the range that the brain naturally employs in its communication network (e.g., 16 Hz [Knyazeva et al., 2006]; 60–250 Hz [Edwards et al., 2005]; up to 1000 Hz [Mochizuki and Ugawa, 2005]), this opens up the possibility that the exogenous (mobile phone) ELF may interfere with the endogenous (neural) ELF.

Recent achievements in the repetitive electric (i.e., 'Direct Current Stimulation', DCS) and Transcranial Magnetic Stimulation (TMS) in the brain research have suggested that cortical excitability can be changed by varying the stimulation frequencies, such that the low-frequency (< 1-Hz) repetitive TMS caused inhibition whereas repetitive stimulation at higher frequencies (> 1-Hz) produced excitation [Lemon, 2002]. Studies have shown that synchronizing the stimulation rates of repetitive TMS (rTMS) with the

sleep/waking EEG frequencies can modulate the behavioural state of the brain accompanied by changes in the frequency and spatial coordination of the rhythmic bioelectrical activities in the neocortex, and such effects may be outlasting even after the cessation of the stimulation. For example, 0.8-Hz rTMS over the sensorimotor area at anytime during Non-Rapid-Eye-Movement (NREM) sleep was reported to trigger sleep slow-wave (1-4 Hz) activities [Massimini et al., 2007] while 5-Hz rTMS over the primary motor cortex during the pre-sleep waking was reported to trigger the same effect in the premotor cortex during sleep after stimulation cessation [Huber et al., 2007]. Given that (i) microwave excitable resonances may be strongly damped by interaction with their aqueous biological environment and (ii) the mobile phone ELF may interfere with the brain ELF by synchronization, it is possible any effects caused by the EMF exposure on the bioelectrical activity of the human brain is dependent on the ELF spectral components of mobile phone signals.

2.3 RESEARCH GAPS

2.3.1 Effects of Real ELF Pulse-Modulated Mobile Phones Signals Emitted at Talk, Listen and Standby Modes

As previously mentioned, ELF pulse modulation of EMF is important for inducing neurophysiology changes and most studies claimed the observed effects being generated by exposing to EMFs simulated to the common GSM handsets with ELF components of either only 217 Hz or a combination of 2, 8, 217 Hz. However, there still remains the question: whether these signals used by previous studies can be 'generalisable' to the real mobile phone signals transmitted at 'talk', 'listen' and 'standby' modes?

It should be noted that a lot of studies appearing to look at GSM 'talk-mode' signals (900 MHz with 217 Hz modulation) have not considered the permanent low-frequency modulation at 8 Hz [e.g. Mann et al., 1996; Wagner et al., 2000; Wagner et al., 1998; Croft et al., 2002; Curcio et al., 2005; D'Costa et al., 2003; Loughran et al., 2005]. Furthermore, those studies that did include this 8 Hz component [i.e. Huber et al., 2002; Huber et al., 2003 ('handset-like' signals)], are not purely looking at either talk or listen mode, but a synthesis of both (ref: Synthesized 'Handset-Like' Signals in Figure 2. 2) which include the spectral components of 2, 8, 217 Hz and the corresponding harmonic. Table 2. 8 summarised the low-frequency pulse modulation components in the GSM signals that have been studied so far. As shown, there is a

research gap regarding the EEG effects of the real mobile phone signal emitted at 'talk' and 'listen' (full silence) mode.

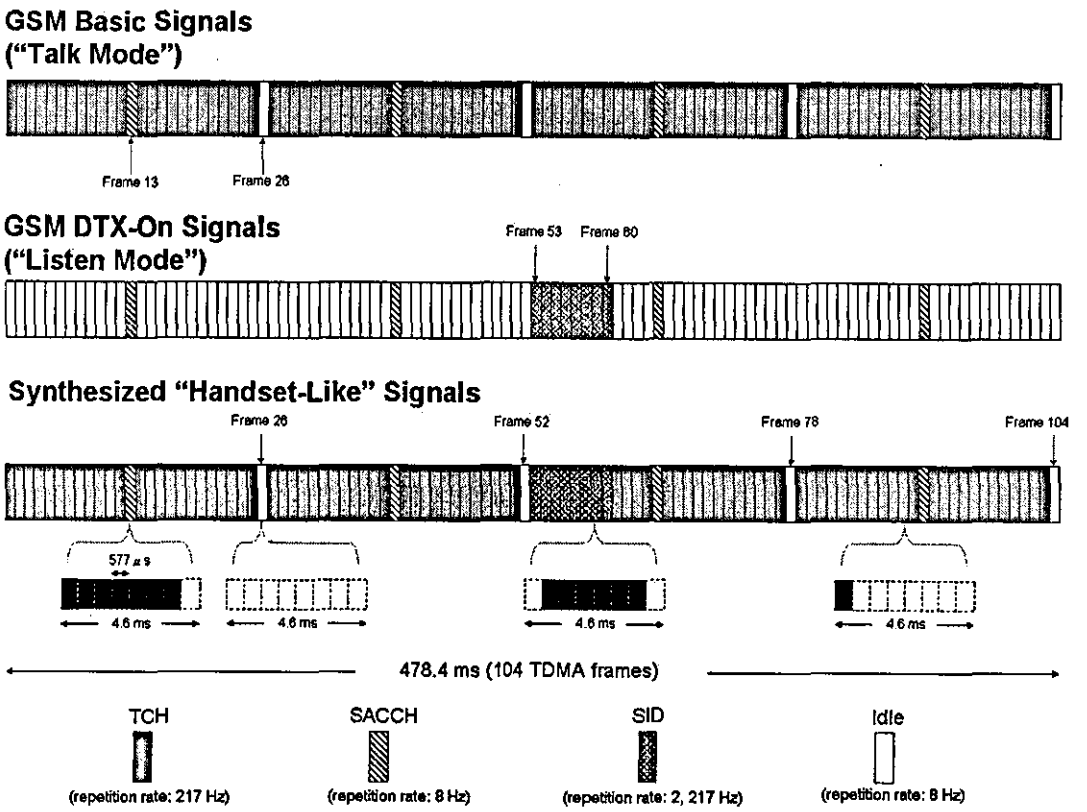

Figure 2. 2 GSM pulse structures of 'Talk Mode', 'Listen Mode' and 'Synthesized Handset-Like Signals' [Huber et al., 2005; Ebert et al., 2006]. The pulse structure of the 'handset-like' signals combines the frame structure of the 'basic GSM mode' ('talk mode') and the 'DTX mode' ('listen mode').

Table 2. 8 Summary of the ELF components of the GSM handset signal used by other relevant EEG studies, in comparison with our study.

Mode of signals	ELF components	Other studies
Talk	8, 217 Hz	
Listen (100% silence)	2, 8, 217 Hz	
Talk + Listen	2, 8, 217 Hz (stronger 217-Hz spectral power than our Listen mode)	Huber et al. [2002, handset-like]; Huber et al. [2003, handset-like]
Standby	1-32 Hz	D'Costa et al. [2003]
Not applicable	Only 217 Hz	Mann et al. [1996]; Wagner et al. [1998]; Wagner et al. [2000]; Croft et al. [2002]; D'costa et al. [2003]; Curcio et al. [2005]; Loughran et al. [2005]

2.3.2 Functional Interpretation of Observed Sleep/Waking EEG Effects

In the field of bio-electromagnetic interaction, EEG is the most popular technique to study human neurophysiological effects. EEG measures the spontaneous rhythmic electrical activity occurring in multiple frequency bands, which reflects the size of thalamic and cortical neuron populations that synchronously oscillates in these frequency modes [Steriade & Amzica, 1998]. Provided numerous mobile phone effects have observed change in the spontaneous EEG spectrum (either during sleep or resting wakefulness), however, few attempts have been made to interpret these observations in the context of sleep/waking regulation or sleepiness. Here we reviewed some well-established EEG representatives of these respects in order to further discuss our own EEG data later.

2.3.2.1 Circadian and Homeostatic Correlates of EEG Delta (1-4 Hz) and Sigma (12-16 Hz) Activity during REM sleep

Delta (1-4 Hz) Activity during NREM Sleep

EEG 'delta' activity (defined as EEG waves in the frequencies between 1-4 Hz, also referred to as 'slow-wave activity', SWA) and 'sigma' activity (defined as EEG waves in the frequencies between 12-16 Hz, also referred to as 'spindle frequency activity', SFA) during the human sleep cycle are modulated by an interaction of two processes: a 'circadian process' generated in the suprachiasmatic nuclei (SCN) of the hypothalamus, and a 'sleep homeostatic process' representing the sleep-wake dependent pressure for sleep [Daan et al., 1984; Dijk & Czeisler, 1995]. Forced desynchrony experiments and observations during spontaneous desynchronization between the sleep-wake cycle and the circadian system have demonstrated that slow-wave sleep duration and EEG delta activity during NREM sleep decrease throughout the course of sleep at all circadian phases, suggesting they are not substantially modulated by circadian but homeostatic factors [Weitzman et al., 1980, Dijk & Czeisler, 1995]. These data are in accordance with the hypothesis that these low-frequency EEG components during sleep are an electrophysiological marker of the dissipation of homeostatic sleep pressure, which increases as a function of preceding waking duration and decreases during sleep [Borbély et al., 1981]. Sleep deprivation and nap experiments had demonstrated a monotonic relationship between waking duration and the subsequent EEG delta power during sleep-onset [Borbély et al., 1981; Dijk et al., 1993; Werth et al., 1996]. Lesion of SCN in rodents does not abolish this increase of delta activities in response to an extension of wakefulness [Tobler et

al., 1983]. The increase of delta power density during NREM sleep varies along the antero-posterior axis and shows a 'fronto-central' predominance [Cajochen et al., 1999a; Finelli et al., 2001b; Knoblauch et al., 2002]. The delta activity in the frontal region, when compared with other regions, is more susceptible to sleep homeostatic challenge during an extension of wakefulness (i.e. a 40 h sleep deprivation). However, when sleep is satiated (by a reduction of wakefulness with a 40 h multiple nap paradigm), the dissipation of sleep pressure (as revealed by a reduction of delta power across a late nap and post-nap sleep) is not confined to frontal brain areas and rather manifests itself in more occipital region [Knoblauch et al., 2002]. Thus, EEG delta activities, especially those at the frontal region, are a reliable marker of the sleep homeostatic process [Dijk et al., 1997; Knoblauch, et al., 2002].

Sigma Activity during NREM Sleep

Current concepts of sleep-wake regulation still lack crucial understanding of EEG sigma activity regulation, but there is a general consensus that it is under both circadian [Dijk et al., 1997; Knoblauch et al., 2003a,b] and homeostatic control [Dijk et al., 1993; Knoblauch et al., 2002]. Regarding the circadian regulation, human EEG studies analysing sleep spindles 'during' and 'outside' the circadian phase of melatonin secretion have found an inverse circadian phase relationship in the low-frequency and high-frequency sigma activity falling at the spindle-frequency ranges (called 'Spindle-Frequency Activity', SFA, see Dijk et al. [1997]; Knoblauch et al., [2003a]). For example, SFA in the low-frequency range (12.25-13 Hz) coincides with the peak, and SFA in the high-frequency (14.25-15 Hz) with the nadir of the endogenous rhythm of melatonin secretion [Dijk et al., 1997]. Knoblauch et al. [2003a] further indicated the frequency-specific circadian variation is topographically dependent, such that the low-frequency (11-14.25 Hz) SFA was maximal in the parietal (EEG derivation: Pz) and minimal in the frontal region (EEG derivation: Fz) during the biological night.

Evidence supporting sleep homeostatic modulation of the EEG sigma activity is from sleep deprivation and nap studies. After sleep deprivation, EEG sigma power is reduced and shows an inverse relationship to EEG delta power during the recovery night [Borbély et al., 1981; Dijk et al., 1993; Finelli et al., 2001a]. The reduction in sigma power is limited to the upper frequency range [15 Hz bin, Borbély et al., 1981; 13.75-14 Hz, Dijk et al., 1993], whereas the low-frequency spindle power is unaffected [Borbély et al., 1981; Dijk et al., 1993] or enhanced [Knoblauch et al., 2002]. In a nap

study, where the duration of prior wakefulness varied from 2 to 20 h, a significant decrease of power density with increasing duration of prior wakefulness was observed in the 15 Hz-bin, but not in the lower spindle frequency range [Dijk et al., 1987]. These and other findings indicate that sigma activity in the higher frequency range (~13.75-16.5 Hz) is more sensitive to sleep pressure than that in the lower frequency range, and fluctuates inversely with sleep pressure.

Most studies describing the effects of different sleep pressure levels on the sigma activity used only one or two EEG derivations (C3, C4, or a fronto-occipital bipolar derivation) [Borbély, et al., 1981; Dijk et al., 1987, 1993, 1997]. However, sleep spindles may not be a homogeneous group of EEG waves: their frequency-specific distribution over different brain locations was recognized as early as 1950 [Gibbs & Gibbs, 1950]. This study reported that sleep spindles with a frequency range of 11-13 Hz exhibit an anterior dominance, whereas spindles with a frequency range of 13-15 Hz were most prominent in more posterior derivations. This frequency-specific topographical distribution[7] was later confirmed by several authors [Jobert et al., 1992; Werth et al., 1997; Zeitlhofer et al., 1997; Zygierewicz et al., 1999, Anderer et al., 2001]. A dose-response relationship between the amount of prior wakefulness and its repercussions on frequency- and derivation-specific SFA during NREM sleep has been reported by Knoblauch et al [2002]. Using EEG spectral analysis, they found that the power density of the high-frequency SFA (13.75-16.5 Hz) at the central-parietal region (EEG derivations: Cz, Pz) was enhanced in the recovery sleep after 'low sleep pressure' (ten 75/150 min sleep/wake cycles) but reduced after 'high sleep pressure' (40 h sleep deprivation). In contrast, the power density of the low-frequency SFA (12.25-13.25 Hz) at the central, parietal and occipital brain regions (EEG derivation: Cz, Pz, Oz) was increased after both manipulations. This study further reveals a topographic-dependent homeostatic regulation of high-frequency sigma activity (13.75-16.5 Hz), as the high-frequency sigma activity recorded from the central-parietal brain area is more venerable to the change of sleep pressure (and thus EEG delta power) than the high-frequency sigma activity recorded from other brain regions.

[7] Knoblauch et al. [2003a, see discussion] indicated their data did not corroborate the concept that frontally and parietally scalp-recorded sleep spindles originate from two functionally distinct thalamic sources. They think that difference between frontal and parietal scalp-recorded sleep spindles rather represent a topography-dependent modulation of one single type of spindle oscillations, whose origin can be traced back to the thalamic reticular nucleus from where it disseminates to distant sites within the thalamus.

Relationships between Delta (1-4 Hz) and Sigma (12-16 Hz) Activity During NREM Sleep

It should be noticed that the inverse relationship between EEG delta and sigma activity resulted from their differences in the dynamics during nocturnal baseline sleep and their response to sleep deprivation was observed when EEG delta power was substantially high and was not taken into account the time of day effects. However, within each NREM sleep episode when EEG delta power is low (i.e., at the 'stage 2 sleep' of a NREM sleep episode and at the 'NREM-REM sleep transition'), EEG sigma activity exhibit a positive correlation with delta activity [Aeschbach et al., 1993; Dijk et al., 1993; Uchida et al., 1994]. Although a negative correlation does exist between these two EEG activities in the middle part of a NREM episode (where EEG delta activity shows a peak and sigma activity a trough), the negative correlation subsides in the subsequent episodes and no longer reaches statistical significance beyond the third episode [Aeschbach et al., 1994, 1997b]. This suggests: (i) delta and spindle activity fluctuate inversely only when the delta power is sufficiently high and, (ii) when the sleep pressure is dissipated and sleep need is satiated in the later part of sleep, sigma activity is no longer associated with delta activity. Furthermore, when EEG sleep pressure (i.e. delta power) is remained at a relatively constant low level (e.g., during the early morning and daytime hours of an extended sleep from 19:00-7:00 h or 24:00-15:00 h), the frequency-specific circadian modulation of EEG sigma activity becomes more evident especially in the high-frequency bins (14.25-15 Hz) [Aeschbach et al., 1997a].

To sum up, both EEG delta and sigma activities during NREM sleep are under circadian and homeostatic modulation. Experiments employing forced desynchorony protocol have revealed that the phase of the endogenous circadian pacemaker has a prominent influence on the EEG sigma activity, whereas the influence on delta activity is minor [Dijk & Czeisler, 1995]. The circadian modulation of EEG sigma activity is predominant in the central and parietal regions of the brain, where exhibit a frequency-specific circadian phase variation -- the sigma activity in the low-frequency (12.25-13 Hz) coincides with the peak and that in the high-frequency (14.25-15 Hz) coincides with the nadir of the endogenous rhythm of melatonin secretion [Dijk et al., 1997; Knoblauch et al., 2003a]. In addition, the circadian modulation of parietal high-frequency sigma activity (~13.75-16.5 Hz) is vulnerable to sleep homeostatic regulation, which shows a negative correlation between the delta activity when the sleep pressure is sufficiently high, a positive correlation at the beginning and end of

SWS transitions (i.e. stage 2 sleep and the NREM-REM transition), and no correlation when the sleep is satiated [Aeschbach et al., 1997 a,b]. The homeostatic modulation of EEG delta activity is predominant in the frontal-central region, which delta power works as reliable marker of the sleep homeostatic process at all circadian phase [Dijk & Czeisler, 1995].

2.3.2.2 EEG Correlates of Sleep Promoting and Sleep Preserving: NREM Sigma (12-16 Hz) and Frontal-Central Alpha (8-12 Hz) Activity

NREM Sigma (12-16 Hz) Activity

Speculation regarding the functional significance of EEG sigma activities has also focused on inhibitory correlates of sleep spindles observed in studies conducted at both cellular and behavioural levels. Early investigations detailing the neuronal basis for sleep spindles emphasized the contribution of inhibitory postsynaptic potentials (IPSPs) to the generation of this activity [Andersen & Sears, 1964; Andersen et al., 1967]. These observations have been confirmed and extended by Steriade and his colleagues showing the increased conductance of IPSPs in thalamocortical neurons during sleep spindles further diminishes the probability of faithful synaptic transmission to the cortex through thalamus [Steriade & McCarley, 1990a, 2005; Steriade 1993a; Steriade et al., 1993c; Timofeev et al., 1996]. A negative correlation between regional cerebral blood flow (rCBF) in the medial thalamus and EEG spindle activity during sleep has been reported and interpreted as reflecting the loss of consciousness and sensory awareness during sleep [Hofle et al., 1997]. Consistent with these cortical disconnectionary features of sleep spindles are reports of increased arousal thresholds [Rechtschaffen et al., 1966; Busby et al., 1994], diminished auditory evoked responses [Elton et al., 1997] and reduced motor activity and excitability [Sterman et al., 1981; Pivik & Bylsma, 1982] in association with sleep spindles. These findings have been interpreted as a sleep-promoting or preserving role for sleep spindles, as are reports of a greater spindle density following hypnotics [Johnson et al., 1976; Johnson et al., 1979b; Borbély et al., 1985; Trachsel et al., 1990; Brunner et al., 1991][8] and in conditions of hypersomnia [Bove et al., 1994] or experimentally-induced arousals from sleep [Pivik et al., 1999].

[8] Studies also indicated hypnotics did elevate arousal threshold [Bonnet et al., 1979; Johnson et al., 1979a].

NREM Frontal-Central Alpha (8-12 Hz) Activity

EEG alpha (8-12 Hz) activity, being among the first characterized activity in human brain recordings [Berger, 1929], is universally accepted as an indication of a state of relaxed wakefulness [Brazier, 1968]. Furthermore, decreased amount of alpha is employed in sleep stage scoring systems to indicate sleep onset [Rechtschaffen & Kales, 1968], and alpha activity occurring during sleep is generally presumed to be a sign of arousal, particularly when associated with other signs of physiological arousal such as EEG (e.g. K-complex), autonomic (heart rate acceleration and deceleration) and motor (body movement activity) events [Bonnet et al., 'ASDA report', 1992]. This long-standing interpretation of arousal-associated EEG alpha activities is presumed to have an occipital-central focus [Bonnet et al., 'ASDA report', 1992]. However, there were reports of fatigue or non-restorative sleep in clinical populations exhibiting dramatic amounts of alpha intrusion during sleep ('alpha-delta sleep') without awakening or decreasing their auditory arousal threshold [Hauri & Hawkins, 1973; Moldofsky et al., 1975; Mahowald, et al., 1989; Moldofsky, 1993]. This calls into question whether the interpretation of this EEG alpha activity to be a correlate of arousal. Situation has been more complicated when there was another report of alpha-delta sleep in normal subjects free from clinical disorders or complaints of sleep disturbance and daytime sleepiness [Scheuler et al., 1983]. By re-examining the defining electrophysiological characteristics, topographic distribution as well as state and behavioural correlates, Pivik and Harman [1995] found the alpha activity identified with 'alpha-delta sleep' differs from the arousal-associated occipital-central alpha activity in their oscillatory frequency (1-2 Hz slower than waking alpha), generation site (thalamus), scalp distribution (frontal-central) and behavioural correlates (e.g. enhancement to stimulation during wakefulness, maximal in the first-half of the night during sleep, with a deeper auditory arousal threshold than stage 2 sleep and in the absence of evidence of sleep disturbances). It is proposed the frontal-central alpha activity is associated with sleep-maintaining processes which may be enhanced in response to sleep-disturbing events.

2.3.2.3 Resting Waking EEG Markers of Sleep Homeostatic Regulation

Theta and alpha frequencies in the awake EEG have been found to be very sensitive to the need for sleep and the subjective feelings of sleepiness (which guide human in their decision to go to sleep). During prolonged waking, EEG power in the theta frequencies is increased (maximum in the frontal area), and power in the sigma band

is decreased (most pronounced over the vertex) [Torsvall & Åkerstedt, 1987; Cajochen et al., 1995; Aeschbach et al., 1997b; Finelli et al., 2000]. The time constant of this increase is similar to that of the waking time-dependent increase of low-frequency activity in NREM sleep (which is an electrophysiological sign of sleep intensity and sleep need) [Cajochen et al., 1995; Aeschbach et al., 1997b]. The rise rate of theta activity in the waking EEG is also positively correlated with the rise rate of slow wave activity (SWA, 0.75-4.5 Hz) in the first NREM sleep episode of recovery sleep after sleep deprivation, with both effects being largest in the frontal area [Finelli et al., 2000]. A forced desynchrony study with a scheduled waking episode of 28 hours showed a monotonic rise of delta and beta activity in the fronto-central derivation in the waking episode [Cajochen et al., 2002]. During prolonged wakefulness, subjective sleepiness correlated positively with resting waking EEG activities at below 0.5 Hz, between 3-8 Hz and 23-29 Hz with a focus in frontal-central derivations, and negatively with 8-12 Hz activity at all derivations [Strijkstra et al., 2003]. A gradual reduction of alpha power and a gradual increase in theta power has been found during transition from eyes-closed, resting conditions to sleeping [Tanaka et al, 1997].

In sum, early studies have shown a detailed picture in awake EEG variables related to homeostatic aspects of sleep regulation: alpha power (8-12 Hz, with eyes closed) shows a gradual global decrease with time awake, whereas theta (4-8 Hz, sometimes extended to delta band at 3 Hz) and beta (23-29 Hz) power increases specifically at the frontal-central location. The dynamics and the brain topography of theta activity in waking and slow-wave activity (SWA) in sleep are similar and point to common underlying mechanisms. The reverse relationship between resting (eyes-closed) alpha and theta power may well represent the level of sleepiness during prolonged wakefulness, which show a strong correlation of sleepiness during prolonged wakefulness [Strijkstra et al., 2003]. It may also represent the high motivation to sleep during the natural sleep entry since the relationship mimics the alpha power decrease following theta power increase in the hypnagogic period [Tanaka et al., 1997].

2.3.2.4 Resting Waking EEG Saptiotemporal Dynamics Associated Altered Attention System During Awake-Sleep Transition

When an awake, alert person gradually falls asleep, the decline in alertness and sustained attention is associated with well-established EEG changes. Some EEG changes in the onset process of state 1 sleep relate to the alpha rhythm

anteriorization: (i) the anterior-posterior EEG ratio (A/P ratio) of alpha activity is found to increase as a function of the EEG stages of the hypnagogic state, and the A/P ratio clearly changes at EEG stages when alpha waves at the posterior areas starts to present < 50% of the epoch [Hori et al., 1994]; and (ii) the dominant area of EEG alpha activity have been shown to move from posterior to the anterior area during the waking-S1 transition [Tanaka et al., 1997]. Other signs associated with decreased in vigilance include increased slow-wave activities (more often in the frontal and central regions) as well as brief runs of anterior beta activity and vertex waves. The transition from awake to stage 2 sleep often involves many transitions between awake and stage 1 prior to stage 2 sleep onset, which is clearly defined by the appearance of sleep spindles and/or K complex [Rechtschaffen & Kales, 1968]. Due to the more precise EEG criterion of stage 2 sleep, the onset of stage 2 sleep is often used to define the real sleep-onset. However, it is apparent there is actually a sleep-onset period beginning while awake and extending to at least stage 2 [Ogilvie, 2001]: the amplitude of EEG sigma power starts to increase from frontal pole to the parietal during the onset of hypnagogic state, and this was related to the activity of the 14-Hz sleep spindes [Tanaka et al., 1997].

2.4 AIMS OF CURRENT STUDY

This PhD work used multiple measures, including sleep/resting waking EEG (visual scoring and power spectral analysis) and psychomotor vigilance task (PVT) performance, to access and differentiate effects of three pulse-modulated microwaves ('talk', 'listen' and 'standby' mode signals) emitted from a standard mobile phone. One aim was to understand the non-thermal effects of each mode in the context of sleep/waking regulation or sleepiness. The other aim was to draw a more adequate conjecture of the specific ELF pulse modulation effects. We used a little explored approach and presented data in Chapter 4, 5, 6 and 7.

Chapter 4: Effects on sleep onset

Post-exposure sleep latency study verified by the analysis of the temporal change in the sleep EEG delta (1-4 Hz) power. The aim was to understand changes in the vigilance level prior to sleep.

Chapter 5: Effects on waking EEG

EEG power spectral analysis of the data acquired during resting wakefulness with closed eyes, including two states:

- immediately after exposure (3-min recording with light-on, during which participants were asked to keep awaked);
- waking before the appearance of the first S1 epoch (3-min recording with light-off, during which participants were asked to try to fall asleep as soon as possible).

The aim was to corroborate findings of Chapter 4 with waking EEG.

Chapter 6: Effects on sleep EEG

EEG power spectral analysis of the data acquired during the 90-min sleep opportunity, aiming to find out:

- Sleep structure changes using EEG visual scoring
- Effects on sleep need: Topographic EEG 1-4 Hz power distribution during the 90-min sleep
- EEG power spectral analysis of S2 and SWS EEG (topographic EEG power distribution at 1-Hz bin over 1-16 Hz frequency range), with specific interests in effects on sleep promoting (EEG maker: S2 spindles) and sleep maintaining (EEG marker: SWS spindles) effects.

Chapter 7: Effects on Psychomotor Vigilance Task (PVT) performance

PVT is a visual reaction time (RT) task, which performance requires sustained attention and frequent responses [Dinges et al., 1985]. Under the concepts of state instability [Horne et al., 1985], recent studies have demonstrated the RT variation on the PVT could be used to detect the fluctuations of endogenous alertness and attention, which was enhanced during sleep deprivation but remained at the baseline level in the circadian waking time zone [Doran et al., 2001; Graw et al., 2004]. In this chapter, we aimed to investigate the between-mode difference of the three mobile phone signals on the PVT performance based on the same concept, using the following three RT measures of PVT performance variation:

- Baseline performance (no-lapse-domain RT) with time on task
- Performance reliability (lapses and false responses) with time on task
- Best psychomotor effort ('optimum responses' = fastest 10% RTs) with time on task

3 GENERAL METHODOLOGY

3.1 AIMS

The aim of the research in this thesis is to explore brain physiological effects of ELF pulse-modulated EMFs emitted by a standard mobile phone operating at 'talk', 'listen' and 'standby' modes. We used sleep/waking EEG and psychomotor vigilance task (PVT) to investigate these effects. Both EEG and PVT studies were designed following a within-subject, crossover, single-blind, sham-controlled paradigm and were maintained with a standardization of the experimental sessions within and between subjects. Participants for both studies were all healthy male young adults recruited with payments and with a generic knowledge of the related protocols. The research has been approved by the Ethical Advisory Committee of the university (Appendix A: Ethical Approval) and conducted with participants' informed consents (Appendix B: Subject's Consent Form).

The methodology as described in this chapter provides generic materials and methods employed for the subsequent experimental chapters (Chapters 4-7). For the detailed methods employed for data analysis, please refer to the methodological section of each individual chapter.

3.2 PARTICIPANTS

Twenty-six healthy males (mean age: 22 +/- 2.7 years, range: 18-28 years) participated in the study (10 for the EEG study; 16 for the PVT study, both recruited separately). All took part in this study after qualifying in an structured interview to detect handedness, general health status, sleep habits, sleep-related problems and their user's behaviours of the mobile phone (See Appendix C: Screening Questionnaire). The in- and exclusion criteria are listed below:

Inclusion Criteria

- aged 18-28 y/o,
- right handed,
- healthy (medication-free),
- of normal weight range for height ($18 < BMI < 28$),
- good sleepers (8±1 hour per night),

- sleeping regular hours,
- infrequent daytime naps (less than once a week),
- no complaints of daytime sleepiness (total Epworth Sleepiness Scores < 10),
- no indicated potential sleep disorders,
- regular mobile phone users

Exclusion Criteria

- irregular sleep/waking patterns,
- shiftworker,
- using hand-free handset
- with migraine or epilepsy or claustrophobia

All participants in the our study kept consistent sleep-wake patterns, with a night-time sleep duration in the 7-8 h range, were not extremely owls or larks and were free of sleep disturbance or daytime sleepiness. All were right-handed and talked with their mobile phones by their ears no more than 1 h/day.

Once qualified, they were fully informed of the experimental procedures before giving informed consent. They were instructed to maintain their regular sleep-wake schedule at least for three days prior to the day of experiment with the help of sleep diary (Appendix D: Sleep Diary). On the night before the experiment, sleep was restricted to 6 hours by delaying the normal bedtime but getting up at the usual waking time. All participants adhered to this sleep restriction procedure themselves at home, and compliance would be checked by actiwatch recording (Cambridge Neurotechnology, UK). Alcohol and caffeine-containing beverages were prohibited from 18:00 h at the night before and on the morning of the trial date. The usage of mobile phones on the trial date was forbidden. All these protocols were approved by the ethics committee of the Loughborough University. The participants were paid for their time and efforts and could withdraw the experiment at any time without giving any reason for this.

3.3 DATA ACQUISITION

3.3.1 Equipments for Sleep/Waking EEG

The polysomnography (PSG) tracings including electroencephalogram (EEG), electromyogram (EMG) and the electrooculogram (EOG) were recorded to determine

stages of sleep and wakefulness by standard criteria [Rechtschaffen & Kales, 1968]. The Embla 7000 system (Embla TM – Flaga hf. Medical Devices, Iceland) and the associated software Somnologica (Version 2.2, Flaga hf. Medical Devices) were used for PSG acquisition and analysis. A Communication Unit was used to communicate between the Embla and the data acquisition computer installed with Somnologica using a Local Area Network (LAN). The Communication Unit also works as an isolation unit to prevent a direct electrical connection between the patient and other external-connected devices. All these equipments, along with the base-station simulator, an intercom system (enabling bi-communication between the participant and the experimenter) and a personal computer (worked as an oral instruction generator and transmitter) were put in the control room (Figure 3. 1).

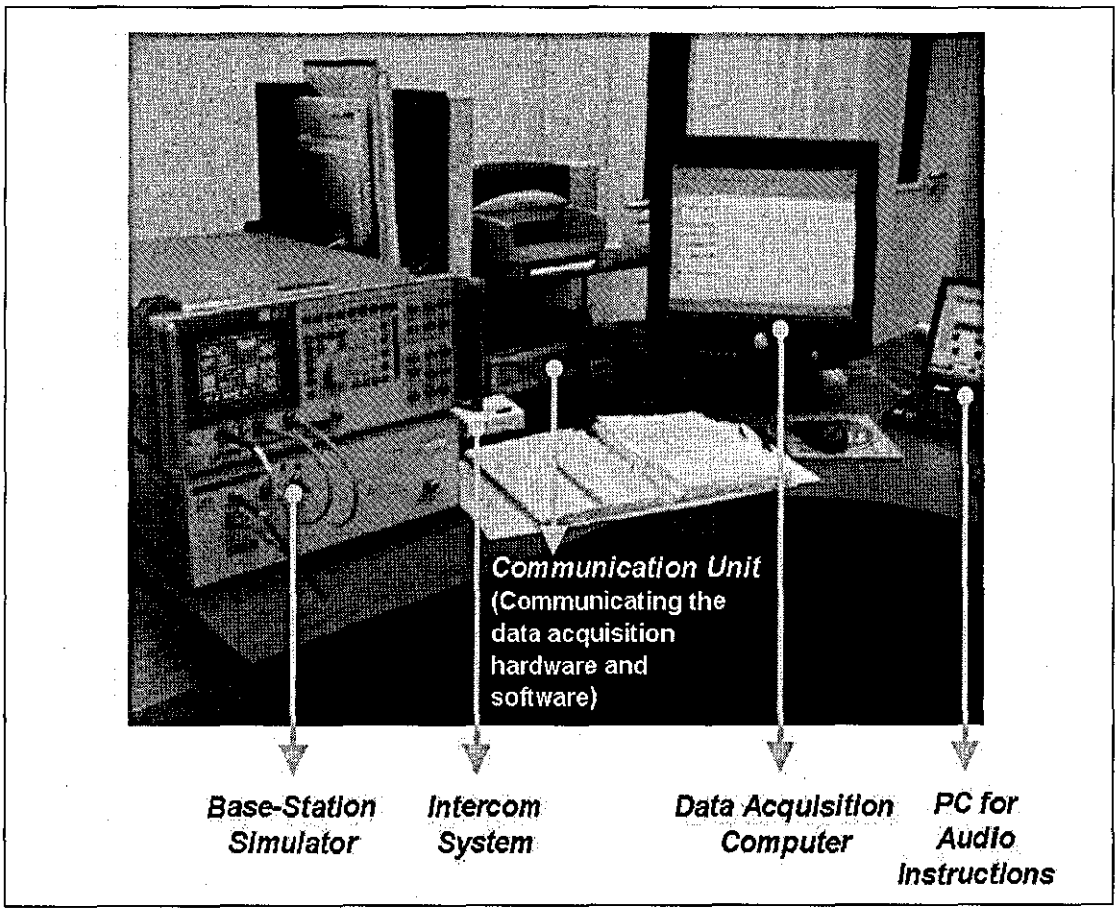

Figure 3. 1 Equipments in the control room.

3.3.2 Polysomnography (PSG)

EEG, EOG and EMG signals were collected using silver chloride cup electrodes. Scalp EEG electrodes used 10-20 as the conductor and secured with collodion glue. Facial electrodes used double-sided adhesive tabs and a conductance gel (SLE). The electrode impedance of EEG, EOG and EMG were maintained at below 5, 10 and 5 kΩ, respectively.

All EEG, EOG and EMG signals were continuously recorded using Embla 7000 system and Somnologica 2.2. The online digitized sampling rate of EEGs and EMGs were set at 100 and 200 Hz, respectively. EEGs were low-pass filtered at 20 Hz and high-pass filtered at 0.3 Hz.

3.3.2.1 EEG Electrode Position

The EEGs were recorded with 11 electrodes (F3, F4, C3, C4, P3, P4, O1, O2, A1, A2, Fpz), which were placed on the participant's head according to the international 10-20 electrode position classification system. Electrode Fpz was used as a general ground channel for all electrodes. The A1 and A2 electrodes were scalp referents placed on the left and right mastoid respectively.

Bipolar EEG Montage

Six bipolar derivations, covering the whole head, were used for EEG recording (see Figure 3. 2): F3-C3 (LF, left frontal), C3-P3 (LC, left central), P3-O1 (LP, left parietal), F4-C4 (RF, right frontal), C4-P4 (RC, right central), P4-O2 (RP, right parietal). The six derivations were later subjected to power spectral analysis in order to investigate how EMF changes the energies of specific EEG rhythm frequencies at individual derivation.

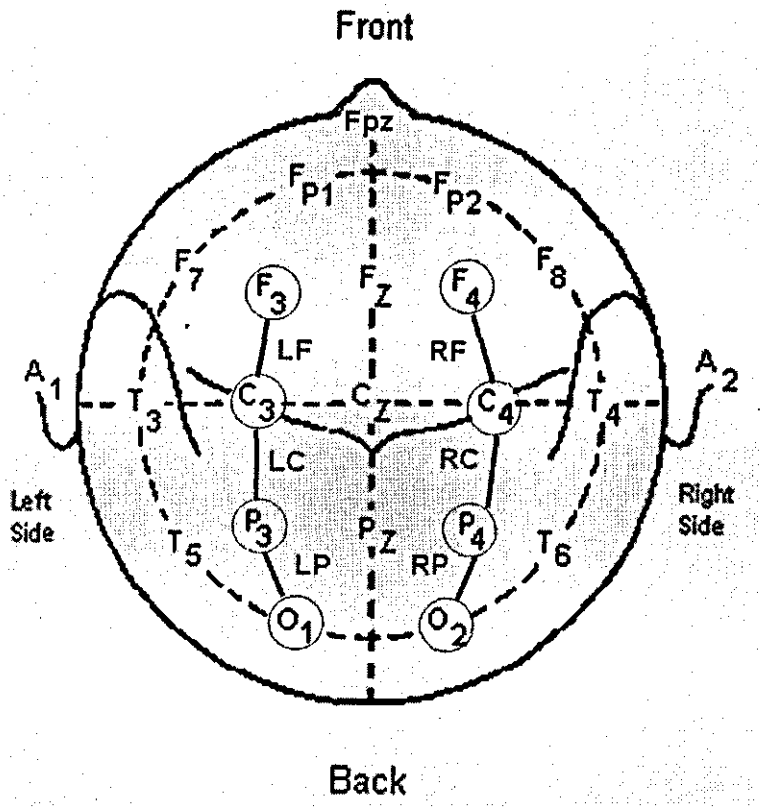

Figure 3. 2 EEG montage for bipolar recordings.

Specific EEG Montage for Sleep Stage Scoring

Two unipolar EEG channel (C3-A2 and C4-A1), bipolar chin EMG (recording muscle activity from mental and submental areas) and EOG (recording eye movements by putting one electrode at 1 cm above the right canthus and the other electrode at 1 cm below the left outer canthus) were used for scoring of sleep stages during the 90-min light-off session after EMF exposure in each trial. Sleep stages were visually scored for 30 s epochs based on the recommendation of standard criteria [Rechtschaffen & Kales, 1968]. Visually scored data on sleep onset time had good inter-scorer reliability (correlations > .80) using an experienced independent blinded scorer (CA).

3.3.2.2 RF Interference

The possibility of contamination of EEG signals with pick-up from mobile phone emission was investigated in a pilot study. Continuous standard sine waves (wave duration: 250 ms, amplitude: 25 μV) generating by a calibration system (Oxford, Calibrator XL-90-B) were used as simulated EEG/EMG/EOG signals which passed through the electrodes. The mobile phone antenna was placed against the EEG electrode during mobile phone active-mode (talk, listen and standby modes)

transmission and the change in the sine wave's shape and amplitude was observed. Results showed no change of the sine wave shapes during or after exposing to the three modes. Thereby there should be no RF interfering effects with the EEG leads.

3.3.3 Subjective Sleepiness

The Karolinska Sleepiness Scale (KSS, Figure 3.3) was used in this study as a sleepiness/vigilance evaluation from participants themselves. Åkerstedt & Gillberg [1990] suggested it could be used as a supplementary measurement of sleepiness (or vigilance) – EEG signifies sleepiness when the KSS rating reached 7 or above.

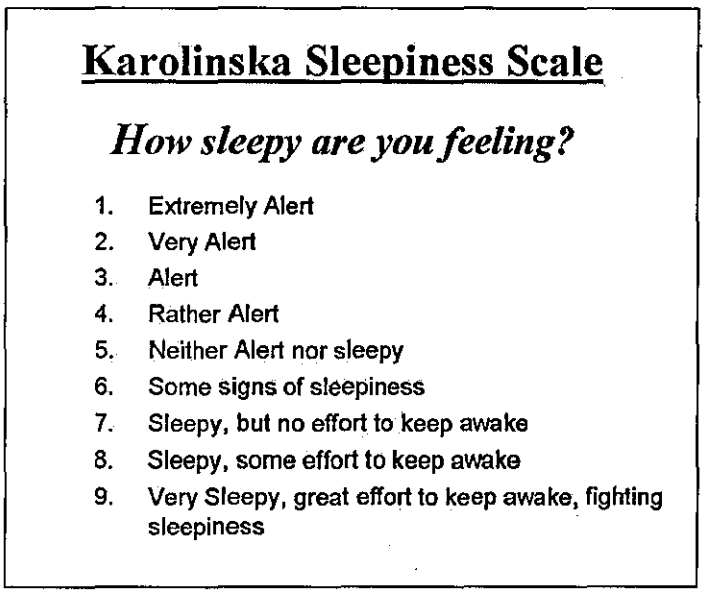

Figure 3. 3 The Karolinska Sleepiness Scale [Åkerstedt & Gillberg, 1990].

3.4 EXPERIMENTAL DESIGN

The study used a within-subject, repeated-measurement and sham-controlled design to test the EEG and PVT effects of mobile phone talk-, listen- and standby-mode exposure. Each exposure was conducted in a random-scheduled, single-blind order and was separated one week apart in order to ensure that any potential carry-over effect was minimized.

The experimental procedure for each trial is depicted in Figure 3. 4. At the night before each experiment, the participants' night-time sleep was restricted to a total of six hours (with their bedtime six hours before the normal getting-up time). On the trial day, they came to the lab before 12.30-13.00 hr for EEG preparation and the experiment time started in the early afternoon at between 13.30-14:00 hr.

For the trial, the participant lay in a sound-proof bedroom, remained silent waking, and stared at a wall marker during the exposure and the resting waking EEG recording sessions. Bipolar EEGs were recorded continuously, and subjective ratings of sleepiness (KSS) was obtained every 3 min during the EMF exposure and the resting waking (3-min eye open and 3-min eye closed) sessions before and after the exposure (Figure 3. 4). During the EMF exposure, a thermally insulated GSM 900 MHz handset was positioned at the participant's right ear (with the longitudinal axis of the phone being aligned with the ear-mouth line) using a phone cradle (Figure 3. 5). For the 90-min nap after EMF exposure, the phone was removed, the base-station switched off, the bedroom darkened, and a 90-min sleep opportunity followed with an instruction 'to fall asleep as soon as possible.'

The experimental procedure for the PVT study is identical with the waking/sleep EEG study. The only difference is no actual EEG data was collected during the resting waking and EMF exposure sessions, and after the exposure, the participant was subjected to a 30-min PVT testing in a light-off room.

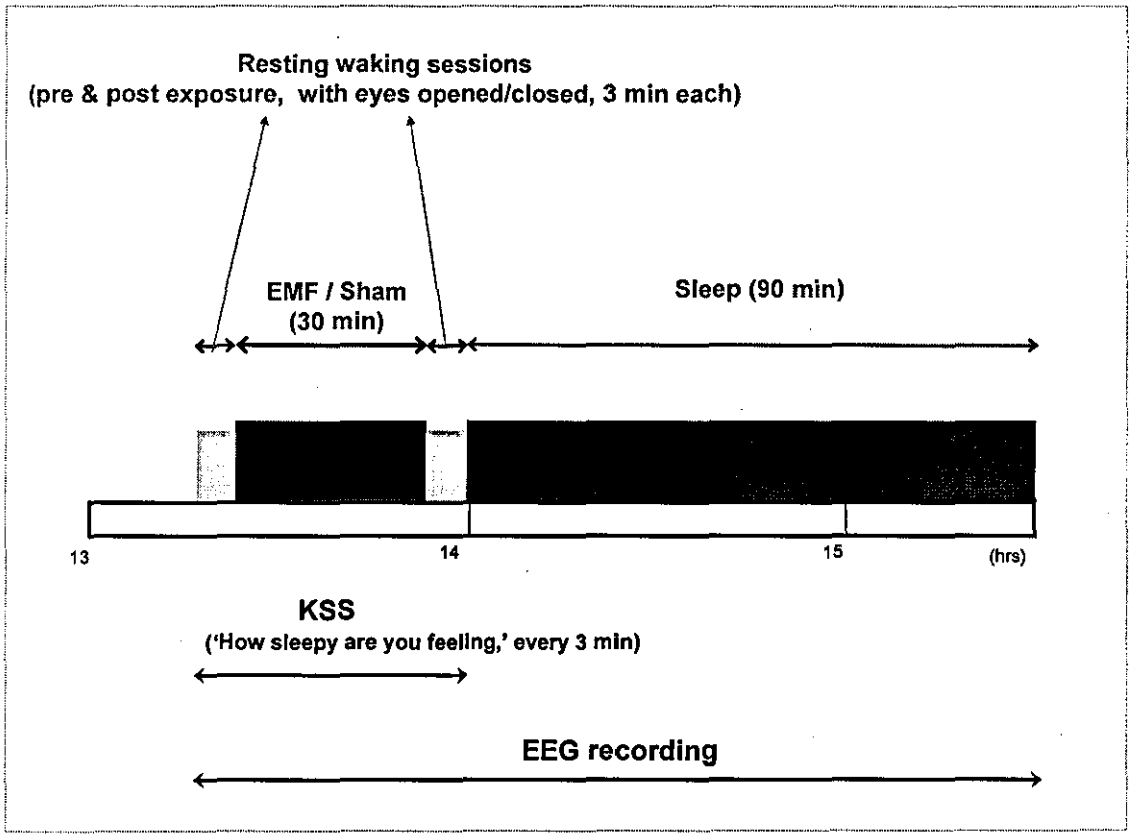

Figure 3. 4 Experimental procedure. See text for details.

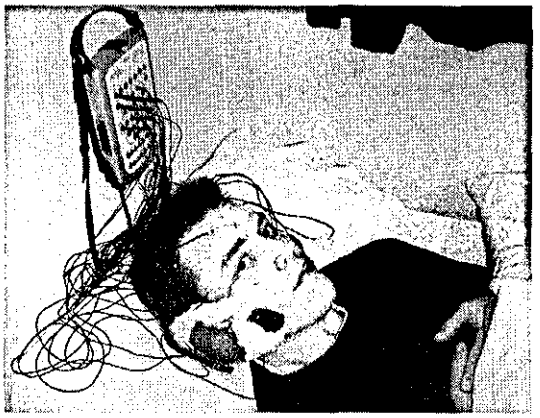

Figure 3. 5 Subject conditions during the EMF exposure: six bipolar EEG, EOG and EMG were recorded continuously during the trial and the mobile phone was put at the participant's right ear with a phone cradle. The phone was covered with cotton to insulate from possible heat.

3.5 GENERATION OF MOBILE PHONE TALK, LISTEN AND STANDBY MODES

The talk- and listen-mode of mobile phone signals were both generated by the GSM 902.4 MHz handset (Nokia 6210e) but controlled via the laboratory base-station simulator (HP 8922M GSM/DCS Mobile Station Test Set). Both signals were activated by turning the discontinuous transmission (DTX) function within the handset 'off' (talk mode) or 'on' (listen mode). Configuring the DTX function to be 'off' or 'on' was set remotely through the base-station simulator.

When the DTX function was off, the mobile phone would transmit continuously (with the signal pulsing at 8 and 217 Hz) irrelevant of any voice signal input. When DTX function was on, the mobile phone would not transmit all the time unless there was a voice signal input; or if there was not any voice input, the mobile phone would transmit 3 frame blank and the 4th with background noise in every 120 ms. The current study employed the base-station simulator to take control of the mobile phone's DTX function so that the talk- and listen-mode exposure in real conversation could be simulated without actual voice inputs from the participant. Furthermore, to avoid any voice signals that might contaminate the field spectra of the listen-EMF signal, the handset was modified with its microphone disabled. The speaker of the handset was also disabled to eliminate the just-perceptible 'buzz' emanating from circuit components during the EMF transmission.

The standby-EMF signals were allowed to originate from the same GSM handset but without control from the base-station simulator. Unlike talk- and listen-EMFs, the standby-EMF signal was generated by switching on the power of the mobile phone to register it to the base-station simulator without an active call. In this mode of operation, the mobile phone would emit EMF signals of very low data rate and very infrequent compared to an active call (talk-mode). In the real world, it simply allows the mobile phone service provider to direct a phone call (or accept one from the user's mobile phone) via the closest (best quality-connected) base station.

The distance between the handset and the base-station simulator in the present EMF exposure setups was 1.5 m. This distance could ensure reliable bi-directional radiocommunication between the base-station stimulator and the phone handset to be maintained for 30 minutes with the requested constant handset power output. In a pre-study to the formal experiment, we found that, at this distance and when the DTX function was switched off (talk mode), the handset with its battery full charged could allow radiocommunication uninterrupted for 2.5 hours before the battery level declined to 80% charged. When the energy-saving DTX function was on (listen mode), the radiocommnunication could be maintained longer before the phone's battery dropped to the same level.

For the purpose of the current experiment, a fully-charged handset was always used so that the phone could remain consistent power emission over the critical half-hour period of active exposure. If there was any signal disconnection, the trial would be aborted and rescheduled. In the current experiment, there were three talk-EMF trials aborted due to this reason. Since on these occasions, the EMF signal dropped connection when the battery was full charged, the interruption is likely to have resulted from breaching of very sensitive radio range thresholds designed for tight control of the handset performance by the base-station simulator. Because signals to and from the mobile phone were more intense during the talk-EMF exposure session than during the listen- or standby-EMF session, it might enhance the susceptibility of the talk-EMFs to external radio interferences.

3.6 DOSIMETRY

Specific Absorption Rate (SAR) measurement of EMF was conducted inside a Specific Anthromorphic Mannequin (SAM) phantom using a precision robot RF dosimetric Assessment System (DASY4). Without the EEG recording apparatus in

place, the SARs of talk = 0.133 mW/g, listen = 0.015 mW/g, and standby < 0.001 mW/g (10 g of tissue average) was measured in line with the phone's antenna approximately over the 'temporal lobe.' These SAR values are significantly below the International Commission on Non-Ionizing Radiation Protection (ICNIRP) restriction limit (2 W/kg) [9]. Although a detailed dosimetry assessment (i.e. dosimetric measurement uncertainty, variations due to head movement, differences in anatomy, etc. cf. Huber et al. [2003]) is not available, the resultant brain temperature rise, when calculated at the SAR of the current-use mobile phone (as mentioned above) and taking into account of the current setup and the exposure time, should be able to fulfil the requirements of EMF exposure in human studies in the context of health risk assessment of mobile phones [Kuster et al., 2004].

3.7 VARIABLES OF VISUAL SLEEP STAGE SCORING

Sleep stages (resting waking, S1, S2, S3, S4, REMS: rapid-eye-movement sleep, MT: body movement) were visually scored for 30-s epochs according to standard criteria [Rechtschaffen & Kales, 1968]. The definition of these sleep variables are explained by Figure 3. 6 and Table 3. 1.

[9] At this ICNIRP general public basic exposure limit for the uncontrolled environment, the maximum temperature rise in the brain is 0.11 degree Celsius (ICNIRP, 1998) and for the worst-case exposure scenario, a maximum temperature rise in the brain is 0.25 degree Celsius as predicted by Hirata and Shiozawa (2003).

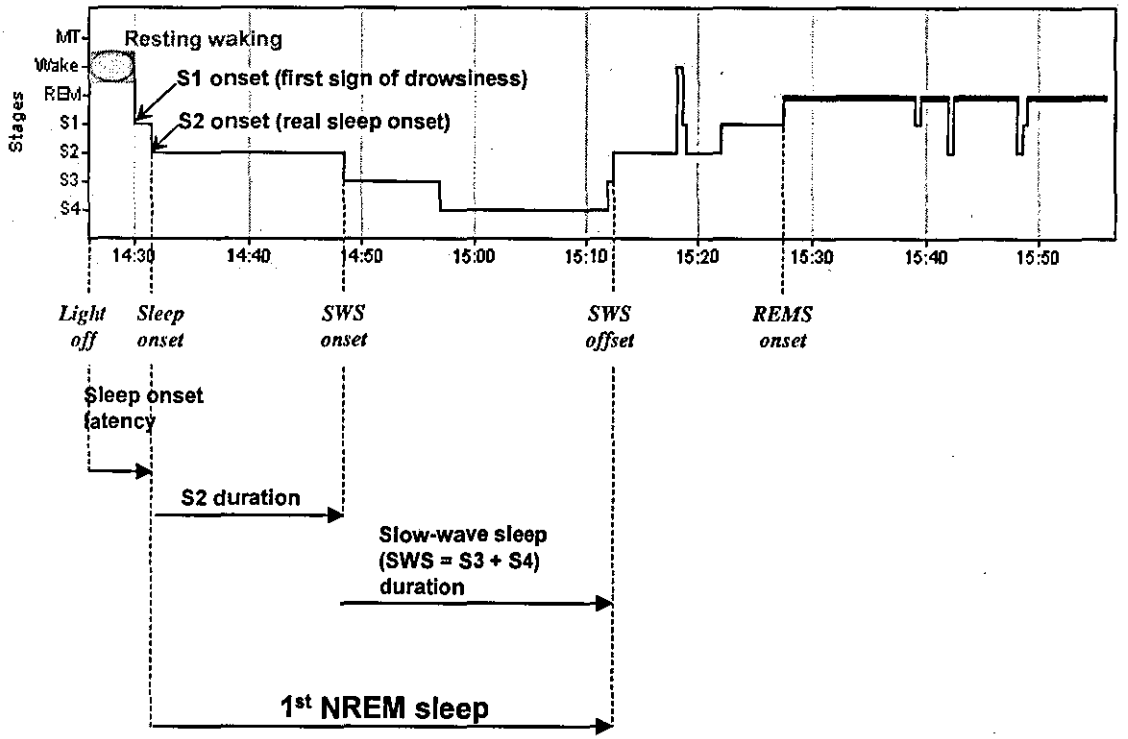

Figure 3. 6 Sleep structure during a 90-min nap (an example after sham-mode exposure). See Table 3.1 for a description on how the sleep variables are defined.

Table 3. 1 Definition of sleep variables

Sleep Variables	Description
Total time in bed (minutes)	Light-off period (90 minutes) after EMF exposure.
Total sleep time(minutes)	Time spent asleep after the onset of sleep, minus time spent in wakefulness and body movement during this period.
Sleep efficiency (%)	Total sleep time as a percentage of total time in bed.
Resting waking	Waking period after light off and before the first epoch of S1
Sleep onset	First occurrence of consecutive S2, lasting for at least 3 minutes.
SWS	Consecutive epochs of S3 + S4 (beginning at the first consecutive epoch of S3; lasting for at least 4 minutes uninterrupted).
Sleep-onset latency	Interval from light off to sleep onset
SWS-onset latency (S2 duration)	Interval from the first epoch of consecutive S2 to the first epoch of consecutive SWS (a period spent in continuous S2 before going into SWS).
SWS duration (minutes)	Time spent in consecutive epochs of S3 + S4.
REMS latency (minutes)	Interval from the end of 1st cycle of SWS to the epoch before occurrence of consecutive REMS.
1st NREM sleep (minutes)	Time spent asleep from sleep onset to the end of 1st cycle of SWS.

S1: stage 1 sleep; S2: stage 2 sleep; S3: stage 3 sleep; S4: stage 4 sleep; SWS: slow-wave sleep; REMS: rapid-eye-movement sleep; NREM sleep: non-rapid-eye-movement sleep.

3.8 EEG SPECTRAL ANALYSIS

Spectral analysis seeks to describe the frequency content of a signal based on a finite set of data. The power density spectrum or power spectrum displays the distribution of power over the frequency components of a signal.

For the present EEG study, the sleep/waking EEG recordings from the six bipolar derivations during the 3-min, eye-close resting waking sessions (pre- and post-EMF exposure) and the post-exposure 90-min nap session in each trial were subject to an off-line spectral analysis with a Fast Fourier Transform (FFT, epoch length: 5 s for sleep and 2 s for waking EEG recordings, FFT sampling rate: 128 Hz, the FFT epoch was overlapped by 50% to retain as much data as possible). Power spectra of consecutive 30-second epochs (averages of six 5-s epochs or fifteen 2-s epochs) were computed for each EEG derivation in 1-Hz bins across 1-16 Hz frequency bands to assess any changes in power spectrum due to conditions.

4 EFFECTS OF SLEEP ONSET

4.1 INTRODUCTION

4.1.1 Fundamentals of Pulse Modulation of Mobile Phone Signals

Mobile phone signals operating at 900 MHz of the Global System for Mobile Communications (GSM 900 MHz) are low-frequency pulse- modulated fields. These are associated with Time Division Multiple Access (TDMA) and/or the Discontinuous Transmission (DTX) technologies implemented during 'talk-mode' and 'listen-mode' transmission. The TDMA technology allows 8 mobile phones to communicate with a base-station in 4.6 ms (during which each phone holds the channel for 577 µs), resulting in a basic repetition frequency of 217 Hz with every 26 pulses being grouped together causing another low-frequency pulsing at around 8 Hz (by definition, the 13th pulse transmits information about the radio-link and the 26th pulse is idle, Figure 4. 1, GSM Basic Signal). The latter, unlike the 217 Hz pulsing, is unaffected by the call density and is a permanent feature of GSM signals. In GSM phones utilizing DTX technology (for battery power saving), there is an additional 2 Hz pulsing during listen-mode (Figure 4. 1, GSM DTX-On Signal). If the phone is only switched-on for registration with the base-station, without an active call ('standby-mode'), the carrier frequency pulses less periodically, at < 2 Hz. In addition, these pulse modulations affect a phone's power output, causing the three modes to differ in the amount of radiation absorbed by adjacent tissue (specific absorption rates – SARs, talk > listen > standby ≈ 0 mW/g, all averaged to 10 g of tissues). In sum, the 'talk', 'listen' and 'standby' modes of GSM 900 MHz differ in their low-frequency spectral composition and SAR rates [cf. Hyland (2000) & IEGMP (2000) for detailed technical review]. These factors must be taken into account when comparing experimental results obtained from simulated signals in the laboratory.

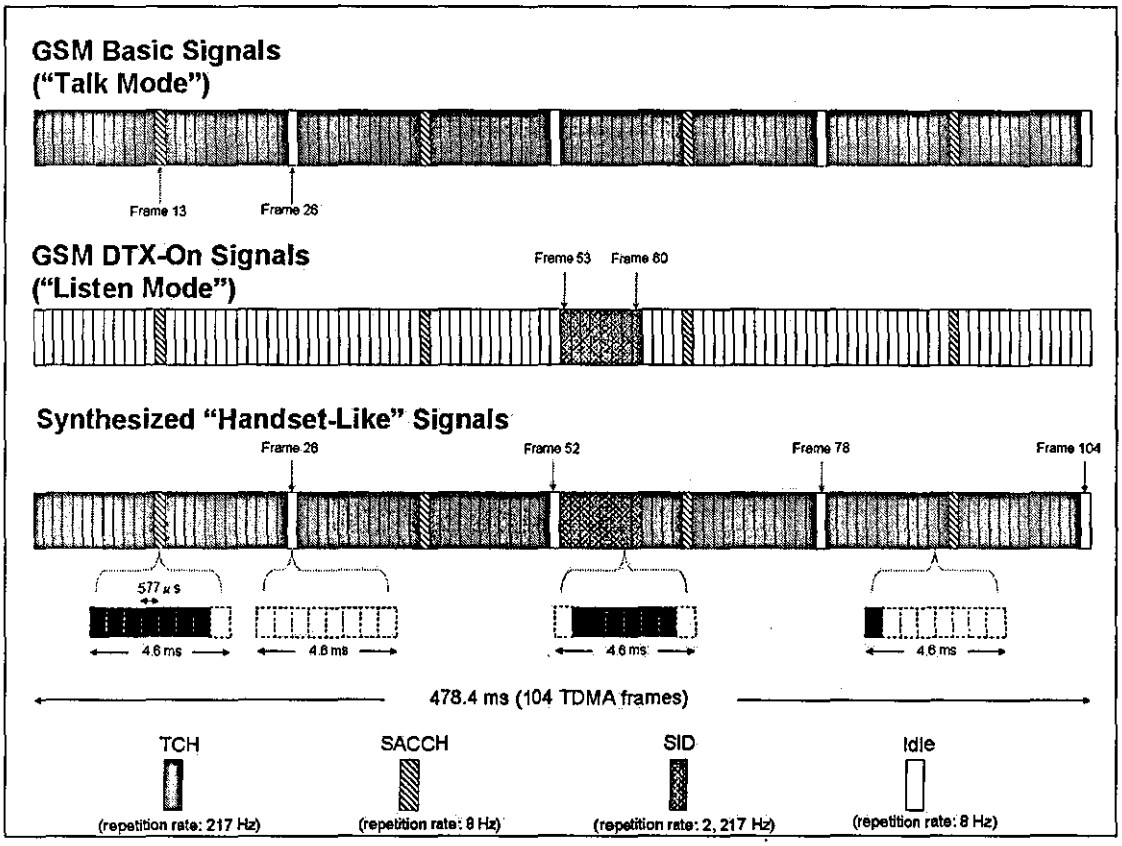

Figure 4. 1 GSM pulse structures of 'Talk Mode', 'Listen Mode' and 'Synthesized Handset-Like Signals' [Huber et al., 2005; Ebert et al., 2006]. The pulse structure of the 'handset-like' signals combines the frame structure of the 'basic GSM mode' ('talk mode') and the 'DTX mode' ('listen mode').

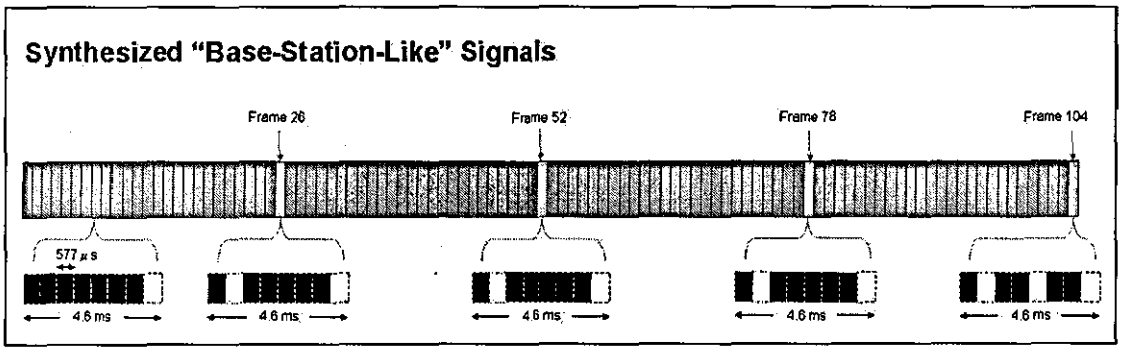

Figure 4. 2 Synthesized GSM base-station-like signals. The base-station-like signal approximates the modulation characteristics from a GSM base station in communication with 8 mobile phones (proposed by Schüller et al. [2000]). Seven (slot 0-6) of the eight bursts of the TDMA frame were on with the 7th slot off. Frame 26, 52, 78, and 104 of a super frame (104 TDMA frames) were modified: in addition to the 7th slot, the 1st slot was also idle for frames 26, 52, 78; but for frame 104, the 1st, 4th and 7th slot were idle. This signal structure results in the spectral components of 2, 8, 217 Hz and the corresponding harmonics. However, the ratio between pulse peak power and the time-averaged power (crest factor) of the base-station-like signal (= 1.2) was one-forth of that of the handset-like signal (= 4.8).

4.1.2 Previous Research on the Mobile Phone Signals

With respect to brain function reflected in the electroencephalogram (EEG), and especially in relation to sleep or rest, there is accumulating evidence that low-frequency pulse modulation of the radiofrequency carrier has some influences. However, it is not known whether the different low-frequency composition of talk and listen modes will result in different sleep effects. This is because most studies appearing to look at GSM 'talk-mode' signals (900 MHz with 217 Hz modulation) have not considered the permanent low-frequency modulation at 8 Hz [e.g. Mann et al., 1996; Wagner et al., 2000; Wagner et al., 1998; Croft et al., 2002; Curcio et al., 2005; D'Costa et al., 2003; Loughran et al., 2005]. Furthermore, those studies that did include this 8 Hz component (i.e. 'handset-like' signals[10]. in Huber et al. [2002]; Huber et al. [2003]) are not purely looking at either talk or listen mode, but a synthesis of both modes (Figure 4. 1). Table 4. 1 summarized the low-frequency pulse modulation components in the GSM signals that have been studied so far.

Table 4. 1 Summary of the low-frequency pulsing components of the GSM signals used by other relevant EEG studies, in comparison with our study. See text for details.

Our study	Low-frequency pulsing components	Other studies
Talk	8, 217 Hz	
Listen (100% silence)	2, 8, 217 Hz	
Talk + Listen	2, 8, 217 Hz (stronger 217-Hz spectral power than our Listen mode)	Huber et al. [2002, handset-like]; Huber et al. [2003, handset-like]
Standby	1-32 Hz	D'Costa et al. [2003]
Not applicable	Only 217 Hz	Mann et al. [1996][11]; Wagner et al. [1998][12]; Wagner et al. [2000]; Croft et al. [2002]; D'costa et al. [2003]; Curcio et al. [2005]; Loughran et al. [2005]

[10] Here we mainly discussed effects of the 'handset-like' GSM signals but NOT of the 'base-station-like' GSM signals [c.f. Borbély et al., 1999; Huber et al., 2000 and Huber et al., 2003] although both signals share the same carrier and pulse modulation frequencies. This is because the low-frequency spectral power of 'base-station-like' signals is by 4 times less than the 'handset-like' signals (Figure 4. 2) and not the usual signals emitted by the mobile phone.
[11] Repeating study of Mann et al. [1996], with more participants.
[12] Repeating study of Mann et al. [1996], with greater power flux density from 0.5 W/m^2 to 50 W/m^2.

4.1.3 Supporting Evidence for Pulse Modulation Effects

Evidence pointing to low-frequency pulse modulation inducing neurophysiological changes, has been shown, for example, in recent brain imaging and EEG studies by Huber et al. [2002, 2005] and Regel et al. [2007a]. They found it was the pulse-modulated 900 MHz microwaves, rather than the continuously emitted 900 MHz itself, that subsequently increased waking alpha (11-11.25 Hz [Huber et al., 2002]; 10.5-11 Hz [Regel et al., 2007a]) and sleep spindle (12.25-13.5 Hz [Huber et al., 2002]) EEG activities. The post-exposure waking regional cerebral blood flow (rCBF) imaging showed the dorsolateral prefrontal cortex to have been particularly affected by this pulse modulation, which led the authors to speculate that this region was a focus for the pulse modulation [Huber et al., 2002]. Their later investigation [Huber et al., 2005], which used rCBF imaging to replicate their previous findings, further revealed "the stronger the ELF spectral power, the more pronounced the waking rCBF effects." This adds considerable support to the notion that any biological effects of mobile phone exposure are likely related to the low-frequency components of the mobile phone signals.

4.1.4 Current Research Aims

Given that there may be different effects of low-frequency components on sleep, no sleep study has differentiated talk, listen and standby modes systematically, nor done so in relation to the potential effects on the EEG during the process of falling asleep or the propensity to fall asleep. This unexplored area formed the basis of our study.

4.2 MATERIALS AND METHODS

4.2.1 Exposure Characteristics

Talk, listen and standby modes were generated by a GSM900 Nokia 6210e mobile phone, controlled with a test SIM card and a GSM900 base-station simulator (HP8922M) located 1.5 m away in another room. The transmission power was at about only 12.5 % (23 dBm) of maximum power. SARs for talk mode = 0.133 W/kg, listen mode = 0.015 W/kg, and standby < 0.001 W/kg (all averaged to 10 g of tissue). The ELF pulse modulation for these modes is shown in Table 4. 1.

4.2.2 Subjects

Ten paid participants (healthy, un-medicated, normal-sleeping, right-handed men, mean age: 22 ± 2.7 y, range: 18-28 y) were screened and recruited via an advertisement on the campus, having given their written informed consents. They were regular mobile phone users but with an average talk-time of less than 1 h/day. They maintained their regular sleep-wake schedule for at least three days prior to each trial (monitored by wrist-worn actimeters and personal sleep diaries). Alcohol and caffeine-containing beverages were prohibited from 18:00 hr at the night before and on the morning of each trial. Their mobile phone use ceased after 22:00 h the evening before trials. Their prior night's sleep was restricted to 6 h (by a delayed bedtime as verified by actimeters).

4.2.3 Procedure

A fixed afternoon routine for experimentation began with the participant lying on a comfortable bed, in an individual sound-proof and lit bedroom. The experimental phone was harnessed beside the right ear, and any possible heat from the battery or any seemingly inaudible 'hum' were insulated from the ear by a 2 cm thick cotton-wool wadding. At precisely weekly intervals, participants were exposed ('blind' and 'randomly') to one of: talk, listen, standby and sham (nil signal) modes, for 30 min, commencing at 13:30 h, with the exposure orders counterbalanced between participants. Throughout all exposures the phone generated no sounds (the phone's speaker was disabled). Participants remained silent, and fixed their eyes on a wall marker. Subjective ratings of sleepiness were assessed using the Karolinska Sleepiness Scale (KSS [Åkerstedt et al., 1990]) every 3 min (before, after and during the exposure). After the exposure, the phone and base-station were switched off, the phone removed, the bedroom darkened, and a 90 min sleep opportunity followed with participants being instructed to close their eyes and try to fall asleep as soon as possible

4.2.4 EEG Recordings

Six bipolar EEGs (F3-C3; F4-C4; C3-P3; C4-P4; P3-O1; P4-O2) were sampled at 100 Hz using Embla 7000 system (EmblaTM-Flaga hf. Medical Devices). Prior to sampling, EEGs were band-pass filtered at 0.3-20 Hz, with the electrode impedance being always kept < 5 kOhm. EOGs and EMGs were also obtained according to the established method [Rechtschaffen & Kales, 1968].

4.3 DATA ANALYSIS

4.3.1 Subjective Sleepiness

The KSS was used to collect the participant's self-evaluation of sleepiness/vigilance every 3 min before, during and after exposure. The KSS values reported during exposure were standardized by the mean KSS values reported before exposure within each condition.

4.3.2 Sleep Onset

Left central EEG (derivative: C3-A2), chin EMG, and horizontal and vertical EOG were used for visual sleep scoring. With regard to determining the period of falling asleep (the aim of this chapter), two methods were used:

i) Visually scored latency to sleep onset from 'lights out' - with sleep-onset defined as, 'the first appearance of a consecutive period of stage 2 sleep, lasting for at least 3 min' [Rechtschaffen & Kales, 1968]. This was determined by two independent scorers (one of the scorers was an experienced independent blinded rater; inter-rater reliability on sleep latency: correlation > 0.80).

ii) EEG power spectral analysis (Fast Fourier Transform: epoch length: 5 s; sampling rate: 128 Hz; Hanning window; frequency resolution: 0.2 Hz across the a frequency range of 1-16 Hz). The EEG power of adjacent frequency bins were added up to form the following broad-band bins: 1-4, 5-7, 8-10, 10-12 and 10-12 Hz. The original 90-min data of each broad-band bin in 5-s epochs were deducted by averaging across six 5-s epochs.

4.3.3 Statistics

Sleep latency data was submitted to one-way repeated measure ANOVAs to compare the 'condition' effect (4 levels: talk, listen, standby and sham). For any significant result, Student-Newman-Keuls (SNK) range test was conducted for post hoc comparisons. A two-way repeated measures ANOVA (rANOVA, conditions x time) was used to examine the temporal changes of 'KSS' and 'EEG 1-4, 5-7, 8-10, 10-12 and 12-14 Hz spectral power' of different conditions. When ANOVA results showed significant interaction effect, post hoc comparisons using SPSS Helmert tests was conducted.

4.4 RESULTS

4.4.1 Subjective Sleepiness

Before all exposures, mean subjective sleepiness [Åkerstedt et al., 1990] was similar for all conditions (at around score 5 –'neither alert nor sleepy'), which rose over the 30 min exposure in a similar manner for all conditions, reaching values between levels 7 ('sleepy') or 8 ('sleepy, some effort to stay awake') (see Figure 4. 3). A two-way rANOVA (conditions [4 levels: talk, listen, standby, sham] x time [10 levels: 10*3-min intervals]; dependent variable: ten KSS values collected 'during' each exposure, being transformed into percentage values with respect to the mean KSS value obtained before exposure) showed neither a main effect of condition ($F_{[3,30]} = 0.6$, $P = 0.62$), nor an interaction effect of condition x time ($F_{[27,270]} = 0.8$, $P = 0.72$), but a significant effect on time ($F_{[9,90]} = 9.4$, $P < 0.0001$). This result validates the visual observation that the time course build-up of subjective sleepiness did not differ between the varying mobile phone signals.

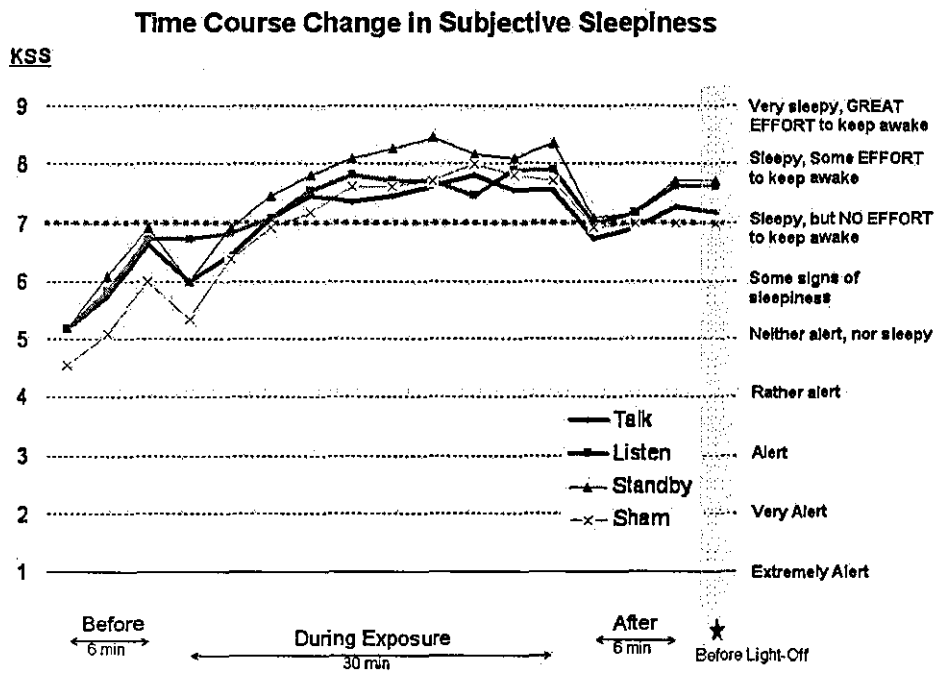

Figure 4. 3 Time course changes of subjective sleepiness scored by KSS before, during and after exposure.

4.4.2 Sleep Onset Latency

Although the subjective sleepiness did not differentiate varying mobile phone signals, however, post-exposure, the visually scored sleep latencies (talk-mode: 48.8 ± 7.9

min, listen-mode: 22.1 ± 6.1 min, standby mode: 32.9 ± 8.5 min, sham mode: 23.8 ± 4.6 min) revealed a significant condition effect ($F_{[3,27]} = 3.4$, $P = 0.03$, one-way ANOVA for repeated measures). SNK ranges tests showed that sleep latency following talk-mode exposure was significantly delayed comparing with listen and sham modes (Figure 4. 5, upper panel).

The sleep-onset delay after talk-mode exposure may result from an increased restlessness during the sleep-onset process, where the time spent in waking, stage 1 sleep and stage transition was more often longer in talk-mode condition than in the other conditions (see Table 4. 2), though the differences between conditions did not reach statistically significant level (one-way ANOVA, factor: conditions, $P > 0.05$ for all dependent variables, see results in Table 4. 2).

Table 4. 2 Variables deferring sleep onset.

Variables	Talk	Listen	Standby	Sham	$F_{3,27}$	P value
Time spent in waking	27.2 ± 9.2	11.0 ± 3.5	17.1 ± 6.9	11.2 ± 3.2	2.6	0.076
Time spent in stage 1 sleep	15.7 ± 3.9	8.0 ± 2.2	9.6 ± 2.2	8.3 ± 1.5	1.8	0.169
Time spent in stage 2 sleep	5.9 ± 1.7	3.2 ± 1.5	6.2 ± 2.9	3.9 ± 2.1	0.7	0.567
Time spent in stage transition	6.4 ± 1.5	3.1 ± 0.8	5.2 ± 1.3	3.4 ± 0.8	1.8	0.160

Mean ± s.e.m. in min are shown for talk, listen, standby and sham modes. $F_{[3,27]}$ and P values of one-way ANOVA examined if there is any difference between four modes. Sleep onset was defined as 'the first appearance of a consecutive period of stage 2 sleep, lasting for at least 3 min.'

4.4.3 Temporal Changes of EEG 1-4, 5-7, 8-10, 10-12, 12-14 Hz Power after Exposure

The temporal changes in the EEG delta (1-4 Hz), theta (5-7 Hz), alpha (8-10 and 10-12 Hz) and sigma (12-14 Hz) power of the talk-, listen-, standby- and sham-mode condition occurred at EEG derivation, F3-C3, are demonstrated in Figure 4.4[13]. Significance of between-condition difference in the temporal changes of the spectral power in these frequency bands occurred at the six EEG channels are listed in Table 4.3 ($F_{[24,216]}$ and P values of the 'time x condition' effect yielded by 30 tests with two-way rANOVAs, significance were considered when P values < 0.001). The between-

[13] Although statistical analysis were always performed for the six EEG derivations, no significant differences were found between conditions in the temporal changes of EEG 1-4, 5-7, 8-10, 10-12 Hz power in most of the EEG derivations except F3-C3 (where EEG 1-4 Hz power showed a significant between-condition difference, see Table 4.3). Hence, figure 4.4 only show data of F3-C3.

condition difference was most evident with the changes in 1-4 Hz EEG frontal power, especially from the left frontal channel (Figure 4.4 and the lower panel of Figure 4.5), where a two-way [conditions x time (10-min intervals; 9 levels)] ANOVA for repeated measures showed a significant interaction effect ($F_{[24,216]} = 2.43$, $P = 0.0004$, see Table 4.3). Post hoc comparisons using SPSS Helmert tests showed this EEG 1-4 Hz power to rise significantly ($P < 0.006$ - applying Bonferroni correction) in the second 10-min period after listen- and sham-mode exposures, the third period after standby-mode exposure, but for no period after talk-mode exposure.

Table 4. 3 Significance of between-condition differences in the temporal change of EEG power at 1-4, 5-7, 8-10, 10-12 Hz occurred at the six recording regions.

		1-4 Hz	5-7 Hz	8-10 Hz	10-12 Hz	12-14 Hz
Brain region		$F_{[24, 216]}$ P	$F_{[24, 216]}$ P	$F_{[24, 216]}$ P	$F_{[24, 216]}$ P	$F_{[24, 216]}$ P
Frontal	L	2.43 (***0.0004***)	1.60 (0.043)	1.34 (0.142)	1.15 (0.288)	1.39 (0.115)
	R	1.76 (0.019)	2.18 (0.002)	1.47 (0.080)	1.07 (0.376)	1.58 (0.047)
Central	L	1.95 (0.007)	2.25 (0.001)	0.59 (0.937)	1.01 (0.454)	1.07 (0.380)
	R	1.20 (0.241)	1.05 (0.408)	1.04 (0.414)	0.94 (0.553)	1.07 (0.378)
Parietal	L	2.15 (0.002)	1.81 (0.014)	0.89 (0.611)	1.51 (0.065)	1.30 (0.169)
	R	1.16 (0.283)	1.04 (0.418)	1.06 (0.397)	1.02 (0.437)	1.07 (0.383)

Results showed here are the $F_{[24, 216]}$ and P values of the interaction effect yielded by two-way rANOVAs [factors: condition and time, 30 tests, considering significance when P values < 0.001 (as shown by ***Italic Bold*** font type), N = 9]. L: left hemisphere; R: right hemisphere.

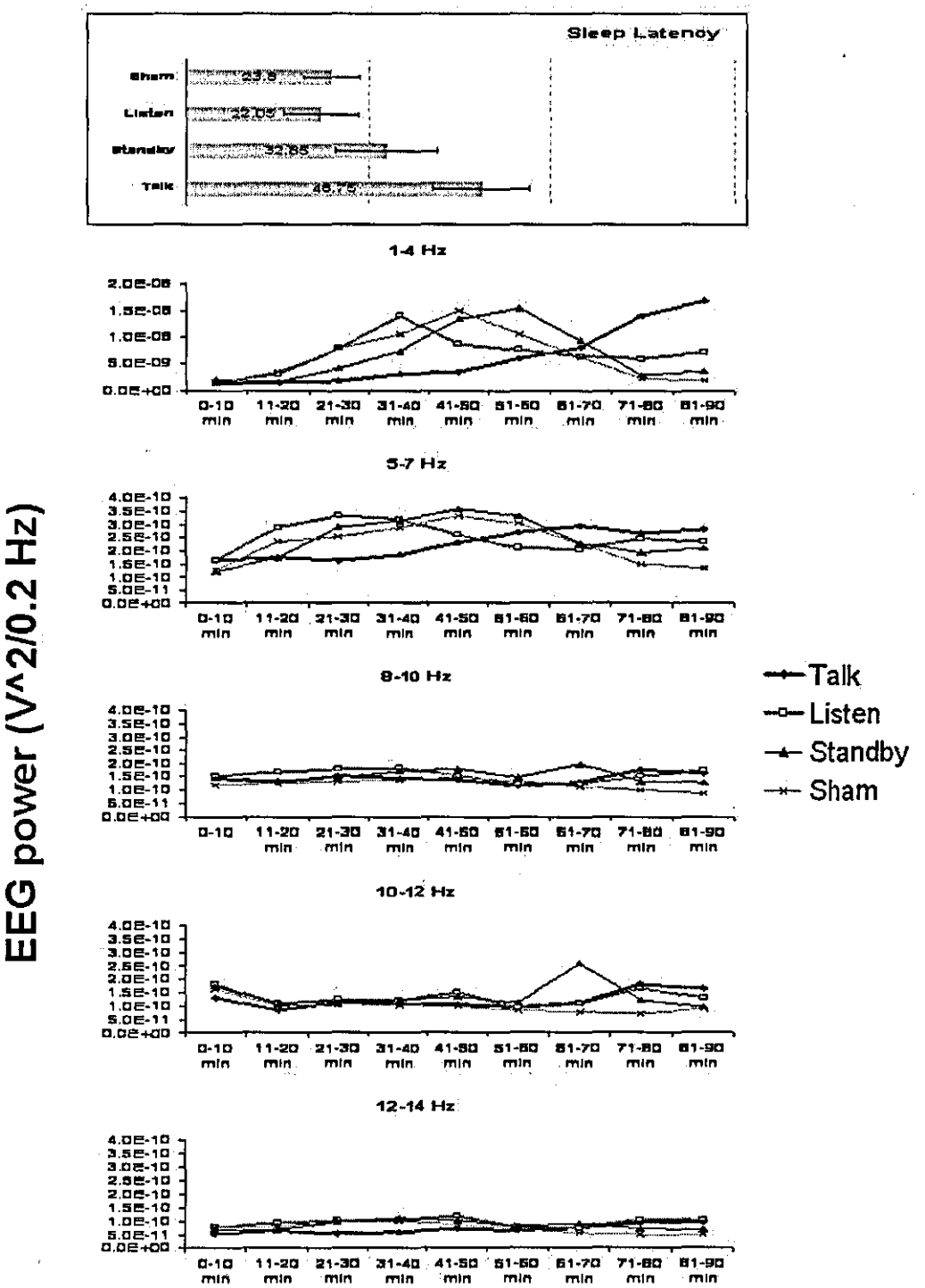

Figure 4. 4 Visually scored sleep latency and time course change of EEG delta (1-4 Hz), theta (5-7 Hz), alpha (8-10 and 10-12 Hz) and sigma (12-14 Hz) power at the left frontal channel (F3-C3) during the 90-min sleep session after varying mobile phone exposures.

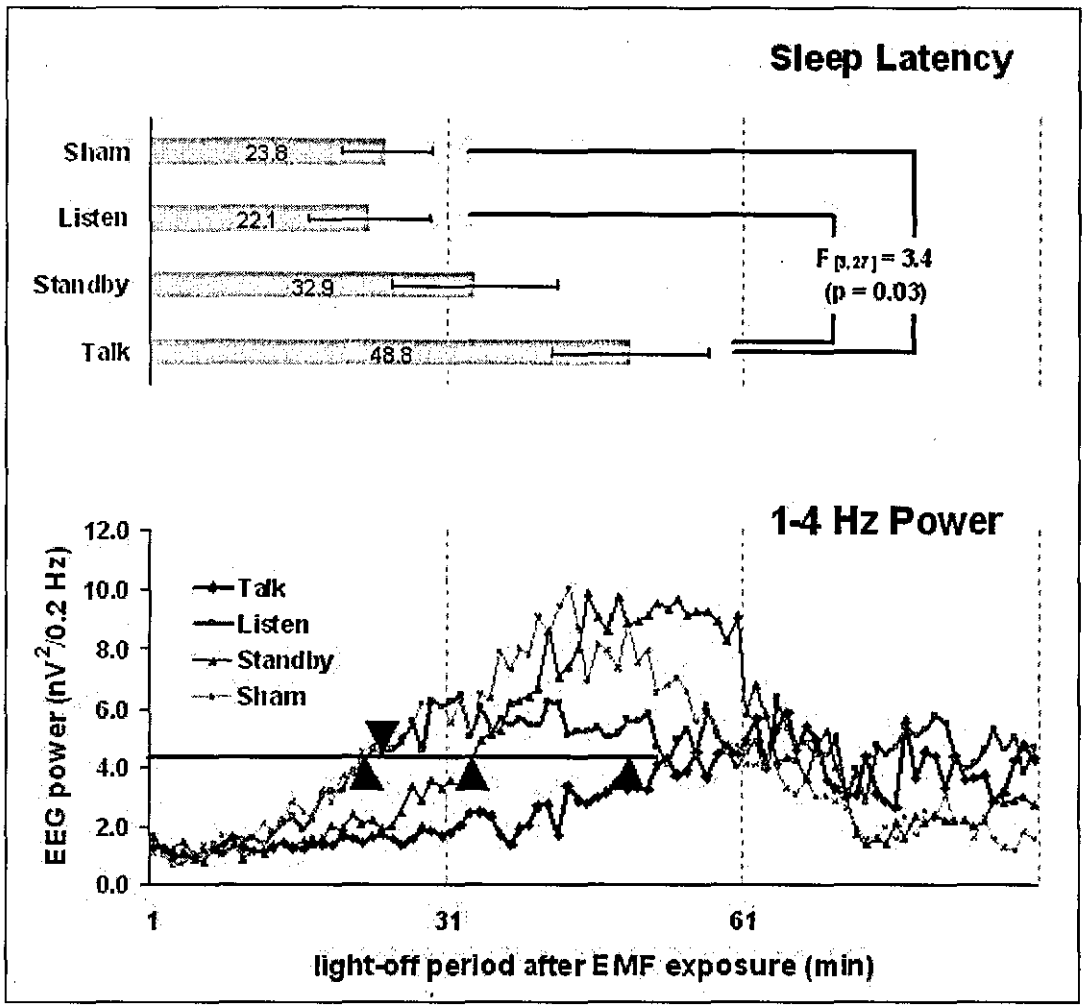

Figure 4. 5 90-min sleep EEG recordings after different exposure modes. (Upper) visually scored sleep-onset latency (mean and s.e.m.) for the four conditions. (Lower) changes in EEG 1-4 Hz power shown for the left frontal (F3-C3) EEG. The filled triangles superimpose the mean visually scored sleep-onsets. A horizontal line can be drawn through these triangles, indicating consistency between the two independent methods of analysis.

4.5 DISCUSSION

To our knowledge, this is the first study where actual talk, listen and standby modes have been compared in a systematic manner, and separated in relation to sleep-onset. Ostensibly, the apparent alerting effect of talk-mode is inconsistent with findings from previous studies claiming to look at the same signal (involving GSM900 carrier frequency but with only a 217 Hz modulation), where sleep latency was found to be either shortened [Mann et al., 1996] or not affected [Wagner et al., 1998; Wagner et al., 2000; Loughran et al., 2005]. However, it should be noted that a number of factors may contribute to this incongruence.

4.5.1 Comparisons with Previous Studies

4.5.1.1 Exposure Condition

First of all, these studies differ from ours in the low-frequency composition of the phone signals. Our talk-mode signal was real, having the permanent low-frequency component at 8 Hz. Furthermore, rather than assessing sleep-onset at a normal bedtime after limited control of circadian confounding and pre-trial sleep, we utilized the natural, early afternoon circadian 'dip,' titrated by actimetrically monitored pre-trial sleep restriction, with all exposure sessions starting at the same time. Thereby, we produced a standard amount of sleep homeostatic pressure and controlled for circadian effects before each exposure within-participants. These other studies also varied in exposure set-up and duration, the phone's position, power outputs and SAR levels. Thus, our finding with talk-mode on sleep-onset is unique, and cannot directly be compared with previous sleep studies using only 217 Hz pulsed GSM900 signals. Moreover, we compared talk-mode with three other conditions (listen, standby and sham modes) within-participants (single-blind) under standardised conditions, and found a specific effect.

4.5.1.2 Experimental Design

Although the sample size of the current study is smaller (N = 10) when compared with earlier studies (N = 12 in Mann et al., 1996; N = 50 in Loughran et al., 2005), however, the talk-mode effect on sleep onset was unambiguously replicated in eight out of ten participants. Furthermore, we had a strong control for the participants' homogeneity as our participants were all recruited from the same gender and the similar age group. We also controlled the residual effects, which may resulted from inter-subject differences, by using a within-subject and repeated measurements. The first-night effect (a slight sleep disturbance caused by the unfamiliarity with the experimental setup) was counteracted with a random-order and counterbalanced design. And our post-hoc comparison method (SNK range test, comparing means in pairs after the sleep data showed a significant one-way ANOVA result) has altered alpha level to avoid type-I error. With these methods that we introduced to handle our small-sample study, the current talk-mode effect should appear based on observed results and not simply by odds.

4.5.2 EEG Markers for Sleep Onset and Sleepiness

4.5.2.1 Rechtschaffen & Kales' Sleep-Onset Criteria [1968]

With regard to the EEG at sleep-onset, the inconsistence in sleep-onset criteria among labs may also contribute to different findings. Earlier studies adopting 'stage 1 sleep' (Mann et al., 1996) or 'the first appearance of stage 2 sleep' (Loughran et al., 2005) as sleep-onset criteria, may cause great deviation in determining the actual sleep-onset point between different scorers owing to the discontinuity nature during the wakefulness-sleep transit. We have realized this problem as our two independent scorers found out that the discontinuous stage 2 sleep (epochs with K complex and/or spindle waves) were sporadically appear between stage 1 sleep and waking epochs, showing participants might dip in and out of drowsiness and light sleep. Hence, we decided to take a more conservative definition of sleep onset based on not only the first appearance of K complex or spindle waves (stage 2 sleep) but also the stability of these activities (continued for more than 3 min, without transitions back to stage 1 sleep or wakefulness). As shown in the results, this criterion is more valid as it corresponds to the time-course change of the left frontal EEG power at 1-4 Hz, a principal indicator for sleepiness and sleep [Rechtschaffen & Kales, 1968; Werth et al., 1997].

4.5.2.2 EEG Spectrum During Sleep-Onset Process

Indeed, within the EEG spectrum that has been extensively studied in the wakefulness-sleep transition, the linear increase of 1-4 Hz power (with anterior-posterior gradients, more prominent at the frontal region) is the most consistent EEG feature of increasing sleepiness from wakefulness through drowsiness to stage 2 sleep [Werth et al., 1997; De Gennaro et al., 2001a]. Furthermore, studies assessing single-Hz EEG activity from 1-11 Hz during sleep onset reported that only delta power, particularly at 3-4 Hz, best showed this change, as well as from sleep to brief awakening [Badia et al., 1994; Wright et al., 1995; De Gennaro et al., 2001b]. Theta power in the range of 6-7 Hz lacks significant change during this transition period [Wright et al., 1995; De Gennaro et al., 2001b]. Although alpha power at 10 Hz reflects the transition from waking to sleep, this is not the case for the reverse transition [Badia et al., 1994]. Moreover, sleep onset differentially affects broadband alpha power (8-12 Hz, central derivation), which displays a quadratic trend: a progressive decrease during wakefulness, a minimum point during stage 1, and a subsequent increase during stage 2 [De Gennaro et al., 2001b]. Alpha-like activity at

frontal, central and occipital brain regions does not always occur concurrently during the first 30 min of sleep onset [Ferreri et al., 2002][14], and the correlation between alpha and delta/theta power (at all derivations) differs between frontal and occipital alpha at sleep onset [Ferreri et al., 2002]; all of which creates difficulty in using alpha activity for determining sleep onset. We concur with the literature that the temporal change of delta power is a more sensitive and reliable marker for stage 2 sleep.

4.5.3 Talk Mode vs. Listen Mode

4.5.3.1 No Sleep-Onset Effects of Listen Mode: Comparing with Huber et al. [2000]

Our finding of a nil effect of listen-mode compared with the sham condition is similar to the outcome from of Huber et al. [2000], where their 30-min GSM 900 MHz 'base-station-like' signals (sharing the same low-frequency components with our 'listen mode' at 2, 8, 217 Hz but with more low-frequency spectral power at 2 and 8 Hz and 217 Hz) had no influence on sleep latency in a subsequent 3-h day-time sleep in healthy young men, having had their prior night's sleep restricted to 4 h. To the extent that our low-frequency pulsing characteristics and findings with listen mode seem to reproduce those of Huber et al., and with a similar experimental listen-mode protocol, then we believe that the outcome from our unique incorporation of talk mode, is not a random effect, and thus the difference between talk and listen effects on sleep-onset seems to be real.

4.5.3.2 Contribution by Different SARs?

The actual cause of the significant difference between talk and listen effects on sleep onset is unknown. It might be due to the typical SAR value for talk mode being about nine times higher than that for the listen mode. We cannot exclude this possibility, as there are technical problems in trying to equate talk and listen-mode in terms of SARs, which are integral to pulse modulations. However, Regel et al [2007b] have measured possible dose-response effects on the sleep EEG, by varying the intensity of SARs of the GSM900 mobile phone signals (with low-frequency components at 2, 8, 217 Hz) and reported nothing of note in this respect. For example, a SAR value of 0.2 W/kg resulted in a sleep-onset latency of 19.4 ± 2.4 min, compared with the

[14] EEG alpha activity (7-10.75 Hz) shows topographical differences in the first 30 min of sleep (anterior-posterior gradient af the first 5 min, with maximal power over the frontal lead; and then, alpha power decreased at all derivations except the frontal one)

similar 20.7 ± 2.8 min for a SAR value of 5 W/kg. It should also be noted that any possible 'far-field' influence of our GSM900 base-station signal can be excluded, as it was switched off during the sleep recording session.

It is unlikely that brain heating effects could be the cause for our findings with talk-mode, especially when our relatively low SAR values are considered. Hirata and Shiozawa [2003] calculated the SARs and resultant brain temperature rises for 660 exposure conditions (e.g. phone pressed against the ear, flattening it against the head, or thermally insulated from the ear and head, under exposure to GSM carrier frequencies between 900 MHz and 2.45 GHz, with horizontal or vertical polarisation, and 18 different antenna feed points using a dipole, monopole and helical antennae). At 2 W/kg per 10 g of tissue (about 16 x our talk-mode value, and at the ICNIRP [1998] recommended limit), the predicted worst-case brain temperature rise would be about 0.25°C. Thus for our SARs, any putative, localised rise in brain temperature would probably be nominal, especially when the naturally rapid heat clearance by blood from the brain is further considered.

4.5.3.3 Contributions by Different Low-Frequency Components?

For the reasons described, together with our lower SARs for both talk and listen mode compared with those utilised by Regel et al [2007b], we suspect that the significant difference between talk and listen-modes on sleep-onset has something to do with their respective spectral composition. Both these modes share the same low-frequency components at 8 Hz and 217 Hz, and it seems that one or both these components (as in talk-mode) seem to delay sleep onset. Furthermore, as listen mode does not affect sleep, and contains another low-frequency component at 2 Hz, then it is possible that the latter component may negate this sleep delaying effect.

Previous studies using 217 Hz pulse-modulated GSM900 signals have produced equivocal findings with sleep-onset across laboratories, and even within the same laboratory the results are not replicated when better methodological controls are adopted. For example, Mann et al [1996] with their single pulse modulated low-frequency component at 217 Hz reported a shortened sleep-onset, but this could not be replicated by expanding participant numbers [Wagner et al., 1998] nor by increasing exposure dosimetry [Wagner et al., 2000].

Thus to summarise so far, it might seem that the delayed sleep-onset effect of talk mode is a result of the 8 Hz component alone or the integration of both 8 Hz and 217 Hz pulsing. Whilst this remains a poorly investigated possibility in humans, a review on animal studies suggests that low-frequency pulse modulations between 8-16 Hz may be critical for physiological effects of GSM mobile phone signals [cf. Introduction of Hinrikus et al., 2004]. We speculate that the 8 and/or 217 Hz electromagnetic field alters the electrical properties of brain cells on the exposure side, making cells more excitable. Interestingly, a recent study [Ferrara et al., 2006] using transcranial magnetic stimulation to investigate the effect of a 45-min GSM900 MHz (with 217 Hz modulation) exposure, reported a neuro-excitatory effect on motor neurons adjacent to the exposure area. This may lend support to the current alerting effect of the talk mode.

4.5.4 Conclusions

The present systematic study comparing talk, listen, and standby modes of GSM 900 mobile phone signals, together with sham mode, revealed distinctive effects on the post-exposure nap following talk-mode exposure:

- A delayed sleep latency
- A dampening of the normal enhancement of the frontal-central EEG 1-4 Hz power

These results suggest the mobile phone talk-mode signal has an alerting effect in the process of sleep onset. This may be related to its different composition of low-frequency modulation frequencies.

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5 EFFECTS ON WAKING EEG

5.1 INTRODUCTION

The approach in this chapter focused on investigating the effects of 'talk', 'listen' and 'standby' mode of mobile phone signals on the resting waking EEG. In the literature reviewed (Section 2.2.2), most evidence indicates enhancing resting waking alpha activities during (Table 5. 1) and following exposure (Table 5. 2). Few studies, on the other hand, have reported a reduction of alpha and beta power (i.e. Huber et al. [2003]; D'Costa et al. [2003], during exposure] or no change in the resting waking EEG spectrum (i.e. Roschke & Mann [1997]; Perentos et al. [2007], post exposure). Such inconsistencies were partly explained by the susceptibility to artefact confounding in waking EEG [Huber et al., 2003], shorter exposure length (i.e. Roschke & Mann [1997], 3.5 min) or less homogeneous exposure distribution or carry-over effects [Perentos et al., 2007].

It is possible, however, that some inconsistencies are related to the varying ELF components of the pulse-modulated EMFs. Most studies did not investigate different ELF compositions of the emitted RF radiation. Nevertheless, by comparing post-exposure EEG effects between those induced by EMFs 'with' and 'without' ELF pulse modulation (i.e. 2, 8, 217 Hz), experimental studies have demonstrated ELF pulse-modulation is essential to induce changes in the resting waking and sleep EEG [Huber et al., 2002, Regel et al., 2007a]. This notion was further substantiated by a neuroimaging study conducted by the same research group [Huber et al. 2005]. They found ELF pulse modulation was also crucial for the EMF-induced alternation in regional cerebral blood flow (rCBF), and this occurred only with EMFs with stronger ELF spectral power.

Furthermore, a recent study directly comparing effects of EMF pulsing at three different ELF (7, 14 and 21 Hz) found an ELF-dependent effect on the resting waking EEG [Hinrinkus et al., 2008]. The EMF modulated at 14 and 21 Hz enhanced the resting waking EEG power in the alpha (8-13 Hz) and beta (15-20 Hz) bands whereas there was no change in the resting waking EEG spectrum at the modulation frequency of 7 Hz during exposure. The authors hence proposed the resting waking EEG power enhancement occurred at the frequency bands that are *close to* or *lower than* the

modulation frequency of the EMF[15]. This findings were consistent to some of the previous research indicating resting waking alpha increment 'during' or 'after' exposure to EMF modulated at 217 Hz [Reiser et al., 1995; Croft et al., 2002; Curcio et al., 2005] or at 16 and 217 Hz [Croft et al., 2008].

However, it is still inconclusive regarding the EEG effect of the EMF modulating at ELF equal or lower than 8 Hz. Although Hinrikus et al.'s findings [2008] implied no EEG spectral effects to be occurred at modulation frequencies below 8 Hz (as revealed by their findings with modulation frequency at 7 Hz), this needs further investigation as their used broad (and fixed)-band spectrum analyses which could not detect some specific sub-band effects or other effects that occurred at frequency bands out of their observation ranges.

In addition, research to date has remained puzzling in the EEG effects induced by the EMF modulating at a combination of ELFs at both ≥ 8 Hz and < 8 Hz. This question is of no less importance than to know the individual EEG effect of each single ELF component since the real mobile phone signals are actually transmitted with ELF fields composed by a combination of 2, 8, and 217 Hz (i.e. talk mode: 8 and 217 Hz; listen mode: 2, 8, 217 Hz). Previous studies examining effects of the GSM 900 MHz pulsing at 2, 8 and 217 Hz (similar to our 'listen-mode' signals) have suggested the main effect was seen in the alpha power during resting waking EEG [Huber et al., 2002, 2003; Regel et al., 2007a; Perentos et al., 2007]. However, the reported findings were inconsistent considering the effect direction, as some showed power enhancement [Huber et al., 2002; Regel et al., 2007], some showed power decrement [Huber et al., 2003], whilst others showed no change to the nil-signal condition [Perentos et al, 2007]. As for EEG effects of the 'talk' and 'standby' modes, to our knowledge, no human laboratory data has been reported.

In chapter 4, we demonstrated a differentiation of effects between talk, listen and standby modes on the EEG-determined sleep onset. What remains unexplored are their effects on the spectral content of EEG during sleep and waking. This and the next chapters are aimed at exploring these questions, with the focus of this chapter being on examining effects of three mobile phone signals on the EEG power change during the 'resting waking' state. We approached this question by comparing the detailed pictures of the awake EEG power in all EEG frequencies (over the range of 1-

[15] Note that no effect was detected in the EEG theta (4-6.8 Hz) power for any modulation frequencies. Changes in the EEG power lower than theta bands was not reported in this study.

16 Hz, in 1-Hz bins) recorded from various scalp locations in two resting waking states after exposure to talk, listen, standby mode, with a sham control. Narrow (1 Hz) frequency bands were used to prevent the loss of information introduced by neurophysiological discontinuities in broad band analysis. EEG changes were monitored with the whole head as the location of EEG changes may be crucial to understand the cortical systems involved in the effects of exposure.

Table 5. 1 Previous observed resting waking EEG effects of GSM signals 'during exposure.'

ELF components	Previous Studies	Delta (1-4 Hz)	Theta (4-8 Hz)	Alpha (8-13 Hz)	Beta (13-35 Hz)	Site of EEG effects (relate to exposure source)
2, 8, 217 Hz	*Huber et al.* [2003]			↓ (central, 10.5-11 Hz)	↓ (central 18.75-19.5 Hz)	Bilateral
217 Hz	*Croft et al.* [2002]	↓ (right hemisphere, 1-4 Hz)		↑ (right hemisphere, 8-12 Hz)		Right hemisphere (exposure at the posterior midline)
	D'Costa et al. [2003]		↓ (frontal: 9 Hz bin, central: 7 & 9 Hz bins, occipital: 7-9 Hz)			(unable to tell, exposure at the posterior midline)
	Curcio et al. [2005]			↑ (central & temporal, 9-10 Hz)		Ipsilateral
16, 217 Hz	*Croft et al.* [2008]			↑ (8-12 Hz, more pronounced at posterior regions)		Bilateral (but more obvious in the ipsilateral site)
1-32 Hz	*D'Costa et al.* [2003]			↑ (frontal, 12 Hz bin)		(unable to tell, exposure at the posterior midline)
7 Hz	*Hinrikus et al.* [2004, 2008]			-		(unable to tell)
14 Hz	*Hinrikus et al.* [2008]			↑ (8-13 Hz, averaged over head)	↑ (15-20 Hz)	(unable to tell)
21 Hz	*Hinrikus et al.* [2008]			↑ (8-13 Hz, averaged over head)	↑ (15-20 Hz & 22-38 Hz)	(unable to tell)

Table 5. 2 Previous observed resting waking EEG effects of GSM signals 'after exposure.'

ELF components	Previous Studies	Delta (1-4 Hz)	Theta (4-8 Hz)	Alpha (8-13 Hz)	Beta (13-35 Hz)	Site of EEG effects (relate to exposure source)
2, 8, 217 Hz	*Huber et al.* [2002]			↑ (central 10 Hz, data including waking and S1 EEG)		Bilateral
	Regel et al. [2007a]			↑ (central 10.5-11 Hz, only appeared in 30-60 min post-exposure)		Ipsilateral
	Perentos et al. [2007]			-		Ipsilateral
217 Hz	*Reiser et al.* [1995]	↑ (1.25-4.5 Hz)		↑ (central & occipital, 9.75-35 Hz)		(unable to tell, exposure at the posterior midline)
	Roschke & Mann [1997]			-		Bilateral
	Curcio et al. [2005]			↑ (central & temporal, 9-10 Hz)		Ipsilateral
16, 217 Hz	*Croft et al.* [2008]			↑ (8-12 Hz, more pronounced at posterior regions		Bilateral (but more obvious in the ipsilateral site)

5.2 MATERIALS AND METHODS

Chapter 4 described the subject's number/characteristics, study design and exposure condition. The description of EEG recordings and the mobile phone signal generation/exposure procedures are provided in the Materials and Methods section of the previous chapter. Please refer to them for details.

5.3 DATA ANALYSIS

5.3.1 Waking EEG Data Sources

Rest waking EEG recordings before (baseline, T0) and after the electromagnetic field exposure (T1), as well as resting waking EEG before the first epoch of stage 1 sleep

(S1) during the 90-min nap (pre-S1 waking, T2), were subjected to EEG spectral analysis. Only nine participants' data were used for resting waking EEG spectral analysis of T0, T1 and T2[16]. The averaged T2 lengths after excluding artefact-contaminated epochs is listed in Table 5. 3, which show no between-condition difference ($F_{[3, 24]} = 0.964$, $P = 0.426$).

Table 5. 3 Resting waking duration before stage 1 sleep (T2 in min, mean ± S.E.M., N=9) for the talk-, listen-, standby- and sham-mode condition, exclusive of artefact-contaminated epochs.

	Talk	Listen	Standby	Sham	$F_{3, 24}$	P-value
Mean (S. E. M.)	12.4 (5.9)	6.6 (2.7)	8.0 (3.0)	5.8 (2.0)	0.964	0.426

In the 'T0' and 'T1' resting waking EEG recording sessions (3 min/session), the light was on and the participant was instructed to 'close eyes, relax but keep awake.' The mean subjective sleepiness assessed by KSS scale [Åkerstedt et al., 1990] before and after the 'T0' were both between levels 7 ('sleepy') or 8 ('sleepy, some effort to stay awake'), without conditional difference (see Figure 4. 3). A two-way rANOVA on the KSS values was neither significant on the 'condition' effect nor on the 'time x condition' effects.

5.3.2 Waking EEG Power Spectral Analysis

The EEG spectrum across the 1-16 Hz range for 0.5 Hz bins was performed with FFT routines (Hanning window, epoch length: 2 s, sampling rate: 128 Hz). FFT epochs contaminated by ocular and/or muscular artefacts were rejected (through a visual inspection of the raw EEG data). The power density values of every two conjunctive 0.5 Hz bins were integrated to form a new series of 1-Hz bins over the entire frequency range (1-16 Hz). For data reduction, continuous, artefact-free, 2-s epochs were averaged over 30-s epochs. Next, the 30-s epochs were further reduced by averaging them over the length of each recording period. This procedure was repeated individually for the six bipolar EEG recordings (LF: F3-C3; RF: F4-C4; LC: C3-P3; RC: C4-P4; LP: P3-O1; RP: P4-O2) of nine participants in the four conditions.

[16] This was due to one participant entered S1 without preceded waking when given the 90-min nap opportunity after light-off (7 min after cessation of exposure) in the sham-mode condition.

5.3.3 Data Transformation

Absolute EEG spectral power was log-transformed in order to attain a relevant reduction of outliers, a better approximation to gaussianity, and higher homoscedasticity. Given there was an intra-participant instability in the baseline (T0) waking EEG across conditions, for each participant, mean resting waking EEG power values of 'T1' and 'T2' were standardized by the mean resting waking EEG power value of 'T0' within the same condition (standardized T1 = T1 / T0; standardized T2 = T2 / T0, repeated for four conditions). Then the standardized T1 and T2 values of three active modes (talk-, listen- and standby-mode) were represented as a percentage of the sham mode (=100%) for each participant.

5.3.4 Statistics

For both 'T1' and 'T2 (pre-S1)' resting waking sessions, group-averaged spectra data of 'talk', 'listen' and 'standby' modes were compared with sham mode by two-tailed paired t-tests for each frequency bin, from each cortical region (considered significant when $P < 0.025$; tests were carried out with transformed data, % of pre-exposure T0). Differences between three modes ('talk', 'listen' and 'standby') were tested with one-way rANOVAs (factor: condition; considered significant when $P < 0.05$; tests were carried out with values of the three modes being expressed relative to the value of sham-mode in percentage). When one-way rANOVA showed a significant main effect of the condition factor, a post hoc comparison using the Student-Newman-Keuls (SNK) ranges test was followed to examine the significance level of differentiation between three modes. The testing was repeated for each recording site (LF: F3-C3, LC: C3-P3, LP: P3-O1, RF: F4-C4, RC: C4-P4, RP: P4-O2). If not otherwise indicated, only significant effects are reported.

5.4 RESULTS

5.4.1 Rest Waking EEG Spectra of T1

The relative EEG power spectra of 'talk', 'listen' and 'standby' modes (= % of sham mode) across the 1-16 Hz frequency range during the 3-min post-exposure T1 resting waking period is summarized in Figure 5. 1. Comparing with 'sham mode', only 'listen mode' induced a significant post-exposure resting waking EEG spectral effect, as demonstrated by an increased 4-5 Hz power density at the left frontal region (Figure 5. 1, panel 'LF', two-tailed paired t-test, $t_{[1,8]} = 2.87$, $P = 0.021$). There is no significant

spectral difference between three modes as one-way rANOVAs yielded no significant condition effects (highest $F_{[2, 16]} = 2.61$; all P values > 0.104, on relative values to 'sham mode').

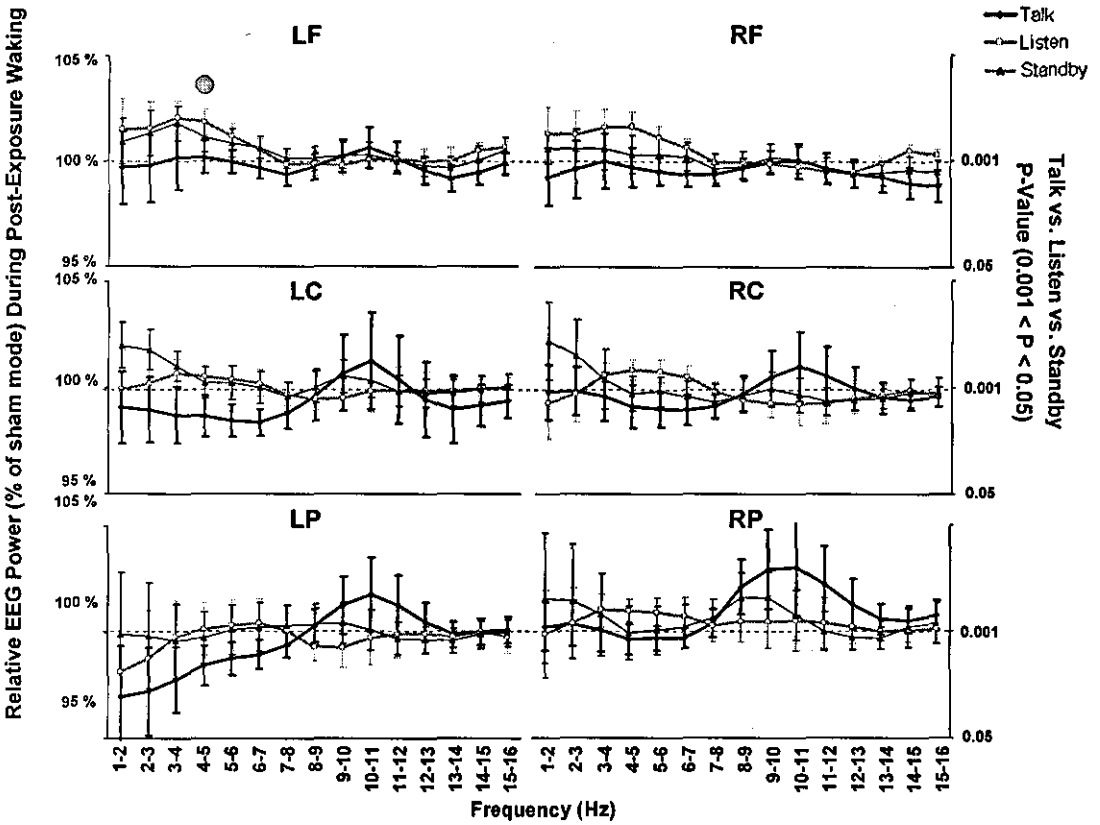

Figure 5. 1 Relative EEG power spectra during T1 waking at the six derivations (LF, LC, LP, RF, RC, RP) after 'talk', 'listen', and 'standby' mode exposure. Mean ± s.e.m. power (n = 9), relative to sham mode (= 100%), are shown per 1-Hz at the range of 1-16 Hz (labels at left). Gray circle appeared near the curve of 'listen mode' at the 4-5 Hz bin in the 'LF' region indicate a significant power difference from sham mode (paired t-test, $P = 0.021$). No difference between three modes was found with one-way rANOVAs (condition factor: 'talk' vs. 'listen' vs. 'standby', all P-values > 0.05). EEG derivations LF: F3-C3; LC: C3-P3; LP: P3-O1; RF: F4-C4; RC: C4-P4; RP: P4-O2.

5.4.2 Resting Waking EEG Spectra of Pre-S1 Waking (T2)

Figure 5. 2 depicts the averaged EEG power spectrum obtained after 'talk', 'listen' and 'standby' exposures (relative to sham-mode condition in percentage) during the 'T2' (pre-S1 resting waking) from different scalp regions. Significant statistical findings from this graph are also summarized in Table 5. 4.

Comparing with sham-mode exposure, both 'listen' and 'standby' mode showed no significant change (Table 5. 4). However, talk-mode exposure induced an obvious

spectral power attenuation in the theta (4-7 Hz) activity over the bilateral frontal-central regions (particularly pronounced at the right frontal and left central regions) while the parietal-occipital alpha activity was significantly enhanced at the range of 8-9 Hz in the right hemisphere (Table 5. 4 and gray squares in Figure 5. 2). Furthermore, one-way rANOVAs yielded conditional differences in the left central EEG 4-7 Hz power (EEG derivation: C3-P3, $F_{[2,16]}$ at least 4.97, $P < 0.021$) and in the right frontal EEG 14-16 Hz power (EEG derivation: F4-C4, $F_{[2,16]}$ at least 7.38, $P < 0.005$). Post-hoc comparisons (SNK ranges tests) revealed the between-condition difference resulted from a lower spectral power after 'talk' mode when compared with 'listen' mode.

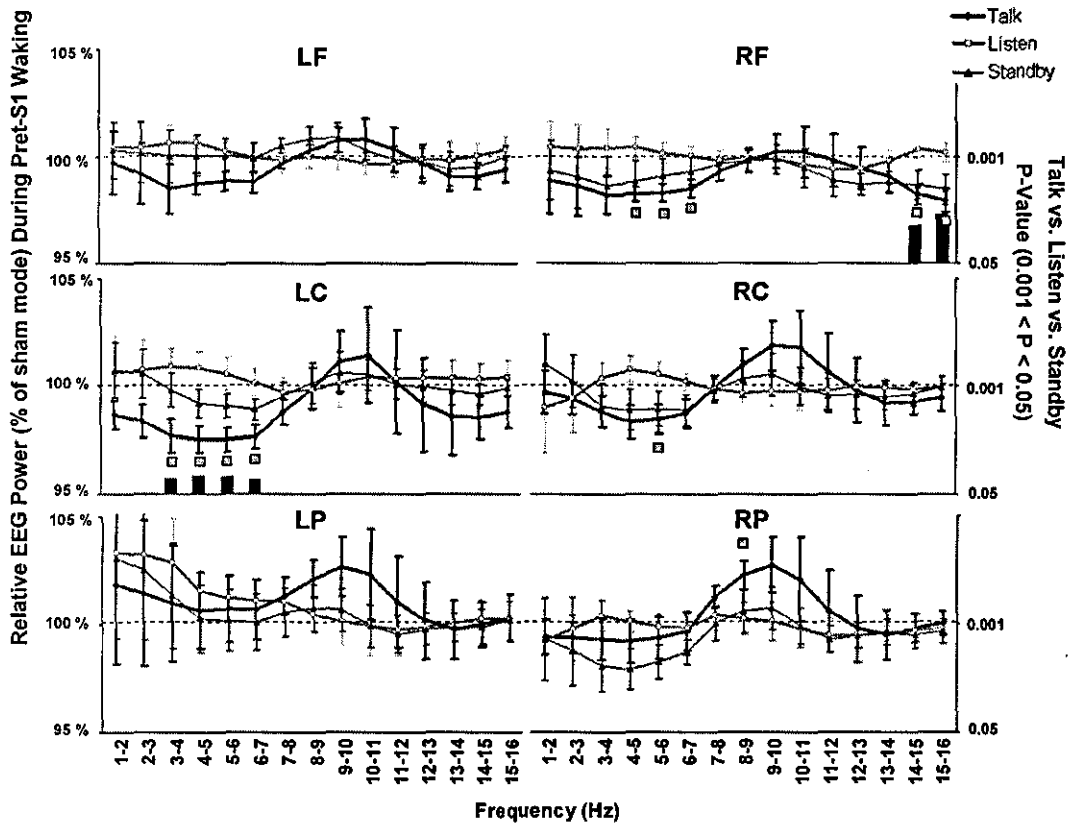

Figure 5. 2 Relative EEG spectra during 'T2' (pre-S1) waking at the six derivations (LF, LC, LP, RF, RC, RP) after 'talk', 'listen', and 'standby' mode exposure. Mean ± s.e.m. power (n=9), relative to sham mode (100%), are shown per 1-Hz bin at the range of 1-16 Hz (see labels at left). Gray squares near the curve of 'talk mode' at bins across the 3-7 Hz range at the LC region, 4-7 and 14-16 Hz at the RF region, 5-6 Hz at the RC region, as well as 8-9 Hz at the RP region, indicate significant power differences from sham-mode condition (paired t-tests, all *P* values < 0.025). Black bars at the bottom of each panel denote significant levels between three modes (one-way rANOVAs, condition factor: 'talk' vs. 'listen' vs. 'standby', P-values are indicated by the label at right). EEG derivations LF: F3-C3; LC: C3-P3; LP: P3-O1; RF: F4-C4; RC: C4-P4; RP: P4-O2.

Table 5. 4 Mobile phone effects on the 'T2' (pre-S1) resting waking EEG spectra.

		Left hemisphere				Right hemisphere			
brain site	Rhythm (Hz)	Talk vs. Sham	Listen vs. Sham	Standby vs. Sham	Talk vs. Listen vs. Standby	Talk vs. Sham	Listen vs. Sham	Standby vs. Sham	Talk vs. Listen vs. Standby
F	4-5	↓ (0.032)	-	-	-	↓ (0.001)	-	-	-
	5-6	↓ (0.039)	-	-	-	↓ (0.003)	-	-	-
	6-7	↓ (0.038)	-	-	-	↓ (0.008)	-	-	-
	14-15	-	-	-	-	↓ (0.008)	-	-	Talk < Listen
	15-16	-	-	-	-	↓ (0.006)	-	-	
C	3-4	↓ (0.015)	-	-	Talk < Listen	-	-	-	-
	4-5	↓ (0.004)	-	-		-	-	-	-
	5-6	↓ (0.002)	-	-		↓ (0.050)	-	-	-
	6-7	↓ (0.002)	-	-		-	-	-	-
P	8-9	↑ (0.037)	-	-	-	↑ (0.009)	-	-	-

↑: power increasing, ↓: power decreasing, -: no change, which indicate the direction of spectral power change when comparing exposure mode with sham mode using two-tailed paired t-tests. Significant levels of paired t-tests are shown in parentheses (*P* values < 0.025 are marked by **Bold** font style; 0.025 < P values < 0.05 are marked by Unbold font style). Brain site F: frontal, C: central, P: parietal.

5.5 DISCUSSION

In the current study, we examined the waking EEG spectral effects of three ELF-modulated mobile phone signals – talk (8, 217 Hz pulsed), listen (2, 8, 217 Hz pulsed) and standby modes (< 2 Hz pulsed) – on two different resting states (T1 and T2/pre-S1) after 30-min mobile phone signal exposure on sleepy participants. Results showed that during the 'T1' resting waking state, effects only occurred after 'listen-mode' exposure, as shown by an enhanced EEG power at 4-5 Hz comparing with sham-mode. However, during the 'T2' (pre-S1) resting waking state, effects were occurred only in the 'talk-mode' condition (when compared with 'sham' mode): the frontal and central EEG power was decreased at delta and theta (3-7 Hz) frequencies (more pronounced at EEG derivations: F4-C4 and C3-P3) and the parietal EEG power was enhanced at the alpha (8-9 Hz) band (more pronounced at EEG derivation P4-O2). Pre-S1 resting waking EEG also provided a differentiation between talk- and listen-mode effects. This was revealed by a lower theta (3-7 Hz) power at the left central region (EEG derivation: C3-P3) as well as a lower sigma (14-16 Hz) power at the right frontal region (EEG derivation: F4-C4) after talk-mode than after listen-mode exposure (note: 'listen-mode' effects were of no difference from 'sham-mode' effects during this state).

5.5.1 Neurobiological Interpretations

5.5.1.1 Cues from Resting Waking Markers of Sleep Homeostatic Regulation

Theta and alpha frequencies in the awake EEG have been found to be very sensitive to the need for sleep and the subjective feelings of sleepiness (which guide human in their decision to go to sleep). Spectral analysis showed that power in the theta band of the waking EEG increases during sleep deprivation [Torsvall & Akerstedt, 1987; Cajochen et al., 1995; Aeschbach et al., 1997b; Finelli et al., 2000]. The time constant of this increase is similar to that of the waking time-dependent increase of low-frequency activity in NREM sleep (which is an electrophysiological sign of sleep intensity and sleep need) [Cajochen et al., 1995; Aeschbach et al., 1997b]. The rise rate of theta activity in the waking EEG is also positively correlated with the rise rate of slow wave activity (SWA, 0.75-4.5 Hz) in the first NREM sleep episode of recovery sleep after sleep deprivation, with both effects being largest in the frontal area [Finelli et al., 2000]. A forced desynchrony study with a scheduled waking episode of 28 hours showed a monotonic rise of delta and beta activity in the fronto-central derivation in the waking episode [Cajochen et al., 2002]. During prolonged wakefulness, subjective sleepiness correlated positively with resting waking EEG activities at below 0.5 Hz, between 3-8 Hz and 23-29 Hz with a focus in frontal-central derivations, and negatively with 8-12 Hz activity at all derivations [Strijkstra et al., 2003]. A gradual reduction of alpha power and a gradual increase in theta power has been found during transition from eyes-closed, resting conditions to sleeping [Tanaka et al, 1997]. In sum, early studies have shown a detailed picture in awake EEG variables related to homeostatic aspects of sleep regulation, where the alpha power (8-12 Hz, with eyes closed) shows a gradual global decrease with time awake, whereas theta (4-8 Hz, sometimes extended to delta band at 3 Hz) and beta (23-29 Hz) power increases specifically at the frontal-central location. The reverse relationship between resting (eyes-closed) alpha and theta power may well represent the level of sleepiness during prolonged wakefulness, which showed a strong correlation of sleepiness during prolonged wakefulness [Strijkstra et al., 2003]. It may also represent the high motivation to sleep since the relationship mimics the alpha power decrease following theta power increase during sleep entry [Tanaka et al., 1997].

From these points of view, the present findings of the inversed direction of frontal-central theta power change with 'talk-mode' (power diminishing during pre-S1 resting

waking state; comparing with sham mode) and with 'listen-mode' signal (nil change of power during pre-S1 resting waking sate; power enhancing during 'T1' resting waking state; both comparing with sham mode), as well as a lower frontal-central theta power with talk-mode exposure as compared with listen-mode exposure (during pre-S1 resting waking), all suggest these two mobile phone signals may have opposite effects on the 'sleep homeostatic regulation' or the 'motivation system serving sleep homeostasis'. Whilst additional analyses on the NREM sleep EEG spectrum are needed to corroborate distinctive effects of both signals on the sleep homeostasis, results of current resting waking EEG spectral analyses incite a speculation that 'talk mode', but not 'listen mode,' reduced the sleep homeostatic need. The reduction of resting theta power of talk mode during T2 (pre-S1) waking may also be related to a lower motivation to sleep and thus account for the delayed stage 2 sleep-onset finding of this mode (see chapter 4).

5.5.1.2 Cues from Spatiotemporal EEG Dynamics in the Transition from Waking to Sleep

The higher parietal-occipital alpha power (8-9 Hz) of waking EEG with talk-mode comparing with sham-mode signal during the hypnagogic state before appearance of S1 (when alpha waves present < 50% of the epoch according to Rechtschaffen & Kales' Criteria [1968]) implied talk mode delayed the normal decline of alpha power before the onset of S1 [Morikawa et al., 2002] and the subsequent entry of the frontal-initial sleep onset process starting from S1. This suspicion can be supported by two resting waking EEG dynamics denoting transition from waking to sleep: (i) the anterior-posterior EEG ratio (A/P ratio) of alpha activity is found to increase as a function of the EEG stages of the hypnagogic state, and the A/P ratio clearly changes at EEG stages when alpha waves at the posterior areas starts to present < 50% of the epoch [Hori et al., 1994]; and (ii) the dominant area of EEG alpha activity have been shown to move from posterior to the anterior area during the waking-S1 transition [Tanaka et al., 1997]. This result, on the other hand, reflects a higher degree of vigilance in the observed resting waking EEG epochs (pre-S1) after talk-mode rather than sham-mode exposure. Again, this reconciles our findings of a delayed onset of stage 2 sleep and a lower level of homeostatic need (lower waking theta power) after talk-mode exposure.

In addition, apart from significantly less EEG theta activity, the right frontal area showed higher power in the 14-16 Hz (sigma) band with listen-mode rather than with

talk-mode signal during the T2 (pre-S1) resting waking state. It should be noted that the EEG epochs analyzed were pure waking epochs without any sign of vertex sharp waves, K-complexes or sleep spindles and the stronger sigma activity with listen- than talk-mode signal is a 'relative' inspection. However, it was well-described that the amplitude of EEG sigma power starts to increase from frontal pole to the parietal region during the onset of the hypnagogic state, and this was related to the activity of the 14-Hz sleep spindles [Tanaka et al., 1997]. Thereby, the higher sigma power in the frontal area may represent a stronger hypnagogic drive induced by listen-mode rather than talk-mode exposure.

5.5.2 Comparing with Previous Studies

The current findings that the listen-mode signal affected the 'T1' resting waking EEG power at 'theta (4-5 Hz)' rather than the 'alpha' band is incompatible to existing studies of the GSM 900 MHz signal pulsing at the same ELF (2, 8, 217 Hz), as previously reported effects mainly occurred at alpha bands after 30-min exposure in resting states [Huber et al., 2002, 2003; Regel et al., 2007a]. Three reasons may explain the incongruent findings. Firstly, previous waking alpha effects have mostly been studied at normal bedtime with limited control of pre-trial sleep duration and has showed equivocal changes in the direction of alpha power [i.e. alpha enhancing: Huber et al. (2002) and Regel et al. (2007a); alpha decreasing: Huber et al. (2003)]. Our listen mode, demonstrating absence of resting waking alpha effects, however, was studied under the natural, early afternoon circadian 'dip,' with a standard amount of sleep homeostatic pressure before each exposure within-participants by actimetrically monitored pre-trial sleep restriction, with all exposure sessions starting at the same time. Secondly, the ELF spectral power of the 217 Hz component is actually stronger in the GSM signals used by the above-mentioned studies (due to a combination of both 'talk' and 'listen' mode emission) and previous research studying GSM exposure with only 217 Hz pulsing at normal phone position have consistently reported a post-exposure alpha power increment in the resting waking EEG [Croft et al., 2002; Curcio et al., 2005]. Thirdly, given the resting waking EEG has been proposed to be affected at the frequency bands that are *close* to or *lower than* the ELF modulation frequency of the EMF [Hinrinkus et al., 2008], it is suspected that the waking EEG frequencies affected by the 2 and/or 8 Hz component of the listen-mode signal would counteract those affected by the 217 Hz component. As our talk-mode signal (sharing the same ELF spectral characteristics of 8 and 217 Hz component with the listen-mode signal, but without the 2-Hz component) did show resting waking EEG

effects on both alpha and theta power with its theta effect being inverse from that of listen-mode, this speculation may be true.

5.5.3 Conclusions

To sum up, the current analyses of resting waking EEG spectrum before the appearance of the first sign of sleep (= the first epoch of S1) indicated further distinct effects of 'talk mode':

- Talk mode decreased the sleepiness-associated frontal-central theta (4-7 Hz) power (=> implying the brain became less sleepy following talk mode exposure);
- Talk mode induced stronger parietal-occipital alpha (8-9 Hz) power (=> suggesting the brain was at a higher degree of vigilance, far beyond the point to develop the frontal-initial sleep onset process after exposure to talk mode).

Results of the power spectral analyses during the same period also suggest that *talk and listen modes have **opposite** effect during the waking-sleep transition*, which is demonstrated by

- Less sleepiness-associated frontal-central theta (4-7 Hz) power after 'talk' than 'listen' mode exposure;
- Less sleep-associated frontal spindle (14-16 Hz) power after 'talk' than 'listen' mode exposure.

Taken together, these findings provide further evidence to support our previous findings of talk-mode signal in delaying sleep onset.

6 EFFECTS ON SLEEP EEG

6.1 INTRODUCTION

6.1.1 Previous Studies of Mobile Phone Effects on Sleep and Sleep EEG

Available human laboratory studies, using double-blind and sham-controlled designs (disentangling physiological effects from psychological influences), have recognized EMFs simulated to the real mobile phone transmission have non-thermal effects on brain physiology. Reported effects include increasing EEG power in the alpha frequency range during resting waking [Croft et al., 2002, 2008; Curcio et al., 2005; Hinrinkus et al., 2008; Huber et al., 2002; Regel et al., 2007a], and in the spindle frequency range during NREM sleep [Mann & Roschke, 1996; Borbély et al., 1999; Huber et al., 2000, 2002, 2003; Loughran et al., 2005; Regel et al., 2007b]. In view of the well-established link between EEG alpha/spindle enhancement and the natural sleep process [for review, see Sec. 2.3.2.2 and 2.3.2.4], these EMF-induced alpha/spindle effects may easily be interpreted as sleep promoting at first glance. However, since most studies showed no concurrent changes in the EEG-determined sleep structure (such as 'shortened sleep latency' or 'reduced waking after sleep onset'), there may be existence of other neurophysiolgical interpretations for the observed alpha/spindle effects. Moreover, spindle enhancement during sleep have not been entirely consistent, with some studies finding the effect varies in terms of particular frequency bands (see Fig. 6.1) and scalp locations, and others failing to replicate effects reported in their earlier studies even with a methodological improvement (e.g., Mann & Rochke's study [1996] could not be replicated in their later studies [Mann et al., 1998; Wagner et al., 2000] with an increased sample size and a homogenous EMF exposure).

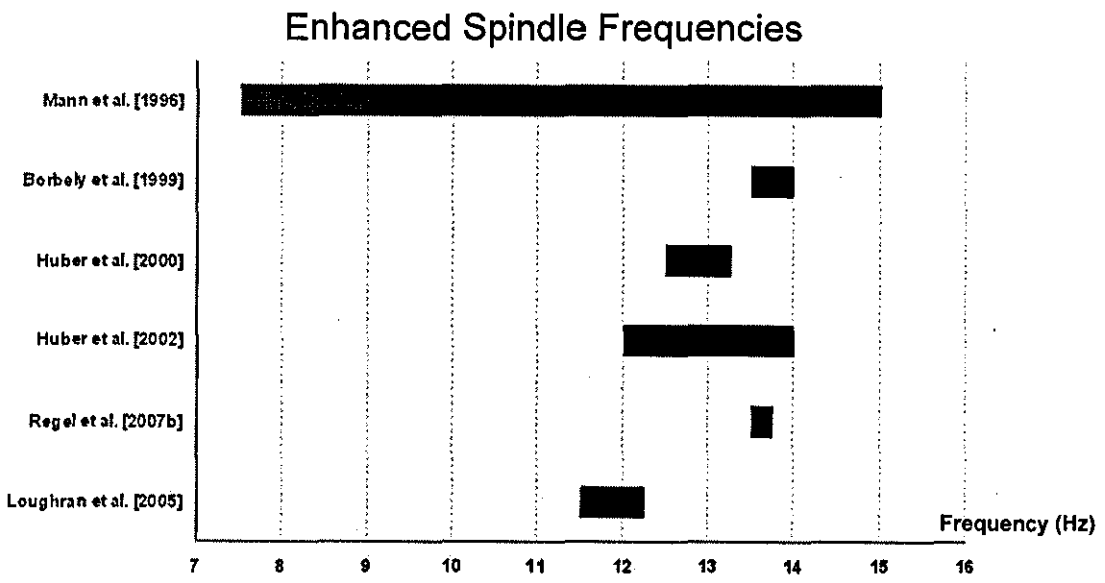

Figure 6. 1 Variances in the enhanced spindle frequencies as reported in different sleep EEG studies.

6.1.2 Our Study and Hypothesis

In our own EEG study of mobile phone EMFs transmitted at talk, listen and standby modes, we have demonstrated mobile phone 'talk-mode' signals induced alerting effects in the process of sleep onset, which was revealed by significantly longer sleep-onset latency after talk-mode exposure in comparisons with sham- or listen-mode exposure (chapter 4). This sleep structure finding of talk vs. sham and talk vs. listen mode also concurred with (i) a dampening of the normal enhancement of frontal-central EEG delta power in the 90-min sleep process after talk-mode exposure (chapter 4); (ii) a reduced frontal-central waking theta power prior to the onset of stage 1 (S1) sleep comparing talk- with sham- and listen-mode condition (chapter 5). Since both sleep delta and waking theta power in the frontal-central area are sensitive to the influence of homeostatically controlled sleep-initiating mechanisms [Finelli et al., 2000], it is suspected the alerting effect of talk mode may have resulted from an attenuated sleep drive on this system. Nevertheless, this was yet to corroborate with changes in the EEG 'during' (stage 2 sleep) and 'after' sleep onset, as other factors (e.g. ineffective closing of thalamic gate and poor sleep maintaining) may also contribute to the talk-mode effect. Furthermore, studies to date haven't paid enough attention to how sleep responds differentially to the waking "plasticity" induced by the three mobile phone signals (Table 6.1), despite these being real signals radiated to almost 2.1 billion users' heads in the world everyday. These handset signals should be of special concern, not only because they are what the human brain is actually

exposed to, but also because they are ELF pulse-modulated ('talk' mode: 8, 217 Hz; 'listen' mode: 2, 8, 217 Hz; 'standby' mode: < 2 Hz). As repetitive TMS at various stimulation frequencies differentially modify the waking cortical excitability [Lemon, 2002] and the subsequent sleep EEG (as mentioned above), we may assume the mobile phone EMF effects on the bioelectrical activity of the human brain is also dependent on the stimulation frequencies. Indeed, human laboratory findings have provided evidence that ELF (i.e. 2, 8, 217 Hz) pulse modulation to be a prerequisite for mobile phone radiofrequency EMFs to induce alternations in brain physiology [Huber et al., 2002; 2005]. However, effects of varying ELF composition corresponding to the real mobile phone EMFs are still under investigation, and cannot be inferred from the previous experimental findings.

The aim of this study was to evaluate the sleep EEG effects of 'talk', 'listen' and 'standby' mode signals on subsequent 90-min sleep using both EEG visual scoring and power spectrum analysis. We assessed the mobile phone signal-induced EEG power change in narrow (1 Hz) frequency bands over the range of 1-16 Hz recorded from six scalp locations (covering the whole head) during the first cycle of NREM sleep, as well as stage 2 (S2), and slow-wave sleep (SWS, a combination of stage 3 and 4 sleep), respectively. It was hoped, through revealing the detailed pictures of sleep EEG spatiotemporal dynamics, that the varying mobile phone ELF pulse-modulation effects on the post-exposure sleep neurophysiology can be more adequately observed. It was also hoped to further elucidate the alerting effect of the talk-mode signal with more theoretical interpretation of the sleep EEG.

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		Mann et al. [1998] (a replication study of Mann & Roschke [1996], with an increased subject number and a lower EMF power)	No significant alternation of EEG; a trend of reducingREM sleep duration and percentage
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LH: left hemisphere; RH: right hemisphere; S2: stage 2 sleep; NREM sleep: non-rapid eye movement sleep; REM sleep: rapid-eye-movement sleep.

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6.3 DATA ANALYSIS

In this chapter, sleep structure and sleep power spectrum during NNREM sleep after talk-, listen- and standby-mode exposure would be assessed. The related data analytic methods are given below.

6.3.1 Definition of Sleep Variables

Left central EEG (derivation: C3-A2), chin EMG, and horizontal and vertical EOG were used for standard visual sleep scoring [Rechtschaffen & Kales, 1968]. As described in Chapter 4, these sleep EEG visual scores were determined by two independent scorers, who were 'blind' to the conditions. Several sleep variables from the visual scoring were defined in order to further investigate effects of different mobile phone exposures on the sleep structure. They have been described in Figure 3. 6 and Table 3. 1. Here is a recapitulation of the variables investigated in this chapter (Table 6. 2).

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Sleep Variables	Definition
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Total waking time (TWT, min)	Total time in bed minus total sleep time
Sleep efficiency (%)	Total sleep time as a percentage of total time in bed.
Sleep onset	First occurrence of consecutive S2, lasting for at least 3 minutes uninterrupted.
Sleep latency (min)	Interval from light off to sleep onset
SWS latency (min)	Interval from light off to the first epoch of SWS (≥ 4 min).
S2 duration(min)	Interval spent in continuous S2 (≥ 3 min) before onset of SWS
Slow-wave sleep (SWS, min)	Consecutive epochs of S3 + S4 (beginning at the first consecutive epoch of S3; lasting for at least 4 min uninterrupted).
SWS duration (min)	Time spent in consecutive epochs of Stage 3 + Stage 4.
REMS latency (min)	Interval from sleep onset to the occurrence of consecutive REMS.

S2: stage 2 sleep; S3: stage 3 sleep; S4: stage 4 sleep; SWS: slow-wave sleep; REMS: rapid-eye-movement sleep.

6.3.2 Sleep EEG Spectral Analysis

90-min sleep EEG recordings were submitted to the Fast Fourier Transform (FFT) algorithm provided by the Somnologica software for power spectrum analysis across the 1-16 Hz range in a 0.2 Hz resolution (Hanning window, epoch length: 5 s, sampling rate: 128 Hz). The five lowest frequency bins (0.11-0.2, 0.21-0.4, 0.41-0.6, 0.61-0.8 and 0.81-1.0 Hz) were excluded from analysis because their sensitivity to low-frequency artefacts. In addition, FFT epochs contaminated by ocular and/or muscular artefacts were rejected (through a visual inspection of the raw EEG data). For data reduction, the power density values of every five consecutive 0.2-Hz bins were integrated to form a new series of 1-Hz bins over the range of 1-16 Hz. Artefact-free 5-s epochs were averaged over 30-s epochs (analogous to EEG sleep staging) to

generate a new time series of data (= 180 × 30-s epochs) for the entire 90-min sleep recording episode. This procedure was replicated in the six bipolar EEG derivations (F3-C3; F4-C4; C3-P3; C4-P4; P3-O1; P4-O2) per recording. In this chapter, results of an extended analysis on the EEG spectra during the first non-rapid-eye-movement (NREM) sleep cycle, as well as the respective EEG spectra of stage 2 (S2) and slow-wave sleep (SWS) during this period, are reported.

6.3.2.1 Data used for representing power spectra of stage 2 (S2) and slow-wave sleep (SWS) during the first NREM sleep cycle

Due to signal loss in the sleep recording session after talk- and standby-mode exposure in one participant, only nine participants' data were used for EEG spectra analysis. Due to inter-individual differences in the length and time series of uninterrupted, artefact-free S2 and SWS EEG during the first NREM sleep cycle, minimum numbers of epochs (S2 = 8, SWS = 10) aligned with respect to the onset of S2 and SWS were selected to calculate the mean S2 and SWS EEG power for each frequency bin. These S2 and SWS epochs were then combined to calculate the mean power of the first NREM sleep cycle for each frequency bin.

Absolute power was log-transformed in order to attain a relevant reduction of outliers, a better approximation to gaussianity and a higher homoscedasticity. For a standard comparison between the three experimental ('talk', 'listen' and 'standby' mode) condition, values of these three modes were represented as a percentage of the sham mode (=100%).

6.3.3 Statistics

6.3.3.1 Analysis of Sleep Variables

Sleep variables were submitted to one-way ANOVAs for repeated measures (one-way rANOVAs) to examine the effects of talk, listen, standby and sham modes. The significant rANOVA results were followed by Student-Newman-Keuls (SNK) range tests for post hoc comparisons.

6.3.3.2 Analysis of Sleep EEG Spectra

EEG spectra data were investigated with the following variables:

i) EEG delta (1-4 Hz) power during S2 and SWS at each recording site, separately. This analysis is used to corroborate the EEG visually scored S2 and SWS onset time. If the S2 and SWS onset time was scored using the same criteria, the EEG delta power of S2 and SWS would be of no difference between the four modes. Also, the normal enhancement of EEG delta power from S2 to SWS would be similar between the four modes.

ii) S2 and SWS EEG power (as well as 'S2-SWS' power difference) in 1-Hz bins across the 1-16 Hz frequency range during the first Non-Rapid-Eye-Movement (NREM) sleep cycle.

For these two variables, spectra data of 'talk', 'listen' and 'standby' modes were compared with sham mode with a two-tailed paired t-test (considered significant when $P < 0.025$; tests were carried out with log-transformed data). Differences between three (talk, listen and standby) modes were tested with one-way rANOVAs (considered significant when $P < 0.05$; tests were carried out with values of the three modes being expressed relative to the value of sham mode in percentages). Significant rANOVA results were followed by a *post hoc* comparison using the SNK ranges test. The testing was repeated for each recording site (**LF**: F3-C3, **LC**: C3-P3, **LP**: P3-O1, **RF**: F4-C4, **RC**: C4-P4, **RP**: P4-O2).

iii) EEG spindle (12-14 Hz / 14-16 Hz power) modulation by 2-4 Hz power during SWS: The standardized regression coefficient (β) and coefficient of determination (R^2) in the simple regression of these two EEG dynamics were computed for each condition in the six EEG recording sites (LF, LC, LP, RF, RC, RP). Both β and R^2 describe the relation between these two EEG activities; in particular, β reveals how strongly the 2-4 Hz power (predictor variable) influences the spindle power (criterion variable) while R^2 indicates the goodness of fit of the regression model. Statistical significance of β for each condition in each recording site was checked by two-tailed *t*-tests of the 95% confidence intervals (where the t values are based on $n-2$ degrees of freedom, $n=9$ in the current case). The *t*-test results were considered significant at *P*-values < 0.025 due to two-tailed tests.

6 EFFECTS ON SLEEP EEG

6.1 INTRODUCTION

6.1.1 Previous Studies of Mobile Phone Effects on Sleep and Sleep EEG

Available human laboratory studies, using double-blind and sham-controlled designs (disentangling physiological effects from psychological influences), have recognized EMFs simulated to the real mobile phone transmission have non-thermal effects on brain physiology. Reported effects include increasing EEG power in the alpha frequency range during resting waking [Croft et al., 2002, 2008; Curcio et al., 2005; Hinrinkus et al., 2008; Huber et al., 2002; Regel et al., 2007a], and in the spindle frequency range during NREM sleep [Mann & Roschke, 1996; Borbély et al., 1999; Huber et al., 2000, 2002, 2003; Loughran et al., 2005; Regel et al., 2007b]. In view of the well-established link between EEG alpha/spindle enhancement and the natural sleep process [for review, see Sec. 2.3.2.2 and 2.3.2.4], these EMF-induced alpha/spindle effects may easily be interpreted as sleep promoting at first glance. However, since most studies showed no concurrent changes in the EEG-determined sleep structure (such as 'shortened sleep latency' or 'reduced waking after sleep onset'), there may be existence of other neurophysiolgical interpretations for the observed alpha/spindle effects. Moreover, spindle enhancement during sleep have not been entirely consistent, with some studies finding the effect varies in terms of particular frequency bands (see Fig. 6.1) and scalp locations, and others failing to replicate effects reported in their earlier studies even with a methodological improvement (e.g., Mann & Rochke's study [1996] could not be replicated in their later studies [Mann et al., 1998; Wagner et al., 2000] with an increased sample size and a homogenous EMF exposure).

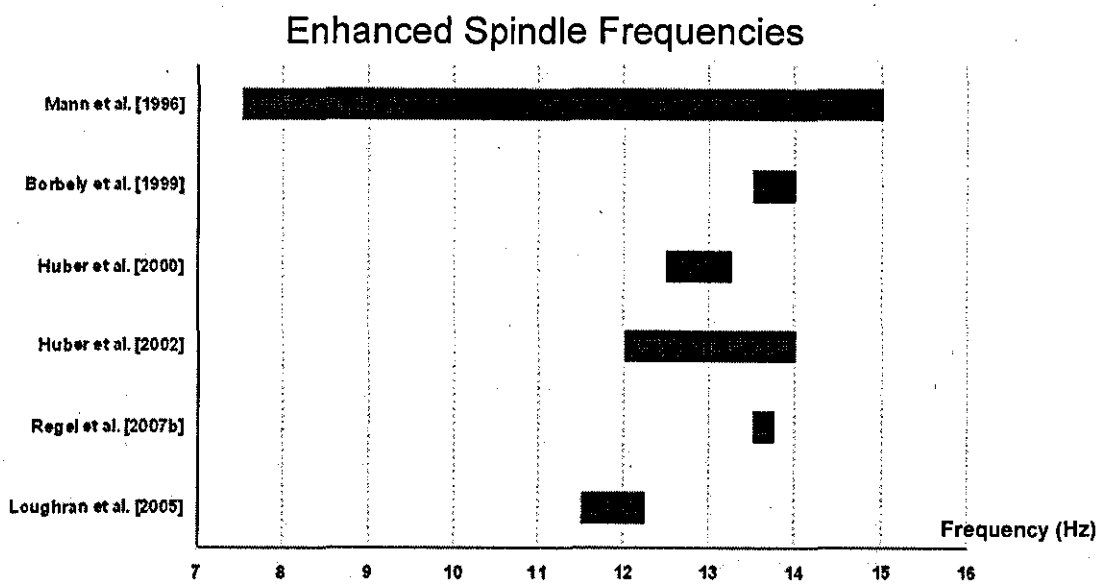

Figure 6. 1 Variances in the enhanced spindle frequencies as reported in different sleep EEG studies.

6.1.2 Our Study and Hypothesis

In our own EEG study of mobile phone EMFs transmitted at talk, listen and standby modes, we have demonstrated mobile phone 'talk-mode' signals induced alerting effects in the process of sleep onset, which was revealed by significantly longer sleep-onset latency after talk-mode exposure in comparisons with sham- or listen-mode exposure (chapter 4). This sleep structure finding of talk vs. sham and talk vs. listen mode also concurred with (i) a dampening of the normal enhancement of frontal-central EEG delta power in the 90-min sleep process after talk-mode exposure (chapter 4); (ii) a reduced frontal-central waking theta power prior to the onset of stage 1 (S1) sleep comparing talk- with sham- and listen-mode condition (chapter 5). Since both sleep delta and waking theta power in the frontal-central area are sensitive to the influence of homeostatically controlled sleep-initiating mechanisms [Finelli et al., 2000], it is suspected the alerting effect of talk mode may have resulted from an attenuated sleep drive on this system. Nevertheless, this was yet to corroborate with changes in the EEG 'during' (stage 2 sleep) and 'after' sleep onset, as other factors (e.g. ineffective closing of thalamic gate and poor sleep maintaining) may also contribute to the talk-mode effect. Furthermore, studies to date haven't paid enough attention to how sleep responds differentially to the waking "plasticity" induced by the three mobile phone signals (Table 6.1), despite these being real signals radiated to almost 2.1 billion users' heads in the world everyday. These handset signals should be of special concern, not only because they are what the human brain is actually

exposed to, but also because they are ELF pulse-modulated ('talk' mode: 8, 217 Hz; 'listen' mode: 2, 8, 217 Hz; 'standby' mode: < 2 Hz). As repetitive TMS at various stimulation frequencies differentially modify the waking cortical excitability [Lemon, 2002] and the subsequent sleep EEG (as mentioned above), we may assume the mobile phone EMF effects on the bioelectrical activity of the human brain is also dependent on the stimulation frequencies. Indeed, human laboratory findings have provided evidence that ELF (i.e. 2, 8, 217 Hz) pulse modulation to be a prerequisite for mobile phone radiofrequency EMFs to induce alternations in brain physiology [Huber et al., 2002; 2005]. However, effects of varying ELF composition corresponding to the real mobile phone EMFs are still under investigation, and cannot be inferred from the previous experimental findings.

The aim of this study was to evaluate the sleep EEG effects of 'talk', 'listen' and 'standby' mode signals on subsequent 90-min sleep using both EEG visual scoring and power spectrum analysis. We assessed the mobile phone signal-induced EEG power change in narrow (1 Hz) frequency bands over the range of 1-16 Hz recorded from six scalp locations (covering the whole head) during the first cycle of NREM sleep, as well as stage 2 (S2), and slow-wave sleep (SWS, a combination of stage 3 and 4 sleep), respectively. It was hoped, through revealing the detailed pictures of sleep EEG spatiotemporal dynamics, that the varying mobile phone ELF pulse-modulation effects on the post-exposure sleep neurophysiology can be more adequately observed. It was also hoped to further elucidate the alerting effect of the talk-mode signal with more theoretical interpretation of the sleep EEG.

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6.4 RESULTS

6.4.1 Sleep Structure

Sleep stage scoring results are presented in Figure 6. 2 and Table 6. 3. One-way rANOVAs (factor: condition) showed a significant effect of 'sleep latency' ($F_{[3, 27]} = 3.4$, $P = 0.031$), 'SWS latency' ($F_{[3, 27]} = 3.62$, $P = 0.025$), 'SWS duration' ($F_{[3, 27]} = 3.0$, $P = 0.046$), and 'sleep efficiency' ($F_{[3, 27]} = 3.2$, $P = 0.038$). Post-hoc comparisons using SNK ranges tests demonstrated that, talk-mode exposure, in comparison with sham-mode exposure, interrupted the succeeding 90-min sleep as evident in 'increased sleep latency' (see chapter 4), 'increased SWS latency', 'reduced SWS duration' and 'decreased sleep efficiency', while the sleep structure after both listen and standby modes showed no change from sham.

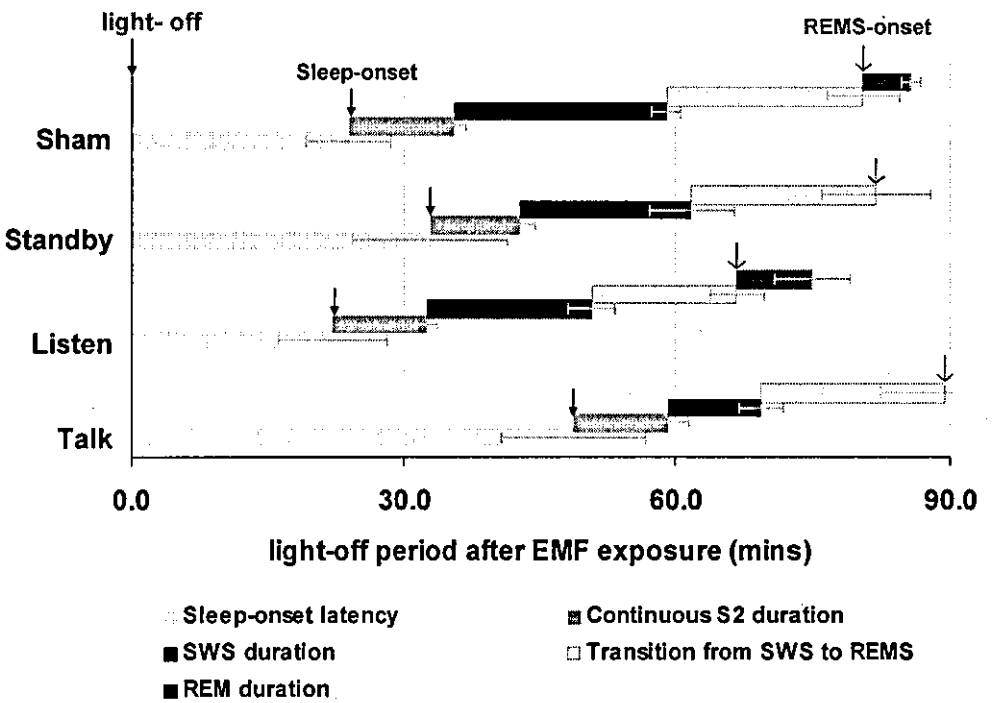


Figure 6. 2 Sleep structure after exposure to 'talk,' 'listen,' 'standby' and 'sham' modes.

Table 6. 3 Effects of 'talk,' 'listen,' 'standby' and 'sham' modes on sleep structure (subject n = 10).

Variables	*Talk*	*Listen*	*Standby*	*Sham*	$F_{[3, 27]}$	P value
Sleep latency (min)	48.8 ± 7.9	22.1 ± 6.1	32.9 ± 8.5	23.8 ± 4.6	3.4	0.031
SWS latency (min)	59.3 ± 7.9	32.5 ± 5.3	42.9 ± 7.9	35.0 ± 3.8	3.6	0.025
S2 duration (min)	11.7 ± 1.4	10.0 ± 1.7	10.5 ± 1.2	10.5 ± 2.3	0.2	0.090
SWS duration (min)	10.2 ± 2.3	18.3 ± 2.6	19.0 ± 4.7	23.5 ± 1.7	3.0	0.046
S3 (min)	8.1 ± 1.4	7.6 ± 1.8	8.1 ± 1.1	5.8 ± 1.6	0.6	0.592
S4 (min)	4.4 ± 1.8	11.4 ± 4.0	10.2 ± 3.0	15.5 ± 2.3	2.5	0.078
REMS latency (min)		44.7 ± 4.6		56.7 ± 4.5		
REMS duration (min)		8.2 ± 4.1		5.2 ± 1.0		
Sleep efficiency (%)	64% ± 9%	79% ± 5%	72% ± 8%	81% ± 5%	3.2	0.038
TST (min)	57.4 ± 8.5	71.1 ± 4.4	64.6 ± 7.4	73.1 ± 4.7	3.2	0.037
TWT (min)	32.5 ± 8.5	18.6 ± 4.4	24.9 ± 7.5	16.6 ± 4.7	3.3	0.035
WBSO (min)	27.2 ± 9.2	11.0 ± 3.5	17.1 ± 6.9	11.2 ± 3.2	2.6	0.076
WASO (min)	5.4 ± 3.2	7.6 ± 2.5	7.9 ± 3.8	5.4 ± 2.1	0.3	0.816

TST: total sleep time; TWT: total waking time; SWS: slow-wave sleep; REMS: rapid-eye-movement sleep; WBSO: waking before sleep onset; WASO: waking after sleep onset.

Additional analysis on SWS composition (Stage 3 + 4 sleep) found no significant effect of condition on time spent in stage 3 ($F_{[3, 27]}$ = 0.6, P = 0.592) or stage 4 sleep ($F_{[3, 27]}$ = 2.5, P = 0.078). However, stage 4 sleep duration was reduction after talk-mode exposure (talk mode: 4.4 ± 1.8 min vs. listen mode: 11.4 ± 4.0 min vs. standby mode: 10.2 ± 3.0 min vs. sham mode: 15.5 ± 2.3 min), although this was just above the acceptable level of significance (P = 0.078).

Owing to the TIB being fixed to 90 min in all conditions, the talk-mode reduction of sleep efficiency (= TST/TIB, in %) apparently resulted from a significant reduction in the TST (talk mode: 32.5 ± 8.5 min, compared with sham mode: 73.1 ± 4.7 min). As the TST is equal to 'TIB-TWT' (see definition in Table 6. 3) while TIB is fixed in this study (90 min), the reduced TST thereby resulted from an increase in the TWT ($F_{[3, 27]}$=3.3, P =0.035, one-way rANOVA). Because the TWT includes waking time spent in both 'before' and 'after' sleep onset (WBSO and WASO), we examined whether varying mobile phone signals could be differentiated by the length of two periods separately. One-way ANOVAs yielded no significant condition effect either with WBSO ($F_{[3, 27]}$=2.6, P = 0.076) or with WASO ($F_{[3, 27]}$=0.3, P = 0.816), albeit data revealed WBSO was slightly longer after 'talk-mode' than 'sham-mode' exposure (talk mode: 27.2 ± 9.2 min vs. sham mode: 11.2 ± 3.2 min, n.s.).

Rapid-eye-movement sleep (REMS) appeared only after listen and sham mode, and both modes did not differ in 'REMS latency' and 'REMS duration' (paired t-tests, P >

0.05). Length of stage 2 sleep was not different between these four modes (one-way ANOVA for repeated measures, $F_{[3, 27]} = 0.2$, $P = 0.090$).

6.4.2 Sleep EEG Spectra

6.4.2.1 EEG 1-4 Hz Power during S2 and SWS Periods

EEG 1-4 Hz power during S2 and SWS at the six recording sites after talk, listen and standby-mode exposures was expressed as a percentage of 'sham mode' (=100%), as illustrated in Figure 6. 3 and Figure 6. 4. Compared with sham-mode, none of the three modes significantly changed the EEG 1-4 Hz power at the six brain regions either during S2 or during SWS period (all *P*-values > 0.025, 18 two-tailed paired t-tests, Figure 6. 3, *top*: S2, *bottom*: SWS). Assessing the difference between the three modes, one-way rANOVAs on the relative EEG 1-4 Hz power values at each recording site and sleep state yielded no significant conditional difference during S2 (Figure 6. 3, top, $F_{[2, 16]}$ at least 0.05, *P* at least 0.951) or SWS (Figure 6. 3, bottom, $F_{[2, 16]}$ at least 0.44, *P* at least 0.652).

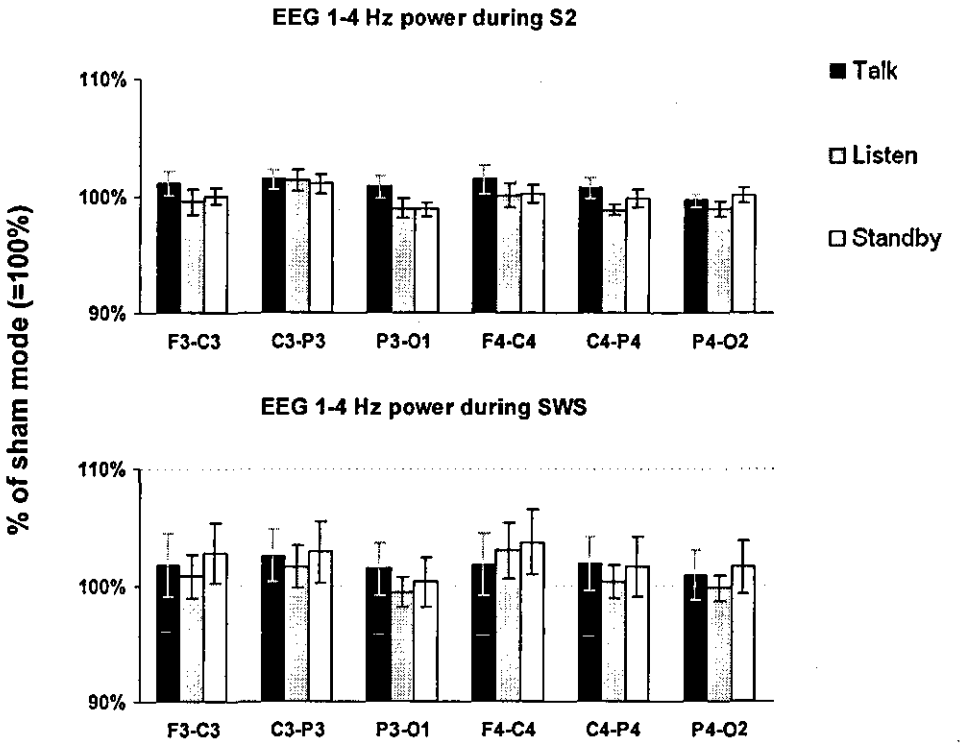


Figure 6. 3 Relative EEG 1-4 Hz power (mean ± s.e. m.) in six EEG derivations during S2 (top) and SWS period (bottom) after 'talk,' 'listen,' and 'standby' modes (values are expressed as '% of sham,' 100% = sham-mode exposure)

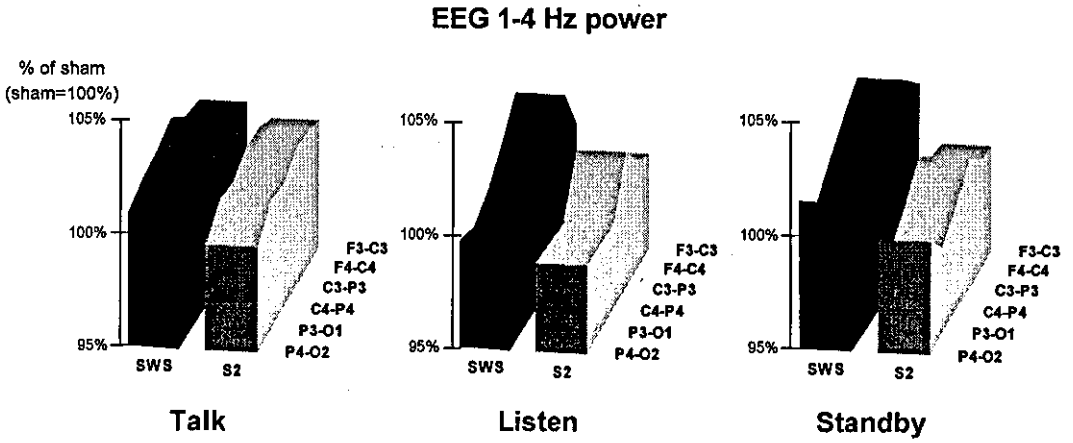


Figure 6. 4 Comparisons of S2 and SWS EEG 1-4 Hz power change after talk, listen and standby mode (values are expressed as '% of sham,' 100% = sham-mode exposure) at six recording sites

Figure 6. 4 shows that the normal EEG 1-4 Hz power enhancement from S2 to SWS in every recording region, for talk-, listen- and standby-mode condition. A two-way rANOVA on the mean % delta increases from S2 to SWS (sham-mode adjusted values) with the factors 'EEG derivation' (six recording sites) and 'exposure condition' (talk, listen and standby modes) revealed no 'main' (factor 'EEG derivation': $F_{[5,40]}$ = 1.568, P = 0.191; factor 'exposure condition': $F_{[2,16]}$ = 0.668, P = 0.527) or 'interaction' effects ($F_{[10,80]}$ = 1.329, P = 0.230). This suggested the normal delta enhancing from S2 to SWS was not topographically different and was not different between modes.

As the EEG 1-4 Hz power during S2 and SWS, as well as the delta enhancing from S2 to SWS, was not different from sham-mode for each mode, this verified that our EEG visual scoring of the onset time of S2 and SWS sleep was valid, and determined by the same criteria among conditions.

6.4.2.2 EEG Spectrum in 1-Hz Bins across the Range of 1-16 Hz

First NREM Sleep Cycle

The mobile phone effects on the EEG power spectra across the 1-16 Hz frequency range during the first NREM sleep cycle are summarized in Table 6. 4. Comparing with 'sham' mode, the 'standby' mode bolstered EEG 11-16 Hz power at the left central region (EEG derivation: C3-P3) and attenuated EEG 8-10 & 13-15 Hz power at the left parietal region (EEG derivation: P3-O1) in seven out of nine participants. 'Listen' mode, when compared with sham mode, increased EEG 11-12 Hz power at both left central region (EEG derivation: C3-P3) and right frontal region (EEG

derivation: F4-C4) while the 7-8 Hz power at the left central region was also enhanced. There was no observable difference from sham mode after 'talk' mode exposure on the power spectra during the first NREM sleep period.

Assessing the difference between the three active modes, EEG 12-13 Hz power at the left central region (EEG derivation: C3-P3) during this period showed an effect of condition, as revealed by less power after 'talk' mode exposure in comparison with 'standby' mode exposure (SNK ranges test, conducted when the one-way rANOVA showed a significant 'between-condition' difference, $F_{[2, 16]} = 3.87$, $P = 0.043$).

Table 6. 4 Mobile phone effects on the EEG spectra during the first NREM sleep

					Talk vs. Listen vs. Standby	
Recording site	**EEG rhythm (Hz)**	**Talk vs. Sham**	**Listen vs. Sham**	**Standby vs. Sham**	**$F_{[2,16]}$ (*P*-value)**	***post hoc* comparison**
LC	**7-8**	-	↑ (p=0.011, n=7)	-	-	-
	10-11	-	-	↑ (p=0.017, n=7)	-	-
	11-12	-	↑ (p=0.017, n=6)	↑ (p=0.007, n=9)	-	-
	12-13	-	-	↑ (p=0.005, n=7)	3.87 (0.043)	Standby > Talk
	14-15	-	-	↑ (p=0.009, n=8)	-	-
	15-16	-	-	↑ (p=0.003, n=9)	-	-
LP	**8-9**	-	-	↓ (p=0.013, n=8)	-	-
	9-10	-	-	↓ (p=0.016, n=8)	-	-
	13-14	-	-	↓ (p=0.003, n=8)	-	-
	14-15	-	-	↓ (p=0.021, n=8)	-	-
RF	**11-12**	-	↑ (p=0.017, n=7)		-	-

↑: power increasing from sham, ↓: power decreasing from sham, -: no power change from sham, as indicated by two-tailed paired t-tests comparing exposure modes with sham-mode, with P-values and replication number (n) of participants shown in parentheses, considered significant when $P < 0.025$.

It should be noted that EEG power spectra of the first NREM sleep cycle integrated spectral components of both S2 and SWS EEG. Therefore, if the effect was reversed between S2 and SWS, NREM EEG spectra would not be able to detect any effect. To

partial out this confound, further EEG spectral analysis was separated for S2 and SWS recordings.

S2 and SWS

Figure 6. 5 depicts the relative EEG spectra (across 1-16 Hz range) during S2 and SWS at six derivations after talk, listen and standby-mode exposures, with data being expressed as a percentage of 'sham-mode' (= 100%). Frequency bins showing significant paired t-test results between 'exposure' and 'sham' modes are summarized in Table 6. 5 and also indicated by 'asterisks' (for S2 EEG spectra) and symbol 'plus' (for SWS EEG spectra) in Figure 6. 5. Power difference between S2 and SWS for each bin was compared between 'exposure' and 'sham' mode by two-tailed paired t-tests (consider significant at P-values < 0.025), replicated for each mode and for each recording site. Frequency bins showing significant S2-SWS power difference are presented with gray-shaded bars in Figure 6. 5.

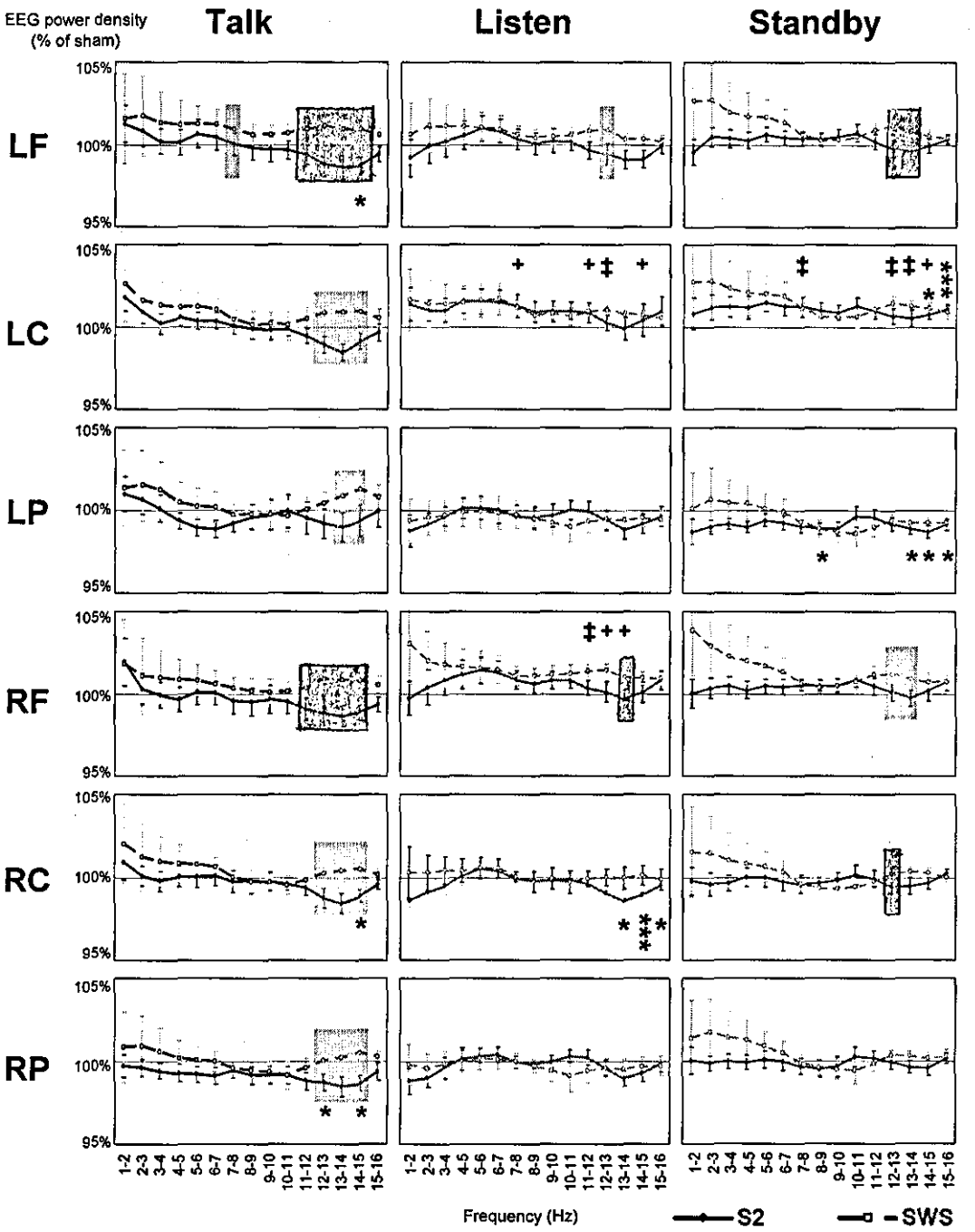


Figure 6. 5 Mobile Phone effects on the S2 and SWS EEG spectra in the 1-16 Hz range.[17]

[17] Relative EEG spectrum (Mean ± S.E.M. for 1-Hz bins, n = 9) of S2 and SWS episodes are depicted with real (S2) and broken (SWS) curves in the six derivations (LF, LC, LP, RF, RC, RP) for the three exposure modes, expressed as a percentage of the corresponding value of sham exposure (= 100%). Shaded areas indicated significant power increasing from S2 to SWS, compared with the power difference between these two states after sham-mode exposure. The P-values of two-tailed paired t-tests between 'exposure' and 'sham' mode for single bins were denoted by *P* value key * (for S2 episode) and + (for SWS episode) in each panel (* & +: $0.01 \leq P < 0.025$; ** & ‡: $0.001 \leq P < 0.01$; ***: $0 \leq P < 0.001$). EEG derivations LF: F3-C3; LC: C3-P3; LP:P3-O1; RF: F4-C4; RC: C4-P4; RP: P4-O2.

Table 6. 5 Significant mobile phone effects on the S2 and SWS EEG spectra.

		S2			SWS		
EEG derivation	EEG rhythm (Hz)	Talk	Listen	Standby	Talk	Listen	Standby
LF	14-15	↓(0.016)					
LC	7-8					↑ (0.022)	↑ (0.005)
	11-12					↑ (0.023)	
	12-13					↑ (0.003)	↑ (0.005)
	13-14						↑ (0.001)
	14-15			↑ (0.021)		↑ (0.023)	↑ (0.013)
	15-16			↑ (0.007)			
LP	8-9			↓ (0.021)			
	§13-14			↓ (0.017)			
	§14-15			↓ (0.010)			
	§15-16			↓ (0.017)			
RF	11-12					↑ (0.005)	
	12-13					↑ (0.011)	
	13-14					↑ (0.021)	
	¥14-15						
	¥15-16						
RC	13-14		↓ (0.011)				
	14-15	↓ (0.010)	↓ (0.0003)				
	*15-16		↓ (0.013)				
RP	¥11-12						
	12-13	↓ (0.011)					
	14-15	↓(0.021)					

↑: power increasing from sham, ↓: power decreasing from sham, -: no power change from sham, as indicated by two-tailed paired t-tests comparing exposure modes with sham-mode, with *P*-values and replication number (n) of participants shown in parentheses, considered significant when $P < 0.025$.

The differences between three exposure modes in the EEG spectra of S2 and SWS were assessed by one-way rANOVAs with the factor 'condition' using relative EEG power values (expressed as a percentage of the sham-mode condition). Significant rANOVA results (see text for P values) were followed by post hoc comparisons using SNK ranges tests. Results of SNK ranges tests were denoted by the following symbols (§,¥,*).
§ talk > listen = standby during SWS
¥ talk < listen = standby during S2
* talk = listen < standby during S2

As shown in Figure 6. 5 and Table 6. 5, S2 and SWS EEG power was significantly reverse at spindle frequency ranges (12-15 Hz) in all recording regions and also at alpha frequencies (7-8 and 11-12 Hz) in the left frontal region after talk-mode exposure. This opposite effect with S2 and SWS spindle after 'talk-mode' exposure was due to spindle power was reduced during S2 but returned to baseline (T0) level during SWS. A decrease in S2 spindle power (from sham-mode) was observed in the whole head but was more pronounced at the EEG 14-15 Hz bin in the left frontal (EEG derivation: F3-C3), right central (EEG derivation: C4-P4), right parietal (EEG derivation: P4-O2) regions, and also at the EEG 12-13 Hz bin in the right parietal region (EEG derivation: P4-O2) (talk mode in Figure 6. 5 and Table 6. 5). Since S2

spindles is a hallmark of cortical disconnection during sleep onset as the thalamic gate for sensory transmission would be closed in this period [McCormick & Bal, 1994; Steriade et al., 1990b], the global attenuation of S2 spindle power after 'talk-mode' exposure suggests this mode may diminish the probability in closing the thalamic gate necessary to provoke sleep-onset.

The S2-SWS EEG spindle power difference was also present after both 'listen' and 'standby' mode exposures (see Figure 6. 5, shaded areas in the 'middle' and 'right' columns). However, this was different to those induced by talk-mode, as (i) its occurrence was restricted at the frontal-central region (EEG derivations: F3-C3, F4-C4); and (ii) its occurrence was due to an increase of SWS spindle power (with S2 spindle power was of no change or increase in these brain regions) when comparing with sham-mode condition.

Note that the increased SWS EEG spindle power in both 'listen' and 'standby' modes did not displace or replace the delta sleep, as both the stage 3 and 4 sleep duration (Table 6. 3) as well as the SWS EEG 1-4 Hz power (Figure 6. 3, lower panel) were not affected when compared with sham-mode condition. Neither did the increased spindle power during SWS show evidence of sleep disturbance or sleep continuity disruption, as the WASO was not enhanced in these two conditions (Table 6. 3). Subjectively, the participants' self-reported sleep quality in the 90-min nap was of no difference to the sham-mode condition (with no indication of non-refreshing or non-restorative sleep, data not shown). These state and behavioural correlates (e.g. enhancement to stimulation during pre-sleep wakefulness, concentration in the first-cycle of NREM sleep, and the absence of sleep disturbances), together with its scalp distribution (frontal-central), are consistent with the activation of a process such as the one hypothesized, which is maximal early in the night and is characterized by increased frontal-central SWS EEG alpha activities associated with 'sleep maintaining process' [ref. Pivik et al., 1995].

Beyond the frontal-central regions, the S2 EEG spindle (13-16 Hz) power after 'listen-mode' exposure was diminished from baseline at the central-parietal region of the right hemisphere (EEG derivation: C4-P4). For the 'standby-mode' condition, the S2 spindle power (14-16 Hz) was enhanced at the central-parietal region (EEG derivation: C3-P3) but decreased (8-9 and 13-16 Hz) at the parietal-occipital region (EEG derivation P3-O1) of the left hemisphere, all compared with sham-mode. During SWS, the spindle power at the left central-parietal region (EEG derivation C3-P3) was

significantly enhanced from baseline after exposure to both modes. The reduced S2 spindle power at the right central-parietal regions (after 'listen-mode' exposure) and at the left parietal-occipital region (after 'standby-mode' exposure) was also compensated and recovered to the baseline level during SWS (Table 6. 3; Figure 6. 3). These S2 and SWS EEG spectrum effects, when combined together, contributed to the NREM EEG spectral effects of both 'listen' and 'standby' mode (see Table 6. 4).

In addition, one-way rANOVAs on the S2 and SWS EEG relative power in the frequency bins between 1-16 Hz at six recording sites were computed with factor 'condition' (talk, listen and standby modes) to access any difference between the three modes. Significant differences were found in the S2 EEG spindle frequency range at the right-hemisphere derivations (RF, 14-16 Hz range: $F_{[2,16]}$ at least 4.14, $P < 0.030$; RC, 15-16 Hz bin: $F_{[2,16]} = 6.23$, $P = 0.028$; RP, 11-12 Hz bin: $F_{[2,16]} = 4.52$, $P = 0.028$) and in the SWS EEG spindle frequency range at the left parietal region (LP: 13-16 Hz range: $F_{[2,16]}$ at least 3.82, $P < 0.044$). Post hoc comparisons with SNK range tests revealed this difference was due to a higher S2 EEG spindle power at the right hemisphere and a lower SWS EEG spindle power at the left parietal region after 'standby-mode' than 'talk-mode' exposure and (Table 6. 5).

6.4.2.3 Interaction between EEG Spindle (12-14 Hz/14-16 Hz) and Delta (2-4 Hz) Activities during SWS

Figure 6. 6 and Figure 6. 7 illustrate the 95 % confidence intervals and significance test results of the standardized regression coefficient (β) of the simple regression lines computed by spindle activities (12-14 Hz / 14-16 Hz power, 'criterion variable') and 2-4 Hz oscillation ('predictor variable') during SWS in the six brain recording sites (LF, RF, LC, RC, LP, RP) after exposure to 'talk', 'listen', 'standby' and 'sham' modes. The goodness fit of each regression, indicated by the coefficient of determination (R^2) between these two EEG dynamics, was calculated for each recording site in Table 6. 6 and Table 6. 7.

Significant tests of β in the simple regression between 12-14 and 2-4 Hz SWS EEG power (Figure 6. 6, two-tailed t-tests of the 95 % confidence interval, considered significant when P-values < 0.025) after 'sham-mode' exposure showed a significant positive correlation in the trends of both 12-14 Hz and 2-4 Hz SWS EEG power in the bilateral frontal regions (LF: $P = 0.008$; RF: $P = 0.006$), where R^2 of these two EEG activities approached 0.7 (LF: $R^2 = 0.653$; RF: $R^2 = 0.685$, Table 6. 6). After exposure

to 'talk' and 'standby' mode, the positive correlations between these two EEG activities enhanced variation in the 95 % of data distribution, thereby reducing the probability of significance detection in the present analysis (Figure 6. 6). Listen-mode, however, conserved the positive correlation in the frontal region (i.e., LF: P = 0.016, R^2 = 0.589, Figure 6. 6, Table 6. 6). The significant relationship between these two SWS EEG dynamics was more pronounced specifically in the posterior recording regions (LC: P = 0.007, R^2 = 0.589; RC: P = 0.003, R^2 = 0.736; LP: P = 0.007, R^2 = 0.676; RP: P = 0.001, R^2 = 0.815, Figure 6. 6, Table 6. 6). However, since the confidence intervals of β values were overlapped in both 'listen' and 'sham' mode, the strong interaction of EEG 2-4 Hz power and 12-14 Hz power was not statistically different between listen and sham modes.

As for the β in the simple regression between 14-16 and 2-4 Hz SWS EEG power (Figure 6. 7, two-tailed t-tests of the 95% confidence interval, considered significant when P-values < 0.025), none of the β values in the six recording regions showed significant results after exposure to 'sham', 'talk' and 'standby' modes. Only after listen-mode exposure, the confidence intervals of β values in the bilateral central and parietal regions did significantly deviate from 0 in the positive direction (LC, P = 0.002; LP, P = 0.005; RC and RP, both P = 0.001, Figure 6. 7), indicating a strong positive correlation between 14-16 Hz and 2-4 Hz EEG activities in these regions during SWS. Especially at the right parietal region (RP, Figure 6. 7), the 95% confidence levels of β reached a statistically significant difference from sham-mode condition, because the lower-limit (= 0.629) of the confidence level in the listen-mode condition was higher than the upper-limit (= 0.554) of that in the sham-mode condition. R^2 at the RP region was also substantially higher in listen-mode (R^2 = 0.828) rather than sham-mode condition (R^2 = 0.149, see Table 6. 7). These findings suggest that, during SWS, listen-mode enhanced the interaction between delta (2-4 Hz) and spindle (14-16 Hz) activities at the posterior brain regions, particularly pronounced at the parietal-occipital region which was near the source of exposure.

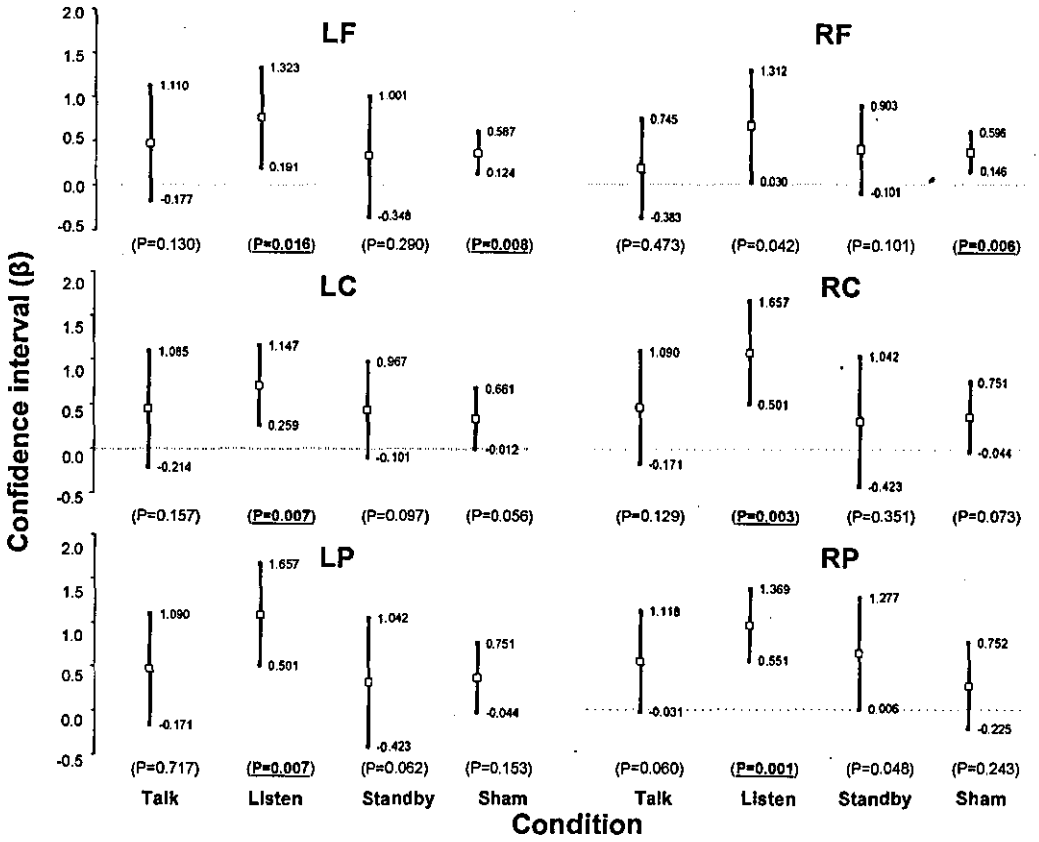


Figure 6. 6 **Confidence intervals (thick lines with upper 95%-limit, lower 95%-limit and mean values) of the standardized regression coefficient (β) in the simple regression of SWS EEG 12-14 Hz and 2-4 Hz power in each condition (talk, listen, standby and sham modes) at the 6 derivations (LF, LC, LP, RF, RC, RP). Significance tests for β were done by two-tailed t-tests (degree of freedom = 7) and results (*P*-values) are shown in parentheses (considered significant when *P*-values < 0.025, marked by underscore).**

Table 6. 6 **Coefficients of determination (R^2) in the simple regression of EEG 12-14 Hz power and 2-4 Hz power in each condition (talk, listen, standby and sham modes), 6 derivations (LF, LC, LP, RF, RC, RP) during SWS.**

Recording site	Talk	Listen	Standby	Sham
LF	0.295	0.589	0.158	0.653
RF	0.076	0.467	0.338	0.685
LC	0.264	0.667	0.344	0.427
RC	0.298	0.736	0.125	0.388
LP	0.020	0.676	0.413	0.268
RP	0.417	0.815	0.449	0.189

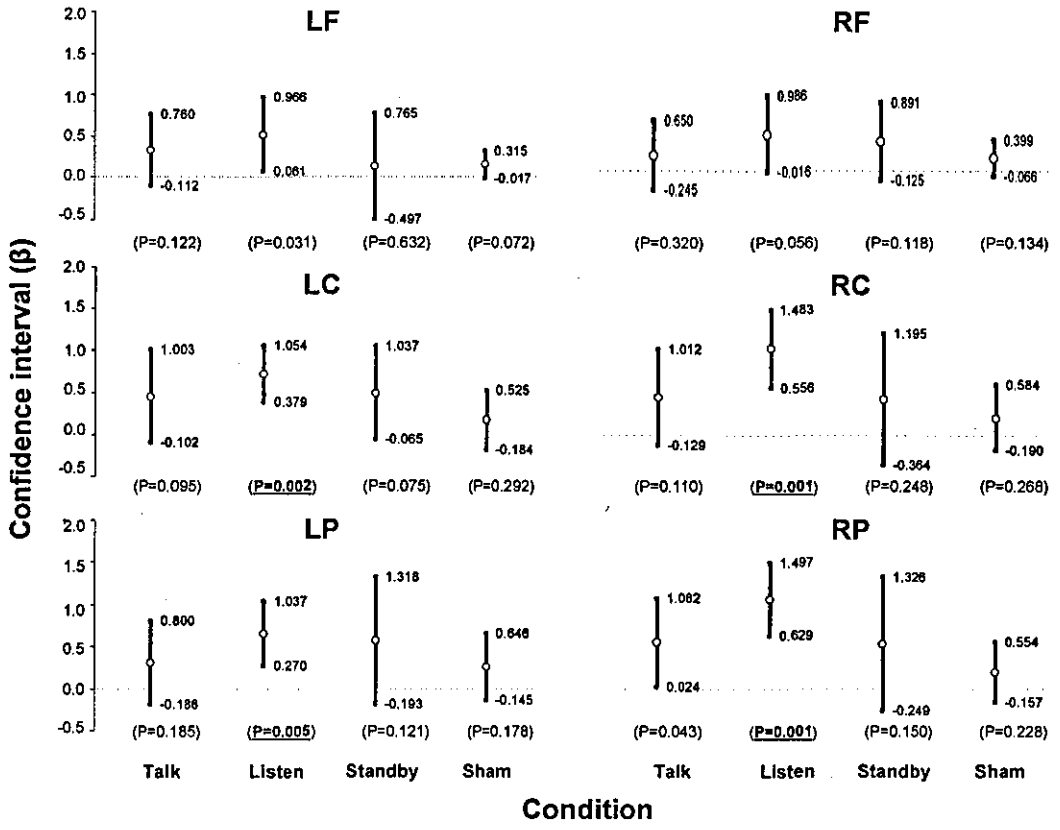


Figure 6. 7 **Confidence intervals (thick lines with upper 95%-limit, lower 95%-limit and mean values) of the standardized regression coefficient (β) in the simple regression of SWS EEG 14-16 Hz and 2-4 Hz power in each condition (talk, listen, standby and sham modes) at the 6 derivations (LF, LC, LP, RF, RC, RP). Significance tests for β were done by two-tailed t-tests (degree of freedom = 7) and results (*P*-values) are shown in parentheses (considered significant when *P*-values < 0.025, marked by underscore).**

Table 6. 7 **Coefficients of determination (R^2) in the simple regression of SWS EEG 14-16 and 2-4 Hz power in each condition (talk, listen, standby and sham modes) at 6 derivations (LF, LC, LP, RF, RC, RP).**

Recording site	Talk	Listen	Standby	Sham
LF	0.307	0.507	0.035	0.390
RF	0.141	0.428	0.312	0.290
LC	0.347	0.783	0.383	0.156
RC	0.323	0.794	0.185	0.172
LP	0.236	0.699	0.307	0.242
RP	0.466	0.828	0.272	0.149

6.5 DISCUSSION

6.5.1 Summary of Current Sleep/Resting Waking EEG Findings

In this and the previous two chapters, we have analyzed EEG effects of three ELF pulse-modulated mobile phone signals ('talk', 'listen' and 'standby' modes) with EEG visual scoring and topographic EEG power distribution during resting waking (before the appearance of S1), S2 and SWS. Table 6.8 summarizes the major findings of sleep/waking EEG effects for each mobile phone signal (in comparison with sham mode).

Table 6. 8 Summary of sleep/waking EEG effects of 'talk,' 'listen,' and 'standby' mode, comparing with sham-mode effects.

Methods	Sleep/Waking EEG effects	Talk (8, 217 Hz)	Listen (2, 8, 217 Hz)	Standby (< 2 Hz)
EEG visual scoring of sleep structure	1. Sleep onset	**delayed**	-	-
EEG spectral analysis	2. Temporal increase of delta (1-4 Hz) power **[sleep pressure]** across the 90-min sleep	**delayed**	-	-
	3. Resting waking EEG before onset of stage 1 sleep: frontal-central theta power **[sleepiness]**	↓	-	-
	4. S2: spindle power **[cortical disconnection]**	↓ **(all channels)**	↓ **(only C4-P4)**	↑ **(only C3-P3) &** ↓ **(only P3-O1)**
	5. SWS: frontal-central spindle power **[sleep preservation]**	-	↑	↑

ELF pulse modulation components of each signal is indicated in the parenthesis.

6.5.2 Opposite Sleep EEG Effects between Talk Mode ('Alerting') and Listen/Standby Mode ('Sleep Preservation')

Current results indicated that the talk-mode (8, 217 Hz pulse-modulated) signal attenuated the subsequent global spindle activities during S2 (result 4 in Table 6. 8). This suggested an alerting effect of talk mode on sleep initiation, referring S2 spindle activities to the inhibition of thalamic sensory gating which means to prevent arousing stimuli from reaching the cortex during the transition from waking to sleep [McCormick & Bal, 1994; Steriade et al., 1990b]. This result was concurred with other EEG signs of increased vigilance after the talk-mode exposure, such as a delayed visually-scored EEG sleep-onset time, a dampening of sleep pressure increasing [EEG index of sleep pressure: delta (1-4 Hz) power; cf. Werth et al., 1997; De Gennaro et al., 2001a] and reduced sleepiness before falling asleep [EEG index of sleepiness: resting waking theta (4-7 Hz) power, cf. Strijkstra et al., 2003] (result 1, 3, 4 in Table 6. 8). By contrast, listen (2, 8, 217 Hz pulse-modulated) and standby (< 2 Hz pulsed modulated) modes induced only 'local' spindle power attenuation during S2 (result 4 in Table 6. 8), not global effect. Furthermore, these two modes did not change the sleep onset time, the normally increasing trend of sleepiness during the 90-min nap, or the pre-sleep sleepiness level from the sham-mode condition (result 1, 3, 4 in Table 6. 8). These EEG results suggest talk and listen/standby mode have opposite effects for sleep initiation, whereby the talk-mode showed an 'alerting' effect whilst the listen/standby mode showed 'no' effect in the process of sleep onset (all comparing with sham-mode condition).

In addition, the EEG spectrum during SWS post-exposure also indicated an opposite effect between the talk and listen/standby mode signals (result 5 in Table 6. 8). Whilst no EEG effect was found after the talk-mode exposure during this consolidated sleep period, enhancement of frontal-central spindle power without delta sleep being displaced or replaced was found after the listen/standby mode exposure (comparing with sham mode, result 5 in Table 6. 8). Such SWS EEG feature of listen/standby mode suggested activation of a process similar to the one characterized by increased frontal-central SWS alpha activities (called 'alpha-delta sleep'), which is associated with effects of 'sleep preservation' [for review, see Section 2.3.2.2: *NREM Frontal-Central Alpha (8-12 Hz) Activity*].

It is noteworthy that the present listen-mode effects on the sleep EEG are in line with the observed outcomes of a prior study [Huber et al., 2000]. That study with a 30-min

exposure to the GSM 'base-station-like' signal (sharing the same low-frequency components with our 'listen mode' at 2, 8, 217 Hz but with more low-frequency spectral power) before a 3-h day sleep in healthy young males reported no influence on the global sleep architecture but an increase of spindle (9.75-11.25 Hz and 12-13.25 Hz) power in the first 30-min NREM sleep (stage 2, 3, 4) for the central derivations (EEG derivations: C3-A2 and C4-A1) without an apparent lateralization effect (after either right or left stimulation). To the extent that our low-frequency pulsing characteristics and findings with listen mode seem to reproduce those of Huber et al., and with a similar experimental listen-mode protocol, we believe that the findings from our unique incorporation of talk and standby mode, are not random effects, and thus the difference between talk and listen/standby effects on the sleep-onset and SWS seem to be real.

6.5.3 Opposite Effects of the Modulation Characteristics of the Mobile Phone Signals: 2 Hz vs. 8 and 217 Hz?

Because the time-averaged SAR of the talk (0.133 W/kg), listen (0.015 W/kg) and standby mode (≈ 0 W/kg) are far below the ICNIRP [1998] recommended limit (2 W/kg per 10 g of tissue), the current sleep EEG results cannot be attributed to thermal action [Hirata and Shiozawa 2003], especially when this effect may be rapidly compensated for by the thermostabilizing properties of the blood circulating in the brain [Adair & Black, 2003]. On such grounds, consistent evidence accumulates that pulse modulation is a pre-requisite for RF EMFs to induce EEG effects [Huber et al., 2002; Huber et al., 2005; Regel et al., 2007a] while the pulse modulation frequencies of mobile phone signals are found to correspond to the frequencies of sleep EEG oscillations (such as brain delta and alpha waves). Accordingly, it is possible the brain is able to recognize and respond to the ELF components of the mobile phone signals. Supporting evidence comes from repetitively reported NREM sleep EEG alpha and spindle effects of the 2, 8 and 217-Hz pulse-modulated RF EMF exposure [present research; Borbély et al., 1999; Huber et al., 2000, 2002, 2003; Regel et al., 2007a]. Furthermore, since bi- as well as unilateral exposure of the cortex with the 2, 8 and 217-Hz pulsed modulated RF EMFs caused changes in the sleep EEG of both hemispheres [Huber et al., 2000, 2003], it was hypothesized the lower-dose SAR present at the non-exposed hemisphere may have been sufficient for a maximal effects [Huber et al., 2003]. Nevertheless, this hypothesis was rejected by the same research group in their later study where they found a dose-response relationship

between the SAR dosage and the stage 2 sleep spindle power: spectral power in the fast spindle frequency range (13.5-13.75 Hz) increased by 7.7 % after the RF EMF exposure at a 10 g-averaged peak SAR of 0.2 W/kg, 10 % after exposure at 1 W/kg, and 13.6% after exposure at 5 W/Kg [Regel et al., 2007b]. In view of this dose-dependent effect, it is believed that the nominal SARs of our talk-, listen- and standby-mode signals may be secondary to the varying ELF composition of these signals accounting for the current sleep EEG effects.

Indeed, it is quite possible that a single frequency component or a mixture of components of the ELF pulse modulation may be responsible for the observed opposite effects between talk and listen/standby mode on the EEG for sleep initiation and sleep consolidation. Although the actual mechanisms are unknown, it is suspected that the 2, 8 and 217 Hz pulsing have distinctive effects on neuronal excitability, which may in turn modify the thalamo-cortical oscillation modes and thus impart inverse effects of talk mode (with 8 and 217 Hz pulsing) and listen mode (with 2, 8 and 217 Hz pulsing) on the post-exposure sleep EEG structure. To be more specific, given both talk and listen mode signals share the same low-frequency pulsing at 8 and 217 Hz whilst the listen mode has an extra 2 Hz pulsing and induce opposite sleep EEG effects as mentioned above, it seems reasonable to suppose the effects induced by the 2 Hz pulsing may have counteracted those induced by the 8 and 217 Hz pulsing and thereby bring about an opposite EEG effects to the talk mode signal.

Future investigations should put emphasis on the mechanism of cellular effects of varying mobile phone ELF components, as it would provide additional understanding in their macroscopic influences on the thalamocortical oscillations to validate the present argument. In line with this view, a recent study [Ferrara et al., 2006] has used transcranial magnetic stimulation to investigate the after effect of a 45-min exposure to a GSM900 MHz with 217 Hz modulation. A neuro-excitatory effect was reported on motor neurons adjacent to the exposure area.

6.5.4 Listen Mode Effect (I): Boosting Post-Exposure Sleep Slow Oscillations?

In this study, mobile phone talk-, listen- and standby-mode effects were also examined by looking at the modulation of EEG sigma activities (12-14 Hz and 14-16 Hz) by delta activities (2-4 Hz) during SWS. Results obtained from simple regression

of these two EEG rhythms showed that, specifically after listen-mode exposure, the EEG sigma activity falling at the spindle frequency range (14-16 Hz) seemed to be modulated by delta activity (2-4 Hz) with a strong positive correlation in the centro-parietal-occipital areas (EEG derivations: C3-P3, P3-O1, C4-P4, P4-O2, all $R2 \geq 0.70$, see Table 6.7). Although the exact neurological meaning of such strong spindle-delta synchronization requires further investigation, this result suggests a yet slower (< 1 Hz) oscillatory pattern known as 'cortically-generated slow oscillations' during SWS [Achermann & Borbely, 1997; Amzica & Steriade, 1998] might be enhanced in concert with the rise and fall of the sleep spindles and delta waves. This speculation is mainly due to these three sleep rhythms, which emanated from the thalamus (such as spindles) or neocortex (the slow oscillations) after their complete disconnection, being coalesced via the reciprocal loops between the neocortex and thalamus [Contreras et al., 1996 a, b; Steriade et al., 1993 b, c].

According to Steriade and coworkers [1996], the slow oscillation is the most fundamental cellular event underlying sleep activity, which have the ability to trigger and group cortical network firing corresponding to activities in the sigma (12-16 Hz) and gamma range (> 20 Hz). The hyperpolarizing phase of the depth recorded slow oscillation (down-state) is associated with a global dysfacilitation in corticothalamic networks, resulting in reduced neural firing. The depolarizing phase (up-state), on the other hand, was found to be accompanied by a corticothalamic facilitation of neural firing. Of note is that the alternation of up- and down-states in cortical neurons have been found to be involved in memory consolidation [Sejnowski & Destexhe, 2000; Steriade & Timofeev, 2003], synaptic homeostasis [Tononi & Cirelli, 2006], and the restorative function of sleep [Borbély & Achermann, 2005; Walsh et al., 2006]. Viewed in this light, the ability of the listen-mode signal to trigger slow oscillations could have important neurological implications. The most obvious one is that it may potentiate the endogenous sleep rhythms noninvasively and nonpharmacologically. This can be seen as indirect evidence to reconfirm the listen-mode effect on 'sleep preservation.

6.5.5 Indexing Waking Brain Plasticity Induced by Pre-Sleep Mobile Phone Exposure with Subsequent Sleep EEG?

It should be brought to attention that the post-exposure sleep EEG effects of (i) listen- and standby-mode signals on increasing SWS spindle power, and of (ii) listen-mode signals on enhancing the post-exposure SWS delta and spindle synchronization may

reflect the waking brain plasticity[18] in thalamocortical / cortico-cortical networks induced by pre-sleep EMF exposure. Recent converging evidence, from the molecular, behavioural and electrophysiological level, has showed that brain plasticity is a continuous process from waking to sleep [for review, see Frank & Benington, 2006]. Furthermore, a wide range of data has suggested the amount of neural plasticity occurred during prior waking leads to changes in sleep regulation as reflected by selective increase in the duration of a certain sleep stage and/or modifications to electrophysiological and/or metabolic brain patterns in specific sleep state. For example, whereas auditory deprivation caused a diminishing in SWS duration [Pedemonte et al., 1997], prolonged waking-auditory stimulation led to an increase in SWS duration [Cantero et al., 2002a] as well as an increase in EEG parietal spindle and whole-head alpha power [Cantero et al., 2002b]. Learning before sleep modulates the regional expression of slow wave activity (SWA) [Huber et al., 2004, 2006] and spindle density [Gais et al., 2002] during subsequent non-rapid eye movement (NREM) sleep, particularly in those cortical regions that were initially involved in learning. Low-frequency transcranial magnetic stimulation (TMS) induced long-term potentiation (LTP)-like facilitation or long-term depression (LTD)-like suppression of regional cortical plasticity during wakefulness was also highly associated with the local regulation of SWA [Huber et al., 2007; Huber et al., 2008; De Gennaro et al., 2008] and sleep spindle density/power during the subsequent NREM sleep [Bergmann et al., 2008]. The latest low-frequency TMS studies [i.e. Huber et al., 2007 and 2008; De Gennaro et al., 2008; Bergmann et al., 2008] are similar with the current mobile phone study in applying transcranial EMF of oscillating potentials within the frequency range that the brain naturally employs in its communication network, which are actually of important referring values here. These studies may also imply the oscillation modes of the thalamo-cortical network could be modulated by synchronizing EMF stimulation frequencies and sleep/waking EEG rhythms.

6.5.6 Interim Summary of Findings in this Chapter

This chapter presents the post-exposure effects of 'talk,' 'listen' and 'standby' mode signals on the EEG spectrum of S2 and SWS in the subsequent 90-min sleep opportunity. Results suggest ***opposite*** *effects between 'talk' and 'listen/standby' mode for sleep onset and sleep consolidation.* These are evidenced by:

[18] Brain plasticity, in general, means an alternation in neuronal properties resulting from experiences, which may evolve from transient changes to permanent formation of new connections [Steriade & Timofeev, 2003].

- ***Opposite*** effects on the cortical disconnection-associated S2 spindle (12-15 Hz) for sleep onset: 'talk mode' induced a ***global*** spindle power decrement whereas 'listen' and 'standby' modes reduced spindle power only in the ***local*** region (EEG derivation: C4-P4 for listen mode, C3-P3 for standby mode). It was suggested that this may be that the inhibition of the thalamic gating for sleep onset was weaker after talk mode than listen/standby mode exposure.
- ***Opposite*** effects on the sleep maintaining-related SWS frontal-central spindle (12-14 Hz) when the brain is progressing into deeper sleep stages: 'talk mode' has ***no effect*** whereas 'listen' and 'standby' modes increased power in this range during SWS.

In addition, after 'listen mode' exposure, a simple regression of EEG sigma activities (14-16 Hz) and delta activities (2-4 Hz) during SWS showed a strong positive correlation between these two rhythms in the centro-parietal-occipital areas (EEG derivations: C3-P3, P3-O1, C4-P4, P4-O2, all $R2 \geq 0.70$). As the rise and fall of the sleep spindles and delta waves are induced by the 'cortically-generated slow oscillations' during SWS [Achermann & Borbely, 1997; Amzica & Steriade, 1998], this result may implicate a potential slow oscillation enhancing effect of listen mode.

6.5.7 Conclusions

Putting together the findings demonstrated in the chapters 4, 5 and 6, the EEG after 'talk' mode exposure was characterized with signs of enhanced alertness during sleep onset. Evidence include:

- Increased EEG-determined sleep latency (chapter 4).
- A decreased resting waking theta power before S1 (chapter 5).
- A reduced S2 spindle power (present chapter).
- A dampened increase of EEG delta power across the time course of the nap (chapter 4).

However, the sleep/waking EEG findings so far indicate no significant effect of 'listen' and 'standby' mode on the sleep onset process.

When turning to look at sleep consolidation, on the contrast, it was only 'listen' and 'standby' mode signals that had a significant influence. This was evident by:

- An enhanced SWS spindle power, an indicator of enhanced sleep preservation, after exposure to both listen and standby mode (present chapter).
- An enhanced synchronization between the spindle and delta rhythms during SWS after exposure to listen mode (present chapter). This implies the slow oscillations might have been potentiated by the listen-mode signal so as to orchestrate the cortico-thalamo-cortical loop in generating these sleep rhythms.

Although the exact mechanism behind these non-thermal mobile phone effects remained unknown, opposite sleep EEG effects between the 'talk' and the 'listen' mode suggested mobile phone effects on sleep may depend on the pulse-modulation frequencies. Given both talk and listen mode share the same ELF pulsing at 8 and 217 Hz whilst listen-mode has an extra 2 Hz pulsing and induce opposite sleep EEG during sleep onset, it is likely that the effects generated by the 2 Hz pulsing may have counteracted those induced by the 8 and 217 Hz pulsing.

7 EFFECTS ON PSYCHOMOTOR VIGILANCE TASK (PVT)

7.1 INTRODUCTION

7.1.1 Previous Studies on Related Topics

Over the past 10 years the exponential increase in mobile phone availability has given rise to questions about possible bioelectromagnetic effects on the users. Since the mobile phone is normally used in close proximity to the user's head and a discrete amount of mobile phone radiofrequencies (RF) has been demonstrated to be absorbed through the skull reaching the brain [Schonborn et al., 1998], it raises public concern as to whether the very low RF electromagnetic field (EMF) emitted from a standard mobile phone has a potential to interact with cerebral activity, with consequent effects on behavioural performances. Numerous research groups have addressed this question with different neuropsychological assessments tools, however, none of them are able to claim a particular behavioural construct that is consistently influenced by mobile phone-like RF EMF exposure (see Table 2.6). Using reported effects on the simple/choice reaction time (RT) task as examples, some results showed an EMF exposure-related increase in reaction speeds but accuracy indices seemed to be unaffected [e.g. Koivisto et al., 2000a; Curcio et al., 2004], while others indicated no effects at all [e.g. Regel et al., 2007a, Curcio et al., 2008]. The situation is further complicated by the fact that the very groups who reported positive effects of mobile phone exposure failed to replicate their own findings even with methodological improvement. For example, Haarala et al. [2004] who attempted to confirm and extend the positive effect of EMF on RTs in 3 out of 12 different RT test [Koivisto et al., 2000a] could not find any significant RT effects in their replication study with a larger sample size, more tests and a double-blind design. The unsettled controversy poses a problem since any suggestion of potential EMF effect would lead to caution as to the use of mobile phones.

7.1.2 Recent Research Spotlight: Extremely-Low-Frequency (ELF) Pulse-Modulated EMF Effects

An important and yet under-studied issue, which may independently contribute to the inconclusive findings, concerns effects of extremely-low-frequency (ELF) pulse-

modulated EMFs such as those transmitted by the mobile phone when operating at talk, listen or standby modes. These signals differ in their ELF (2, 8, 217 Hz) spectral contents and our previous human sleep and resting EEG studies (chapter 4, 5 and 6) have indicated they have opposite effects on the post-exposure sleep process within the same participant, such that, during the sleep onset process, talk mode (8, 217 Hz modulated) induces an 'alerting' effect on the sleep onset while listen mode (2, 8, 217 Hz modulated) and standby mode (< 2 Hz modulated) have no influence. During the consolidated period of sleep, talk mode has no effect but the other two modes induce a 'sleep preservation' effect.

In addition, recent achievements in the electric (i.e., Direct Current Stimulation, DCS) and magnetic field (i.e. Transcranial Magnetic Stimulation, TMS) stimulation in brain research and neurotherapy have accumulated evidence supporting EMF stimulation at low frequencies to modify subsequent EEG activities during sleep. As examples, slow-wave (0.8 Hz) rTMS during NREM sleep [Massimini et al., 2007; Marshall et al., 2007] or theta-wave (5 Hz) rTMS during waking [Huber et al., 2007] were able to trigger sleep delta (1-4 Hz) and spindle (12-16 Hz) activities, with both stimulation frequencies being synchronized with the major rhythms characterized waking drowsiness and NREM sleep process.

Moreover, data from neuroimaging studies comparing RF EMF 'with' and 'without' ELF pulse modulation have verified ELF pulse modulation to be a prerequisite for RF EMF to induce neurophysiological changes. It has been shown that only RF EMF 'with' pulse modulation (but not RF EMF alone) can cause changes in waking and sleep EEG [Huber et al., 2002, Regel et al., 2007a] as well as changes in waking regional cerebral blood flow (rCBF) [Huber et al., 2005] and working memory performance [Regel et al., 2007a]. Furthermore, the rCBF study has found 'the stronger the ELF spectral power, the more significant was the neurophysiological effect (refers to an increase in relative rCBF in the dorsolateral prefrontal cortex on the side of exposure as assessed by PET)' [Huber et al., 2005].

7.1.3 Research Gap: EMF Effects of Mobile Phone ELF Pulse-Modulation Components of 2, 8, 217 Hz

Indeed, increasing research have renewed interests in the effects of ELF pulse modulation (particularly in those ELF synchronizing at the frequency range of the sleep/waking EEG rhythms). Accumulating EEG/behavioural evidence also points to

a significant impact on sleep/waking regulation. Nevertheless, how and to what extent the varying ELF pulse modulation schemes are involved in modification of the link between sleep and waking performance remains to be featured. One hint may come from our sleep EEG study, which indicated the brain state could be differentially influenced by varying mobile phone ELF pulse modulation when facing the pressure of rapid transition from waking to sleep (talk mode: 'alerting' effect versus listen/standby mode: 'no' effect, all in comparison with sham mode). As both talk and listen modes share the same low-frequency pulsing at 8 and 217 Hz whilst the listen mode has an extra 2 Hz pulsing, it is possible that the nil effect of listen mode on sleep onset is due to the additional 2 Hz pulsing component, which may negate the negative effect of 8 and 217 Hz component for sleep initiation. If this is true, in the converse condition where the brain has to stay awake and to resist sleep initiation (or to rapidly transit to waking if inadvertently microsleeps intrude), what would the effect of talk and listen mode be like on task performance? Is it possible that the alerting effect of 8 and 217 Hz component of the talk mode can help as a sleep countermeasure on this vigilance task that otherwise drives the brain to lapse while performing? If so, can the 2 Hz component work to negate this possible alerting effect of 8 and 217 Hz component and make the vigilance performance of the listen mode no different from the sham mode? Furthermore, the problem that the measured alerting effects of talk mode may be very subtle (since the current vigilance measure is during waking performance, not sleep) should not be overlooked. In such case, how can we analyze the waking performance to maximize detection of this alerting effect without being masked by the fluctuated vigilance on task?

7.1.4 PVT as a Probe of the Influence of Elevated Sleep Drive on the Vigilance Performance

The psychomotor vigilance task (PVT) is a relatively high-signal-load, sustained-attention (vigilance) performance task as a measure of endogenous sleepiness [Dinges & Powell, 1985]. It requires a button press response to the onset of a visual millisecond counter presented in the centre of a computer monitor, which shows the reaction time to the light stimulus remained visible and stops counting immediately at the subject's response. All stimuli are presented with a random inter-stimulus interval of 2 to 10 s one test bout. The PVT has virtually no learning curve and all subjects achieve asymptotic responding capability within one test bout.

Since its original development in 1985 by Dinges & Powell, many studies have demonstrated its sensitivity to sleep drive in the clinical, experimental, and operational contexts. As examples, studies have shown PVT to be sensitive to alternations in the homeostatic [Van Dongen et al., 2003; Wright et al., 2002; Dinges et al., 1997; Cajochen et al., 1999b] and circadian systems [Wright et al., 2002; Wyatt et al., 1999], as well as work schedules [Cadwell et al., 2003], age [Philip et al., 1999] and sleepiness countermeasures such as naps [Dinges et al., 1987], bright light [Wright et al., 1997] and caffeine [Wright et al., 1997]. In view of such widely-recognized sensitivity of the PVT to sleepiness or ability to maintain alertness, we used this task to meet the aims of our study (see below).

7.1.5 Metrics of the PVT

The results of PVT are generally interpreted as reflecting the arousal and attentional state of the individual. Within a given test bout, performance (i.e. reaction time [RT]) becomes increasingly variable as what has been termed 'state instability.' State instability refers to increasing fluctuation among alertness, lowered vigilance, drowsiness, and inadvertent microsleep episodes, which is a fundamentally unstable state that cannot be characterized as either fully awake or asleep; that fluctuates within seconds; and that can rapidly progress to physiological sleep if not resisted (and at some point even when resisted, such sleep occurs as those resulting in drowsy-driving crashes) [Horne et al., 1985]. Comparing across conditions (e.g. well rested vs. sleep deprived), the state instability can be revealed within a short (5-10 min) period on the PVT by a combination of three outcomes [Doran et al., 2001; Graw et al., 2004]:

i) increased lapses;
ii) increased false responses (i.e. false starts or wrong button pressings);
iii) increased compensatory efforts resulting in no-lapse-domain RTs for a short period of time.

7.1.5.1 Lapses

LapsesCare periods of much delayed responding (1000 ms ≥ RTs ≥ 500 ms) or of nonresponding (RTs ≥ 1000 ms). The effect of growing sleepiness (i.e. under sleep deprivation) on the number of lapses was found to be similar to the number of slowest 10 % RTs, as both increased under high sleep pressure [Graw et al., 2004]. The effect of the circadian rhythm of sleepiness on both lapses and slowest 10 % RTs are also similar, with high values in the late night and early morning (deterioration of

performance) and low values during the second day [Graw et al., 2004]. During sleep deprivation under the constant routine condition, both indices showed an almost linear change without circadian variation, reflecting the effect of high sleep pressure would be superimposed on the effect of circadian modulation [Van Dongen et al., 2000]. These results suggest both PVT lapses and slowest 10% RTs are of the same PVT metrics, and can be used to represent the endogenous sleep pressure level from the interaction of prior wakefulness and circadian phase.

7.1.5.2 False Responses

False responses refer to the number of error commission, including 'false starts' (RT <100 ms) and 'wrong button pressing.' In subjects during 2-day sleep deprivation, it was found, under high sleep pressure, the sleepy subjects tended to respond more often on a 10-min simple, unprepared visual RT trial (similar to PVT as a high-signal-load RT task). This was shown by a dramatic rise in the false responses by the second night without sleep, though lapses began appearing during the first night [Dinges & Powell, 1989]. The same group [Doran et al., 2001] later demonstrated a strong intercorrelation between the errors of commission (false responses) and errors of omission (lapse) across the total sleep deprivation for 88 h on a 10-min PVT, suggesting the sleepy subjects simultaneously have an increased tendency for nonresponding (lapses) and for responding when no signal present (false responses). The increase in false responses with elevated sleep pressure may reflect an increased misperception of signal presence and a decreased reliability of response inhibition [Dinges, 1992], as well as an increased compensatory efforts for correcting lapses [Doran et al., 2001].

7.1.5.3 No-Lapse-Domain RTs and Optimum Responses

Responses between lapses, termed 'no-lapse-domain RTs,' account for the ability to maintain basal performance as a function of time on task. Among which, the fastest 10 % RTs (the 'optimum responses') represent the best psychomotor efforts in PVT [Dinges, 1992]. Contrary to lapsing, no-lapse-domain RTs are relatively difficult to recognize in the performance of sleep-deprived subject. This is due to lapsing necessarily resulting in a proportionality between mean and variance, which increases variability or skewness in the RT distribution. As sleepiness increases, the mean of each RT performance trial increases linearly as a function of increasing standard deviation. This makes statistical analysis of mean performance data equivocal, since there are such gross differences in variance. A solution to this problem, which was

suggested by Dinges et al. [1987], involves transforming the raw RT data reciprocally (=1/RT). Such approach is proposed to partial out the effects of lapsing on the raw RT scores so as to maximize the likelihood of observing subtle shifts in non-lapse-domain responses [Dinges, 1992].

7.1.6 Time-On-Task Effects

One major effect of sleep drive on sustained attention task that cuts to the heart of the issue of task duration is 'time-on-task' effects. It has been well-established in sleep-deprived subjects that there is a 'time-on-task decrement' in performance, which is attributed to increased frequency of slow RTs (lapses and slowest 10 % RTs) or error commission (false responses) [for a review, see William et al., 1959]. As examples, Williams et al. [1959] consistently found that the response time was an increasing monotonic function of task duration, and their later work showed that within each of three 10-min visual vigilance tasks, there was an increase in the percent errors of omission (lapses) evident with time-on-task during sleep loss [William et al., 1965]. The accentuation of time-on-task decrement in response time on relatively brief, sustained-attention tasks is reported by Donnell [1969]. They used the Wilkinson addition test to find that two nights without sleep results in substantial response slowing by 6 min on task and in increased errors by 10 min on task for the second night without sleep. Lisper and Kjellberg (1972) also showed systematic slowing in RT performance across time on a 10-min simple auditory RT task as a function of only one night without sleep. Although task sensitivity to sleepiness may depend on many factors (for a review, see Horne et al. [1985]; Johnson et al. [1992]), it is remarkable that if analysis is focused on 'lapsing' across time-on-task, and the task involves frequent responding (high-signal-load) task, task duration of 10-15 min are sufficient to reveal the effects of prolonged wakefulness beyond 18 hour [Dinges, 1992].

Whether the non-lapse-domain RTs will be slowed with increasing task duration and whether this time-on-task performance decrement occurs independent of the contribution of increased lapsing, have been an issue of debates. Dinges and Powell [1988] assessed simple visual RT performance on a 10-min task (simple, unprepared visual RT task, similar to PVT) during two days of sleep loss has revealed the minute-by-minute means of reciprocal of RTs (1/RT, which was a resort the authors used to remove the disproportionate contribution of lapses from the raw RT scores) showed a steady decrement (see Figure 12.5 in Dinges [1992]). Thereby, they claimed there is also a time-on-task decrement effect on the normal, no-lapse-domain responses

independent of lapsing. However, for the fastest RTs (the optimal responses) that briefly occurred between lapses within a test bout, later work by the same group [Doran et al., 2001] have shown they do not change or change only modestly during total sleep deprivation (for 88 h) relative to the well-rested state. Taken together, these findings seem to support the state instability hypothesis [Horne et al., 1985]: inadvertent microsleep episodes can be sufficiently compensated resulting in normal RTs only for a short period of time but across the time on task, the rate of decline in RTs accelerated with time-on-task independent of lapsing. The performance in the optimal domain (fastest RT) does not show a time-on-task decrement, neither are they affected by the elevated sleep pressure during sleep deprivation. They represent a compensatory effort or compensatory stimulation takes on a greater role in keeping reliable performance as sleep drive increases.

It should be noted that performance tasks requiring attention seem especially prone to state instability when the sleep drive is elevated [Doran et al., 2001]. The combined decrement in both lapses and non-lapse-domain RTs across the time on task are often most dramatic during the first 10-30 min of task duration [cf. Wilkinson, 1958; Craig, 1984]. Monotonous stimulation or that required sustained attention and frequent responding to inherently-limited stimuli will potentiate vigilance decrements and the pressure to microsleep (i.e. contextual-dependent hypothesis, see Dinges, [1989]). Motivation, incentive or new effort[19] can contribute, or override, the time-on-task decrement, but only for a limited period [Dinges, 1992, Doran et al., 2001]. Thereby, a neurobehaviour probe that seeks to evaluate to what extent a sleep countermeasure can depress the elevated sleep drive on waking performance should be a simple, monotonous task that has high demand of attention and outputs (to accentuate sleep drive); and analysis of performance on it has the ability to detect the subtle shifting of the state lability as a function of time on task as demonstrated by time-on-task-decrement on non-lapse responses. Viewed in this way, PVT seems to offer the entire requirement regarding its nature of task and its sensitivity to measures of sleep pressure during sleep loss.

[19] Lee and Kleitman [1923] proposed that during sleep deprivation ('experimental insomnia'), most abilities could be maximally utilized by a 'new effort' but that "the effect of increased effort disappeared when the test became one of endurance" (quoted from Doran et al. [2001], p. 253).

7.1.7 Hypothesis and Aim of the Current Study

Here we employed the psychomotor vigilance task (PVT) to further explore the talk-, listen- and standby-mode effect on regulating the sleep initiation mechanisms during vigilance performance. We predicted, if the 8 and 217 Hz components of the mobile phone talk-mode signal were to play a role in making the brain more 'alert' (so as to counteract the enhanced sleep pressure driven by PVT), such effects on PVT performance might be best reflected by an enhanced ability to maintain basal performance as a function of time on task. This prediction had been taken into account of the task nature of PVT and based on many empirical results collected during sleep deprivation. We believe the brain would be more prone to state instability when the stimulation and workload or response requirement of the task is repetitive and occurs at a fairly high rate. Thereby, the longer the brain is engaged in the task, the less possible it is to maintain the basal response capacity, and the more susceptible it is to compensatory processes that mediate its basal response capacity. However, due to the compensatory processes can only present a short period of time, it will become harder and harder for the basal response capacity to be timely compensated, and as a result, the time-on-task performance decrement in no-lapse domains appears. Viewed in this light, we may assume the mobile phone 8 and 217 Hz components may underpin the compensatory processes by making it endure in maintaining basal performance so that the time-on-task decrement in no-lapse-domain responses would 'NOT' be possible to develop. In this study, we would base on this assumption to examine and compare the effects of varying mobile phone signals.

7.2 MATERIALS AND METHODS

7.2.1 Exposure Characteristics

Talk, listen and standby modes were generated by a GSM900 Nokia 6210e mobile phone having a test-SIM card and controlled by a HP8922M GSM900 base-station simulator, located 1.5 m away in another room, and transmitting at about only 12.5 % (23 dBm) of maximum power. The ELF pulse modulation composition and SARs for the three modes were shown in Table 7. 1.

Table 7. 1 ELF composition and SARs for mobile phone 'talk,' 'listen,' and 'standby,' modes.

Mobile phone signals	ELF components (Hz)	SAR (W/kg, 10g of tissue averaged)
Talk	8, 217	0.1333
Listen	2, 8, 217	0.015
Standby	< 2	< 0.0001

7.2.2 Subjects

Sixteen paid participants (healthy, un-medicated, normal-sleeping, right-handed men, mean age: 21 ± 0.9 y, range: 18-28 y) were screened and recruited from students on the campus, having given their written informed consents. They were regular mobile phone users but with an average talk-time less than 1 h/day. They maintained their regular sleep-wake schedule for at least three days prior to each trial (monitored by wrist-worn actimeters and personal sleep diaries). Alcohol and caffeine-containing beverages were prohibited at the night before and on the morning of each trial. Their mobile phone use ceased after 22:00 h the evening before trials. Their prior night's sleep was restricted to 6 h (by a delayed bedtime and with their sleep monitored by actimeters).

7.2.3 Procedure

A fixed afternoon routine for experimentation was begun with the participant lying on a comfortable bed, in an individual sound-proof and lit bedroom. The experimental phone was harnessed beside the right ear, and any possible heat from the battery or any seemingly inaudible 'hum' were insulated from the ear by a 2 cm thick cotton-wool wadding. At precisely weekly intervals, participants were exposed ('blind' and 'randomly') to one of: talk, listen, standby and sham (nil signal) modes, for 30 min, commencing at 13:30 h, with the exposure orders counterbalanced between participants. Throughout all exposures the phone generated no sounds (the phone's speaker was disabled). Participants remained silent, and fixed their eyes on a wall marker. Subjective ratings of sleepiness were assessed using the Karolinska Sleepiness Scale (KSS, [Åkerstedt et al., 1990]) every 3 min (before, after and during the exposure). A 30-min PVT task was ensued in 10 min after the exposure.

7.2.4 PVT Task

The PVT is a simple RT task to evaluate sustained attention [Dinges & Powell, 1985]. During the task, the participant saw a blank box in the middle of the screen in a

dimmed room. At random intervals, a millisecond counter started to scroll, and the participant had to press a button (with right hand) to stop the counter as quickly as possible. After pressing the button, the counter displayed the achieved RT for 1 s, providing the participant with feedback on performance. The inter-stimulus interval (ISI) varied randomly between 2 and 12 s and the task was performed for 30 min continuously without any rest.

7.3 DATA ANALYSIS

7.3.1 PVT Variables

The values of the following five PVT variables were calculated in 5-min sessions per test bout (one test bout = six 5-min sessions) after exposing to the talk, listen, standby and sham mode in random orders within the same subject.

1. Frequency of lapses
2. Frequency of false responses ('false starts' + 'wrong button pressings')
3. Frequency of the slowest 10 % RTs
4. Frequency of the fastest 10 % RTs (optimum responses)
5. No-lapse-domain responses (1/RT, mean value of every 5-min session)

Considering there may be nil data present in some of the 5-min sessions for PVT parameters 1, 2, 3 and 4, a data transformation was applied with the frequency calculation using the formula: $\sqrt{x}+\sqrt{x+1}$ (see Graw et al., 2001).

In addition, we also calculated the mean response time (in millisecond) of the fastest 10 % RTs (PVT variable 6) and the slowest 10 % RTs (PVT variable 7) of each test bout.

7.3.2 Statistics

PVT variables 1-5 were firstly analyzed for 'condition' (talk, listen, standby and sham modes), 'time' (six 5-min epochs) and 'time x condition' effects by two-way analyses of variance for repeated measures (rANOVAs). If two-way rANOVAs yielded significant results in the factor 'condition,' mean values of talk, listen, standby and sham modes within each 30-min test bout would be calculated and examined by one-way rANOVAs followed with Student-Newman-Keuls (SNK) range test for post hoc comparisons. If

two-way rANOVAs were significant in 'time x condition' interaction, post hoc comparisons of the time effect within each condition would be conducted by using SPSS Helmert tests. Or the raw data of talk-, listen- or standby-mode would be transformed to be 'percentage difference from sham mode' and compared within each 5-min session by non-parametric tests (such as Friedman two-way ANOVAs by ranks). We did not further analyze significant 'time' effects yielded by two-way ANOVAs as this could not differentiate the effects between conditions.

For the PVT variable 6 and 7 (the mean response time of the fastest and slowest 10 % RTs), data in the talk, listen, standby and sham condition would be submitted to one-way rANOVAs for comparison. If there was any significant effect, post hoc tests would be conducted by using the SNK range test.

We also examined the difference in the KSS score between talk-, listen-, standby- and sham-mode conditions, before and after each PVT trials. This was done by submitting the KSS raw score to a two-way rANOVA (time x condition) test.

7.4 RESULTS

7.4.1 Subjective Sleepiness 'Before' and 'After' PVT

Subjective sleepiness (KSS, mean ± S. E. M., n=16) pre- and post-PVT test of four conditions are listed in Table 7. 2. A two-way rANOVA with factor 'time' and 'condition' did not yield any significant results (factor 'condition': $F_{[3, 15]} = 2.17$, $P = 0.339$; factor 'time': $F_{[1, 15]} = 0.32$, $P = 0.860$; factor 'condition x time': $F_{[3, 45]} = 0.50$, $P = 0.683$). This result suggested the subjective sleepiness was not sensitive to detect the changes induced by either mobile phone exposure or PVT performing.

Table 7. 2 KSS reports before and after PVT testing for four exposure modes.

	Talk	Listen	Standby	Sham
Pre-PVT	6 ± 2	6 ± 2	6 ± 2	6 ± 2
Post-PVT	6 ± 2	7 ± 3	6 ± 3	6 ± 2

7.4.2 PVT Performance

The PVT performance (mean ± S. E. M.) with variable 1-5 of talk-, listen-, standby- and sham-mode exposure was presented in Figure 7. 1. The response time (mean ± S. E. M.) of the fastest and slowest 10 % RTs on the 30-min PVT of the four

conditions is illustrated in Figure 7. 2. Results of two-way ANOVAs with PVT variables 1-5 (frequencies of the 'fastest 10% RT,' 'slowest 10 % RT,' 'lapse,' 'false response' and raw '1/RT') are listed in Table 7.3.

7.4.2.1 'Errors of Omission' and 'Errors of Commission'

Lapses and False Responses

Two-way rANOVAs did not yield any significant result with the variable 'frequency of lapse' (error of omission) and 'frequency of false responses' (error of commission) on the 30-min test bout (Table 7. 3). As shown in Figure 7. 1 (e, f), lapses and false responses occurred at the similar frequency across the time on task for each condition, and both demonstrated only 'time' effect, but not 'condition' or 'time x condition' effect (2-way rANOVAs, see Table 7. 3).

The Slowest 10 % RTs

Figure 7. 1 (d) demonstrated that the slowest 10 % RTs (errors of Omission) were not increased with a function of time on task (time effect, $F_{[3, 45]} = 0.09$, $P = 0.96$), and the enhancing rate had no between-condition difference ('time x condition' effect: $F_{[15, 225]} = 1.43$, $P = 0.13$, results of two-way ANOVAs, see Table 7. 3). The mean response time of the slowest 10 % RTs in the 30-min PVT task was not significantly different between condition ($F_{[3, 45]} = 0.17$, $P = 0.95$; one-way rANOVA; mean ± S.E.M. of each condition is presented in Figure 7. 2).

7.4.2.2 'No-Lapse-Domain RTs' and 'Optimal RTs'

'No-Lapse-Domain RTs' (= 1/RT)

The reciprocal RT (1/RT), a representative of the normal timely RT appearing independent of lapsing (termed 'no-lapse domain RTs,' [Dinges, 1992]), showed a significant 'time' and 'time x condition' effects with two-way ANOVAs (Table 7. 3). Figure 7. 1 (b) illustrates that the mean response time slowed with a function of time on task in all conditions (condition x time effect, $F_{[15, 225]} = 1.80$, $P = 0.036$). However, the RT deceleration was different between conditions. This was indicated by SPSS Helmert tests on the time effect within each condition, which showed that the response time stopped slowing after 10-min on task with talk- and listen-mode, 15-min on task after standby-mode, and 20-min on task after sham-mode exposure [$P < 0.01$ – applying Bonferroni correction]. In addition, comparing between-condition

differences within each 5-min session (with 1/RT scores transformed to be '% difference from sham mode') with Friedman two-way ANOVAs, results indicated talk, listen and standby-mode RTs were all faster than sham-mode RTs in the 20-25 min session [χ^2 = 10.58, df = 3, P = 0.014, also see Figure 7. 1 (a)].

The Optimal RTs (= the Fastest 10 % RTs)

For the number (#) of fastest 10 % RTs in the six 5-min sessions, results of two-way ANOVAs did not show any significant effect of 'condition' or 'interaction' but on the factor 'time' (Table 7. 3). Figure 7. 1 (c) illustrated the frequency of the fastest 10 % RTs of the four conditions was all decreased during the task, without between-condition difference. The mean response time of the fastest 10 % RTs in the 30-min PVT task was not different between conditions ($F_{[3, 45]}$ = 1.06, P = 0.37; one-way rANOVA; mean ± S. E. M. of each condition is presented in Figure 7. 2).

Table 7. 3 Results of two-way (condition x time) ANOVAs with five PVT variables.

	Condition (talk, listen, standby and sham)		Time (six 5-min sessions)		Condition x Time	
	$F_{3, 45}$	*P* value	$F_{5, 75}$	*P* value	$F_{15, 225}$	*P* value
Lapses (#)	1.56	(0.211)	1.91	(0.102)	1.27	(0.223)
False responses (#)	1.93	(0.137)	0.27	(0.928)	0.46	(0.994)
Slowest 10% RTs (#)	0.09	(0.964)	6.41	(5.18×10^{-5})	1.43	(0.134)
Fastest 10% RTs (#)	0.42	(0.739)	26.76	(2.02×10^{-15})	1.50	(0.106)
1/RT	0.92	(0.441)	30.18	(1.12×10^{-16})	1.80	(0.036)

Frequency

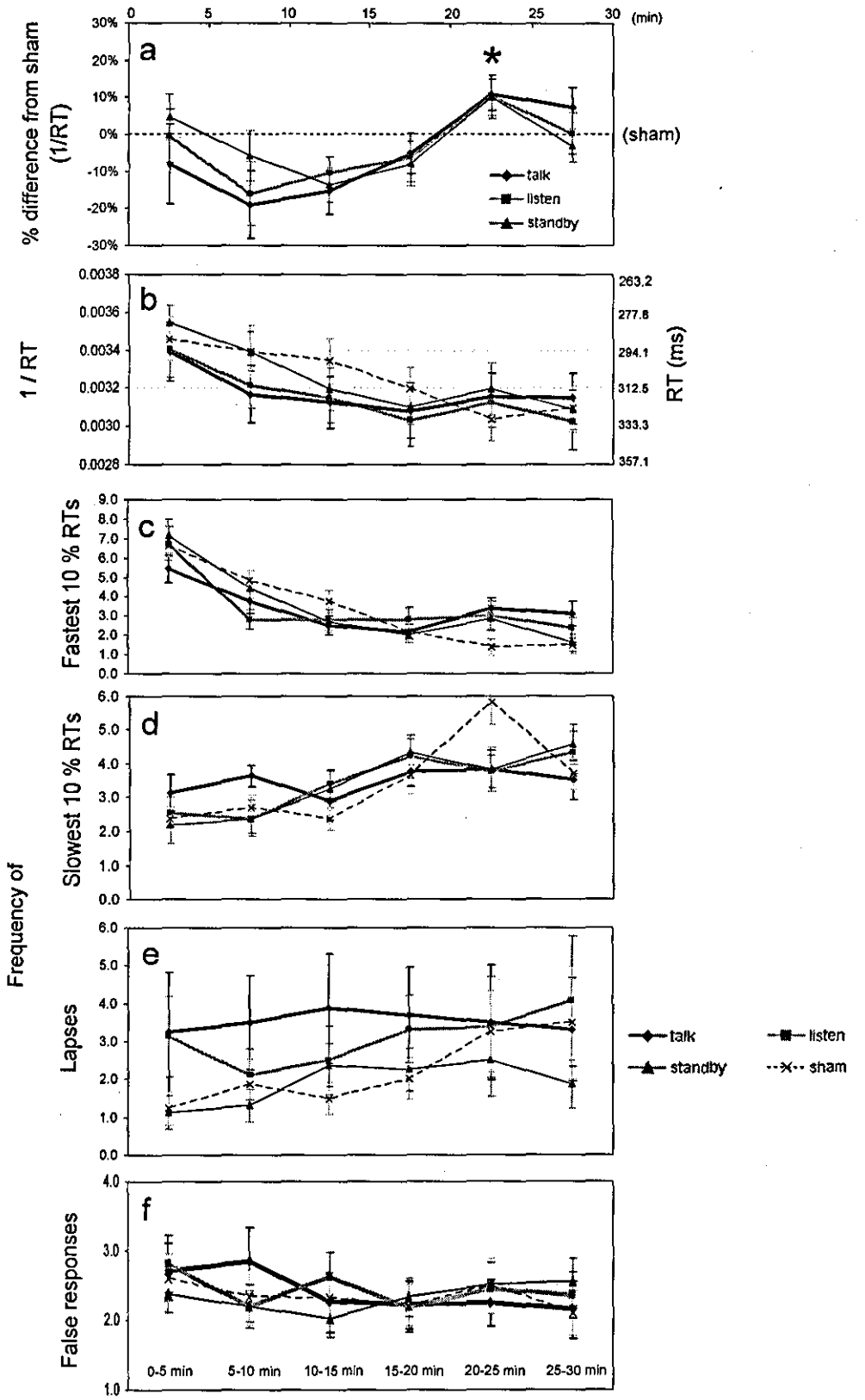
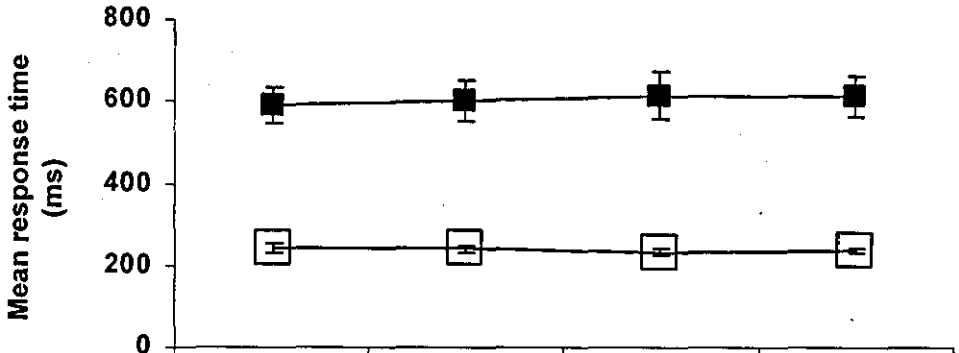


Figure 7. 1 PVT performance effects of talk, listen, standby and sham mode in six 5-min sessions (mean ± S. E. M., n=16): 1/RT, including % difference from sham (a) and raw values (b); frequency of the fastest 10% RTs (c); frequency of the slowest 10 % RTs (d); frequency of lapses (e) and frequency of false responses (f). *$P < 0.05$, Friedman two-way ANOVAs by ranks on the data of every 5-min session, see text for details.



	Talk	Listen	Standby	Sham
Fastest 10%	243.1 ± 10.9	240.3 ± 9.7	233.4 ± 6.7	237.8 ± 6.4
Slowest 10 %	590.4 ± 43.3	601.3 ± 47.3	615.0 ± 57.2	612.1 ± 51.1

Figure 7. 2 Response time (mean ± S. E. M., in ms) of the fastest 10 % and the slowest 10 % RTs on the 30-min PVT task after talk, listen, standby and sham mode exposure (no conditional difference – fastest 10 % RTs: $F_{[3, 45]}$ =1.06, P = 0.37; slowest 10 % RT: $F_{[3, 45]}$ = 0.11, P = 0.95; one-way rNOVAs).

7.5 DISCUSSION

7.5.1 PVT Effects of the ELF Components of 8 and 217 Hz

The main result of this study concerning PVT effects of varying mobile phone signals is their differentiable RT deceleration on the task, observed by RTs in the no-lapse domain [1/RT, Figure 7.1 (b)]. The reciprocal RT (1/RT), which has partialled out the effect of lapsing on raw RT scores [Dinges et al., 1987], showed a normal slowing trend across time on task in all conditions with different slowing rates. With prior exposure to the 'talk' and 'listen' mode, the RT slowing stopped in 10 min of PVT performance initiation; with prior 'standby' mode exposure, it stopped after 15 min; however, with prior nil-signal (sham-mode) exposure, the slowing was not stopped until 20 min of PVT performance initiation. This result followed our hypothesis for the talk-mode effect on vigilance performance based on the state instability concepts that, the sleep pressure driven by task engagement and by experiment-induced afternoon dip can be less effective in the 'talk' mode condition.

Our results regarding mobile phone effects on the lapse domain of the PVT performance (errors of omission and commission) did not show any significant 'time,' 'condition' or 'time x condition' effect. Neither did the mean response time of the slowest 10 % RTs during the 30-min task performance show any conditional

difference. From the perspective of the lapse hypothesis, one might reckon the current results did not support our predicted alerting effect of the talk mode since there was no significant reduction in the frequency or duration of lapsing after talk-mode exposure. Nevertheless, lapsing reduction does not necessarily result in increased alertness, as there is evidence showing the lapse hypothesis can 'not' account for all of the performance deficits seen even on simple sustained-attention tasks such as PVT (for a review, see Horne et al. [1985]; Johnson et al. [1992]). Indeed, results from sleep loss studies have indicated that as sleep drive elevated, sleep-initiating mechanisms begin to occur in the presence of waking neurobiology, trying to make sustained performance labile and increasingly dependent on compensatory mechanisms (see Figure 1-2 in Doran et al. [2001], Figure 2 in Graw et al. [2004]). Therefore, the ability to maintain basal performance as a function of time on task, rather than the elimination of the ability to perform (lapsing), is more sensitive to the neurobiological processes regulation of alertness under sleep pressure. As what is evident for observing vigilance 'decrement' (with sleep loss) should also be evident for observing vigilance 'enhancement' (with sleep countermeasures), hereby the finding of much more endured maintenance of basal performance after talk-mode than sham-mode exposure did obviously support the hypothesized alerting effect of talk mode.

7.5.2 PVT Effects of the ELF Component of 2 Hz

As to the question whether the extra 2-Hz pulsing of the listen mode signal could negate the alerting effects of 8 and 217 Hz pulsing, based on the finding from time-course comparison of no-lapse-domain RT change (1/RT, talk vs. listen), the answer seemed to be 'NO.' However, maybe the PVT measurement could provide sufficient evidence for deciphering this issue, as the alertness negating effect of 2 Hz may be so subtle as to be masked by the 8 and 217 Hz-heightened compensatory processes subserving the vigilance performance on this sustained-attention, high-signal-load task. A number of aspects of our results provide support for this perspective. In our experiment, subjects were pushed to perform to the best of their ability at each PVT test bout. There was no indication in their behaviours at the test console or from their comments after test bouts and post-experimentally that they failed to do so. More importantly, the RT slowing trend with prior exposure to standby-mode signal (only with sporadic pulsing at < 2 Hz) was almost the same as that with prior exposure to sham-mode signal. This further suggested the compensatory efforts or stimulation, even without the beneficial effect of the 8 and 217 Hz component, could be overlay

the effects of ≤ 2 Hz pulse modulation. Accordingly, the present nil difference in the PVT results of the talk- and listen-mode signals is not necessarily objected to the proposed effect of 2 Hz component obtained from our previous EEG studies.

7.5.3 Conclusions

So far, this study examined time-on-task effects of three varying ELF pulse-modulated mobile phone signals (talk, listen and standby modes) on the PVT performance based on the state instability concepts. Key findings include:

- For no-lapse-domain RTs, all conditions (including sham mode) showed response time slowing as a function of time on task. However,
    - o No-lapse-domain RT deceleration stopped earlier with talk- and listen-mode condition: the response time stopping deceleration after 10-min on task with talk- and listen-mode, 15-min on task after standby-mode and 20-min on task after sham-mode exposure.
- There was no between-condition difference in the time-on-task effects with respects to mean quality of PVT performance (= 'lapses,' 'false responses' and 'the optimal RTs').

Present results of no-lapse-domain RTs followed our hypothesized 'alerting' effect of 8 and 217 Hz pulsing, but the hypothesized 'alertness negating' effect of 2 Hz components needs to be further confirmed. It was suggested the negating effect of 2 Hz may be too subtle to unmask the heighten alertness induced by 8 and 217 Hz component on PVT.

It should be noted here that, although there was evidence of reduced RT deceleration of the no-lapse-domain RTs after talk- and listen-mode exposure, the mobile phone effects on the mean quality of performance (in terms of the reciprocal RTs, lapses, false responses, frequency and duration of both the slowest 10 % and the fastest 10 % RTs) was actually not differentiable within these three modes or with that of sham-mode exposure. However, as this is the first study comparing effects of the real mobile phone signals together, and the reported effects are of short-termed exposure, it is beyond the scope of the current study to conclude whether there is a positive or negative effect of mobile phone usage on the neurobehavioural function.

8 IMPLICATION AND FUTURE DIRECTION

8.1 SUMMARY OF THE PRESENT FINDINGS

Mobile phone effects of different ELF pulse modulation (talk mode: 8, 217 Hz, listen mode: 2, 8, 217 Hz, standby mode: < 2 Hz) on human neurophysiology were the main focus of study within this thesis. These effects were examined by the visual scoring of sleep EEG, spectral analysis of waking and sleep EEG as well as the psychomotor vigilance task (PVT). The intermediate conclusions of these analyses were summarized below (also see Table 8.1).

8.1.1 EEG Findings

Overall, results from the EEG analyses showed effects of the mobile phone talk mode signal are 'opposite' to those of the listen/standby mode signal with regard to sleep initiation (result 1-4 in Table 8.1) and sleep consolidation (result 5 in Table 8.1). This conclusion was based on the following observations.

- Talk mode demonstrated an 'alerting' effect on sleep onset but had no influence on sleep consolidation, as findings showed that:
    1. a delayed visually-scored EEG sleep-onset time;
    2. a dampening of sleep pressure increasing [EEG index of sleep pressure: delta (1-4 Hz) power; c.f. Werth et al., 1997; De Gennaro et al., 2001a];
    3. reduced sleepiness before falling asleep [EEG index of sleepiness: resting waking theta (4-7 Hz) power; c. f. Strijkstra et al., 2003];
    4. global decreasing in the thalamic sensory gating inhibition during S2 (a period of emerging deep sleep) [EEG index of thalamic sensory gating inhibition: S2 spindle power, c.f. McCormick & Bal, 1994; Steriade et al., 1990b];
    5. no change in the EEG power spectrum during SWS.
- Listen/Standby mode did not affect the sleep-onset process but exerted a 'sleep preservation' effect afterwards when the brain was progressing to the deeper sleep stage, as shown by:
    1. no change in visually-scored EEG sleep-onset time from sham mode;
    2. no change in the EEG index of sleep pressure increasing from sham mode;

3. no change in the EEG index of sleepiness before falling asleep from baseline (comparable to sham mode);
4. only local decreasing in the thalamic sensory gating inhibition during S2;
5. enhanced SWS preservation [EEG index of SWS preservation: frontal-central alpha (8-12 Hz) power during SWS, c.f. McCormick & Bal, 1994; Steriade et al., 1990b].

In addition, it is noteworthy that the present listen-mode effects on the sleep EEG are in line with the observed outcomes of a prior study [Huber et al., 2000]. That study involved with a 30-min exposure to the GSM 'base-station-like' signal (sharing the same low-frequency components with our 'listen mode' at 2, 8, 217 Hz but with more low-frequency spectral power) before a 3-h day sleep in healthy young males, and reported no influence on the global sleep architecture but an increase of spindle (9.75-11.25 Hz and 12-13.25 Hz) power in the first 30-min NREM sleep (stage 2, 3, 4) for the central derivations (EEG derivations: C3-A2 and C4-A1) without an apparent lateralization effect (after either right or left stimulation). To the extent that our low-frequency pulsing characteristics and findings with listen mode seem to reproduce those of Huber et al., and with a similar experimental listen-mode protocol, we believe that the findings from our unique incorporation of talk and standby mode, are not random effects, and thus the difference between talk and listen/standby effects on the sleep-onset and SWS seem to be real.

8.1.2 PVT findings

In view of the 'opposite' EEG effects between the talk and listen mode on the sleep process, and given that both modes share the same ELF pulsing at 8 and 217 Hz with the listen mode having an extra 2 Hz pulsing, it was argued that the alerting effect of the 8 and 217 Hz pulse modulation might have been counteracted by the 2 Hz component for sleep initiation. This hypothesis was then examined in a converse situation where there was a pressure to stay alert and sustain attention during a 30-min PVT. Analyses were focused on the time-on-task effects of talk, listen and standby mode on the PVT performance measures of basal performance (= no-lapse-domain RTs, 1/RT), performance reliability (= lapse-domain RTs, such as number of lapses, slowest 10 % RTs and false responses) and best psychomotor effort (= number of fastest 10 % RTs). We had predicted that, if the 8 and 217 Hz components of the talk-mode signal were to play a role in making the brain more 'alert' (so as to

counteract the accentuated sleep pressure driven by PVT), such effects on PVT performance might be best reflected by the rate of state lability, such as showing no sign of the time-on-task decrement in the basal .performance. We had also predicted the converse (no change or reduction in the ability to maintain basal performance with time on task) held for listen-mode condition, if the extra 2 Hz component of the listen-mode signal was to negate the alerting effects of 8 and 217 Hz pulsing.

Overall, results of PVT basal performance with time on task followed our hypothesized 'alerting effect' of the 8 and 217 Hz pulsing components but did not follow our hypothesized 'alertness negating effects' of the 2 Hz pulsing component. This was concluded by observing that:

- No-lapse-domain RTs (1/RT) showed a similar rate of RT deceleration after both talk- and listen-mode exposure: the response time stopping deceleration after 10-min on task with talk- and listen-mode, 15-min on task after standby-mode and 20-min on task after sham-mode exposure.

This finding suggested that both talk and listen modes had similar effects on maintaining the basal performance under the PVT performance demands. It was suspected the 'alertness negating' effect of the 2 Hz pulse modulation was not absent but just too subtle when compared with the alerting effect of the 8 and 217 Hz pulse modulation on the PVT performance. This argument was based on an observation that the effect of < 2 Hz pulse modulation (= the standby mode) cannot be differentiated from that of the sham mode, which showed a trend of state instability on the task (a sensitive index of reduced alertness). Nevertheless, it was also possible that the PVT might not be a sensitive task for differentiating varying ELF pulse modulation effects of mobile phone signals.

Regarding mobile phone effects on the mean quality of PVT performance (in terms of RTs of 'lapse domain' – number of lapses, slowest 10 % RTs and false responses and RTs representing the 'best psychomotor efforts' – number of fastest 10 % RTs), the results showed that:

- RTs of lapse domain and RTs representing the best psychomotor efforts occurred during the 30-min task showed no between-condition difference in the mean values;
- Taking the time-on-task effect into account, there was still no between-mode difference in the mean values of these PVT measures across the time on task.

Combining the results of between-condition comparisons in the RTs of both 'no-lapse' and 'lapse' domains, as well as the RTs representing 'the best psychomotor efforts' (to compensate the time-on-task performance decrement) (see Table 7. 3), current evidence indicated that the PVT performance after talk- and listen-mode exposure could not follow the defined 'state instability' concepts by Doran et al. [2001] and Graw et al. [2004] (see section 7.1.5) – as there was no significant increase from sham mode in the number of lapses and false responses while the no-lapse-domain RTs stopping deceleration earlier than sham mode (which implied a stronger compensatory effort resulting in no-lapse-domain RTs for a 'longer' period of time). The PVT performance after standby-mode exposure, on the other hand, partially followed the defined state instability concepts, as the no-lapse-domain RTs showed similar deceleration with the sham-mode condition. To conclude briefly, PVT results of talk- and listen-mode showed a relatively increased state liability compared with sham mode, but results of standby-mode were similar to sham mode, where state instability might exist in the post-exposure PVT performance (finding 6 in Table 8. 1).

Table 8. 1 Major findings of mobile phone talk-, listen- and standby-mode signal effects (comparing with sham mode) in EEG and PVT studies.

Methods	Findings	Talk (8, 217 Hz)	Listen (2, 8, 217 Hz)	Standby (< 2 Hz)
EEG visual scoring	1. Sleep onset time	**Delayed**	-	-
EEG spectral analysis	2. Temporal increase of delta (1-4 Hz) power **[sleep pressure]** across the 90-min sleep	**Delayed**	-	-
	3. Resting waking EEG before onset of stage 1 sleep: frontal-central theta power **[sleepiness]**	↓	-	-
	4. S2: spindle power **[inhibition of thalamic sensory gating]**	**↓ (all channels)**	**↓ (only C4-P4)**	**↑ (only C3-P3) & ↓ (only P3-O1)**
	5. SWS: frontal-central spindle power **[sleep preservation]**	-	↑	↑
PVT	6. State liability	↑	↑	-

8.2 IMPLICATIONS

ELF pulse modulation, a key technology applied in almost all new wireless instruments for radiocommunication, has recently been attributed to be one of the most critical mobile phone mechanisms to account for the non-thermal EMF effects on neurophysiology. This is due to accumulated evidence, from electrophysiological (e.g. sleep or waking EEG studies of Huber et al. [2002]; Regel et al. [2007a]) to haemometabolic studies (e.g. rCBF studies of Huber et al. [2002, 2005]), have strongly suggested the ELF pulse-modulated waves, rather than the RF carrier wave itself, to be the pre-requisite for mobile phone-like EMFs to induce either immediate or outlasting effects on the human brain. However, what remains unknown is whether it is a single frequency component or a mixture of components of the ELF pulse modulations that are responsible for the observed effects. This study looking at EEG effects of varying mobile phone ELF pulse-modulated signals has helped to extend our knowledge on this aspect. Specifically, this study was unique in differentiating sleep effects of talk mode (8 and 217-Hz pulsed modulated) and listen mode (2, 8, 217- Hz pulsed modulated), which was prompted by observing that (i) the ELF pulse modulation contents of these two modes were only different for 'with' or 'without' the DTX pulse frequency at 2 Hz and, (ii) the DTX pulse frequency at 2 Hz and the TDMA pulse frequency at 8 Hz corresponding to brain oscillations specifically at the frequency range of the alpha and delta waves, respectively. It was thus assumed the brain could respond differentially to the varying ELF pulse-modulated RF EMFs via oscillatory aspects of the incoming radiation.

The current sleep and waking EEG studies showing a reverse relationships between talk and listen mode signals on the post-exposure sleep process (talk mode: 'alerting' vs. listen mode: 'sleep preservation') did support the assumption at the outset that the brain could recognize and respond differently to the DTX and TDMA pulsed signals. Although in the current studies the brain activities were not recorded simultaneously during exposure (to prevent any possible RF interfering on the EEG signals), it should be emphasized that the ELF components of the mobile phone signals are within the frequency range that the brain naturally employs in its communication network. Furthermore, it has been confirmed in many brain stimulation studies (using rTMS) that, by synchronizing the stimulation rates with the sleep/waking EEG frequencies, the cortical oscillations can be subsequently modulated and such effects may be outlasting even after the cessation of the stimulation. For example, 0.8 Hz rTMS over the sensorimotor area during stage 2 sleep can trigger EEG slow oscillations in the

following SWS [Massimini et al., 2007] and 5-Hz rTMS over the primary motor cortex during the pre-sleep waking period can trigger the EEG 0.5-4 Hz power enhancement in the premotor cortex during the subsequent sleep after stimulation cessation [Huber et al., 2007]. Moreover, it has been indicated that the modulation of post-stimulation sleep EEG oscillations (such as enhancing the power of sleep spindles and slow oscillations during SWS) by synchronizing with the external stimulation (0.75 Hz transcranial direct current stimulation) can even induce a change in memory performance, probably via the mechanism of sleep-dependent memory consolidation [Marshall et al., 2006].

8.3 DEVELOPING FUTURE RESEARCH

Although the actual physiological mechanism is unknown, the reverse EEG spindle effects of talk and listen mode exposure suggest the DTX frequency of 2 Hz and the TDMA frequencies of 8 and 217 Hz may have distinctive effects on neuronal excitation or inhibition, and may thus impart a change in the oscillatory properties of the cortico-thalamo-cortical loops. To investigate this, future research could combine TMS and other neuroimaging techniques such as EEG, MEG, PET and fMRI for causal mapping of mobile phone effects on neuronal function. Moreover, to further reveal the regional and interregional alternations of neuronal networks, it is suggested that these imaging data be analyzed with source imaging tools (e.g. sLORETA) in conjunction with EEG/MEG connectivity computation tools (e.g. dynamic causal modelling, see Friston et al. [2003]; Chen et al. [2008]).

In addition to this, future research should find out if the mobile phone ELF pulse modulation effect is caused by alternations in the levels of neuromodulatory chemicals, such as cortisol, growth hormone, noradrenaline and acetylcholine. This crucial point requires further exploration, as it is related to the change of behavioural state of the brain (for review, see Jones [2005]). However, a direct measure of these neurochemicals in the human brain is not available with the current neuroimaging tools. Therefore, future work should be conducted in animals integrating EEG recording with neurochemical analytic tools, such as microdialysis combined with high-performance liquid chromatography (HPLC).

In viewing the strong mobile phone listen- and standby-mode effects on the post-exposure SWS spindles (which produce large influxes of calcium ions into cortical neurons, where they can trigger molecular cascades known to strengthen the

connections between neurons acquired during wakefulness, c.f. Steriade et al. [1993a]), future research should investigate the mobile phone field effects on the sleep-dependent neural plasticity. In being able to characterize the differential EEG oscillatory patterns (with related plasticity outcomes) induced by varying field implementation strategies, this would have significant practical implications. For examples, future studies can manipulate 1) the field intensity to see the *dose-dependent* effect, 2) the exposure timing to see the *sleep phase-dependent* effect, and 3) the exposure site to see the *task modality-dependent* effect of sleep-dependent neural plasticity.

8.4 METHODOLOGICAL CONCERNS AND FUTURE IMPROVEMENTS

8.4.1 Resting Waking EEG

In the current study, we did not find any post-exposure resting waking EEG effects with the alpha rhythms for the three mobile phone signals when compared with sham mode, whereas it was often the key finding reported by several authors [Reiser et al., 1995; Huber et al., 2002; Curcio et al., 2005; Regel et al., 2007a; Croft et al., 2008]. Such an absence of alpha EEG power change may be due to an experimental bias in reproducing resting wakefulness, where the subjects is supposed to think or do nothing. In fact, it is experimentally unlikely to reach a perfect state of resting. Therefore, future EEG studies should perform a direct manipulation of several cognitive states of activation and then compare these different levels of information processing with the resting state. On the other hand, the EEG results of the resting state may also differ depending on which part of continuous electrical activity is selected for analysis (e.g. our T1 period versus T2 period, see Chapter 5). As a small change in one part of the EEG does not provide a noticeable change in the energy of the whole recording, nonlinear EEG signal process which are capable of detecting differences in the character of the signals, might be useful in the detection of specific small changes.

8.4.2 The Physiological Implication of EEG Spectral Power Changes

It is well known that EEG power measurements provided by spectral analysis can be the result of an increase in either the 'wave amplitude' or the 'wave incidence.' At the neuronal level, the increase of wave amplitude can be accounted for by reductions in

phase shifts among the outputs of large cortical populations [Pfurtscheller & Lopes da Silva, 1999; Nunez et al., 2001] while the increase of the wave incidences can be accounted for by increments in the number of oscillations within a particular frequency range. Both neuronal behaviours have different physiological implications, as

(i) The enhancement of EEG amplitudes can be attributed to elevations of the extracellular potassium in the neocortex [Louvel et al., 2001], changes in cellular conductivity, or a high level of synchronization in the regional cortical neurons, while

(ii) The increase in a certain wave incidence, on the other hand, may be referred to an increased activation of collaterals between neocortical columns containing the same intrinsic oscillators.

In the present study, we cannot precisely separate these two EEG spectral features while they may be used to better characterize different mobile phone effects. To achieve this, future research should consider to apply 'period-amplitude analysis' technique in all EEG derivations and frequency bins (for details, see Hoffmann et al., 1979). In brief, period-amplitude technique is composed of two different analysis procedures. First, the EEG signal is examined to detect whether a zero-crossing event has occurred. Zero-crossing events are defined as changes in the polarity of the EEG signal crossing 0 V threshold. Each time a zero-crossing event occurs in one EEG epoch, the duration since the last zero-cross event is determined, and the frequency is then identified. Second, the areas under the curve, or the integrated amplitude, provide information about the number of oscillations and the wave amplitude, respectively, in a specific EEG derivation for any frequency band of interest. Of note is that, occasionally, period-amplitude algorithms do not detect fast EEG frequencies superimposed on a background of slow-wave activity. To solve this problem, it is suggested to apply a bandpass filter to the signal before the period-amplitude analysis [Ktonas, 1987].

8.4.3 Experimental Design

The present EEG studies were actually a preliminary study in terms of the number of participant and the single-blind design, though we were quite confident in the reliability of the experimental procedure and the spatial or temporal resolution of the techniques used to pinpoint the EEG effects of varying mobile phone signals. For any future replication study, however, it is recommended that the participant number is increased and a 'double-blind' design is added, to see if the current findings can be confirmed.

8.5 FINAL CONCLUSIONS

Overall, the work as contained within this thesis confirms and builds on a growing body of work suggesting the important role of ELF pulse modulation of the mobile phone EMF effects on human neurophysiology. Specifically, current findings extend knowledge of how varying ELF pulse modulation components of mobile phone signals may affect the brain electrical activity during sleep and waking, as well as the psychomotor vigilance after 30-min exposure. It is unique of this study to observe an opposite EEG effects between 'talk' and 'listen' mode for sleep onset and sleep consolidation. As these two modes share the same ELF pulse modulation components of 8 and 217 Hz while listen mode has an extra component of 2 Hz, it is suggested that the alerting effect of the 8 and 217 Hz pulsing may be negated by the 2 Hz pulsing. Although the actual mechanism is unknown, since these ELF (esp. 2 and 8 Hz) pulsing frequencies of mobile phone signals correspond to brain oscillation frequencies at the delta and alpha frequency bands, it is suspected the brain may be able to respond differentially to the varying ELF components of mobile phone signals via oscillatory aspects of the incoming radiation. Viewed in this light, future investigation should shed light on the effects of varying ELF pulse-modulated EMFs on the regulation of neuronal excitation/inhibition and neuromodulatory chemicals. Conceivable research tools to address this issue in human subjects include using multi-modality neuroimaging (i.e. rTMS + EEG/MEG/fMRI/PET) combined with advanced source mapping and/or functional connectivity computation tools. In addition, as the current study provides a strong suggestion of mobile phone effects on the post-exposure sleep oscillations of the cortico-thalamo-cortical loops, it may be important for future sleep EEG study to find out if the sleep-dependent neural plasticity is also affected differentially by varying mobile phone field implementation strategy (e.g. sleep-dependent neural plasticity changes with varying stimulation frequencies, intensities, timing or sites). Finally, it should be noted that the present study remains informative yet preliminary and further study is required with an improved and advanced methodology to further address whether there is a positive or negative effect of mobile phone usage on the neurophysiological function.

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10 APPENDICES

10.1 APPENDIX A: ETHICAL APPROVAL

ETHICAL ADVISORY COMMITTEE

Loughborough University

RESEARCH PROPOSAL FOR HUMAN BIOLOGICAL OR PSYCHOLOGICAL AND SOCIOLOGICAL INVESTIGATIONS

This application should be completed after reading the University Code of Practice on Investigations Involving Human Participants (found at http://www.lboro.ac.uk/admin/committees/ethical/ind-cophp.htm).

1. Project Title

Electromagnetic Radiation from Mobile Phone: Effect on Human Sleep EEG

2. Brief lay summary of the proposal for the benefit of non-expert members of the Committee

The few human laboratory studies on the effects of electromagnetic radiation (EMR), given at 'mobile phone' intensities, have shown non-thermal effects on the functional state of the brain. These include: sleep enhancement, an increased 'brain-wave' (EEG) power in the alpha range, and an improvement in memory performance. Sleep provides an unique artefact-free brain state for studying EMR effects, an area which has received little attention, non within the UK. At Loughborough University there are the equipment/facilities for generating and monitoring EMR (Centre for Mobile Communications Research) and for studying the sleep EEG (Sleep Research Centre). In a collaborative study that has the full support of both Centres, we are now undertaking a systematic investigation into hitherto unexplored research aspects of the effects of normal mobile phone EMR intensities on the sleep of healthy young people. We shall also be looking at possible effects on waking psychological performance the following day.

3. Details of responsible investigator (supervisor in case of student projects)

Title Prof.. Surname Horne Forename Jim

Department Human Sciences

Email address J.A.Horne@lboro.ac.uk

Personal experience of proposed procedures and/or methodologies.

Over 20 years of experience in all sleep methodologies and procedures to be utilized.

4. Names, experience, department and email addresses of additional investigators

Clare Anderson, Ph.D., Lecturer, Department of Human Sciences. E-mail: C.Anderson@lboro.ac.uk.
Yiannis Vardaxoglou, Ph.D., Professor, Director of Centre of Mobile Communication Research, Department of Electronic and Electrical Engineering. E-mail: J.C.Vardaxoglou@lboro.ac.uk.
Patrick McEvoy, MEng, Research Manager, Centre of Mobile Communication Research, Department of Electronic and Electrical Engineering. E-mail: p.mcevoy@lboro.ac.uk
Ching-Sui Hung, research student, Department of Human Sciences. E-mail: C.Hung@lboro.ac.uk

5. Proposed start and finish date and duration of project

Start date Mar. 1st, 2005 Finish date August 31 2007 Duration 2.5 years

6. Location(s) of project

Sleep Research Centre, Department of Human Sciences, Loughborough University

7. Reasons for undertaking the study (eg contract, student research)

PhD study

8. Do any of the investigators stand to gain from a particular conclusion of the research project?

No

9a. Is the project being sponsored? **Yes** ☐ **No** *

If yes, please state source of funds including contact name and address.

9b. Is the project covered by the sponsors insurance? **Yes** ☐ **No** *

If no, please confirm details of alternative cover (eg University cover).

10. Aims and objectives of project

The current study will investigate the non-thermal effects of EMR from mobile phones at a low intensity, well within safe absorption limits (typical of that commonly transmitted from the phone's antenna) using healthy young participants. We will vary EMR signal transmission modes and examine the subsequent sleep EEG changes. Our particular interest is to specify any key modulation technique that is responsible for the induced effect on sleep EEG. A future study would apply the same EMR exposure protocol to explore the effect on waking behavioural performance.

11. Brief outline of project

The project will first examine the effect of the mobile phone's signal when transmitted in speaking and listening mode on the sleep EEG and subjective sleepiness. We will use within-subject, sham-exposure controlled, single blind and cross-over design.

A) STUDY DESIGN

The design of the study is a 3-way (conditions, days, subjects) latin-square model in order to be able to analyze and to eliminate the carry-over effects. The experiment consists of three sessions of EMR exposure schemes (listening, speaking, sham exposure) separated by one-week intervals. EMR exposure is scheduled according to a randomized, sham-exposure controlled, single blind, cross-over design. Since the uniqueness of the current study in terms of EMR signals being realistic, the EMR exposure intensity used is at the normal-use range of the mobile phone, which is far below the safety guideline for electromagnetic exposure. In the pilot study, we will recruit three participants. The number of participants will be expanded in later experiments.

B) MEASUREMENTS TO BE TAKEN

1 The participant should arrive at the Sleep Research Centre at around 12.30 hours for EEG preparation. The EMR exposure session will begin at around 13.10 with an pre-exposure waking EEG recording with eye open and eye close (each takes 3 minutes). Then the subject will be exposed to an EMR for 30 minutes. Subsequently, the post-exposure waking EEG will be recorded with eye open and eye close. After that, the subject will be put in bed with light off and asked to try to sleep as much as they can for 1 hour.
2 EEG is a non-invasive, risk free measurement of brain electrical activity. When recording EEG, the head of the participant will be placed several electrodes according to a basic EEG montage. The procedure will be fully explained prior to the screening process. The centre has undertaken over 1000 EEG recordings.
3 In addition to EEG recording, the subjective sleepiness of the subject before the 1.5-hour sleep episode will be collected through subject's reported Karolinska Sleepness Scale (Åkerstedt & Gillberg, 1990) report every 180 seconds.
4 It should be noted again that the signal intensity of the mobile phone used in the current study is at the normal-use range found from the conversation mode.

12. Please indicate whether the proposed study:

Involves taking bodily samples	**Yes**		**No**	*
Involves procedures which are physically invasive (including the collection of body secretions by physically invasive methods)	**Yes**		**No**	*
Is designed to be challenging (physically or psychologically in any way), or involves procedures which are likely to cause physical, psychological, social or emotional distress to participants	**Yes**		**No**	*
Involves intake of compounds additional to daily diet, or other dietary manipulation / supplementation	**Yes**		**No**	*
Involves pharmaceutical drugs (please refer to published guidelines)	**Yes**		**No**	*
Involves testing new equipment	**Yes**		**No**	*
Involves procedures which may cause embarrassment to participants	**Yes**		**No**	*
Involves collection of personal and/or potentially sensitive data	**Yes**		**No**	*
Involves use of radiation (Please refer to published guidelines. Investigators should contact the University's Radiological Protection Officer before commencing any research which exposes participants to ionising radiation – e.g. x-rays)	**Yes**		**No**	*
Involves use of hazardous materials (please refer to published guidelines)	**Yes**		**No**	*
Assists/alters the process of conception in any way	**Yes**		**No**	*

Involves methods of contraception	**Yes**		**No**	*
Involves genetic engineering	**Yes**		**No**	*

If Yes - please give specific details of the procedures to be used and arrangements to deal with adverse effects.

13. Participant Information

Details of participants (gender, age, special interests etc)

Healthy participants aged 18-28 years old will be recruited. They will be right-handed, of normal weight range for height, good sleepers, sleeping regular hours and regular mobile phone users.

Number of participants to be recruited: For the pilot study, 3 participants will be recruited but more will be recruited for later study.

How will participants be selected? Please outline inclusion/exclusion criteria to be used.

Inclusion Criteria:

1 aged 18-28 y/o,
2 healthy (medication-free),
3 of normal weight range for height (18.5 < BMI < 28),
4 good sleepers (8±1 hour sleep per night),
5 sleeping regular hours,
5.1 infrequent daytime nappers (less than once a week),
5.2 no complaints of daytime sleepiness (the range of the Epworth Sleepiness Score is within 0-10, *Johns, 1991*),
5.3 no indicated potential sleep disorders,
6 regular mobile phone users

Exclusion Criteria:

7 un-regular sleep/waking pattern,
8 shift workers,
9 using hand-free handset
10 with migraine or epilepsy or claustrophobia

How will participants be recruited and approached?

Advertisements on the University website and posters.

Please state demand on participants' time.

The participant will be required on three separate sessions (each one is one-week apart) to undergo mobile phone signal exposure and the subsequent sleep recording during the afternoon around 12.30-16.00 hours. Three days before each exposure session, the participants are required to keep continuous wrist actiwatch recording and sleep log. Participants will be paid for their time and inconvenience.

14. Control Participants

Will control participants be used? **Yes** [ ] **No** [*]

If Yes, please answer the following:

Number of control participants to be recruited:

How will control participants be selected? Please outline inclusion/exclusion criteria to be used.

How will control participants be recruited and approached?

Please state demand on control participants' time.

15. Procedures for chaperoning and supervision of participants during the investigation

1 During each exposure session: the participant's EEG and behavioural state will be observed through spontaneous recording of Embla N7000 recording system and its corresponding software Somnologica 3.0.
2 EEG electrodes are applied using the recommended methods and sterile products. All electrodes and other equipment are cleaned to the highest standard as recommended by the manufacturers. Electrode placement is in accordance with the standard "10-20" EEG system.
3 The Embla recording system is certified to carry the CE mark (CE 0413). The CE mark is a declaration that Embla is in compliance with the directive set forth by the European Union for medical devices.
4 Participants always supervised by experimenter person of the opposite sex, who always present in the centre when testing occurs. However, there will be at least one investigator of the same sex as the participant be present throughout the investigation.

16. Possible risks, discomforts and/or distress to participants

1 Participants may feel sleepy at times but only the normal "afternoon dip"-merely exacerbated by lying in bed.
2 Participants may feel slightly uncomfortable with the electrodes attached purely due to appearance, but to ensure this is minimal we explain the equipment and demonstrate prior to any consent to participate being given, and ensure participants are fully aware they can withdraw at any time should they feel uncomfortable. As aforementioned, following over 1000 recordings in the centre, we have never had a participant withdraw from our research for this reason.

17. Details of any payments to be made to the participants

Participants will be paid for their time, which will be worked out at a cost of £5 per hour. After the full study, the participant will receive a total of £50, within which £45 will be paid for completing three experimental sessions (3 hours/session*3 sessions) and an extra £5 for completion bonus.

18. Is written consent to be obtained from participants? **Yes** [*] **No** [ ]

If yes, please attach a copy of the consent form to be used.

If no, please justify.

19. Will any of the participants be from one of the following vulnerable groups?

Children under 18 years of age	**Yes**		**No**	*
People over 65 years of age	**Yes**		**No**	*
People with mental illness	**Yes**		**No**	*
Prisoners/other detained persons	**Yes**		**No**	*
Other vulnerable groups	**Yes**		**No**	*

If you have selected yes to any of the above, please answer the following questions:

1 what special arrangements have been made to deal with the issues of consent?

2 have investigators obtained necessary police registration/clearance? (please provide details or indicate the reasons why this is not applicable to your study)

20. How will participants be informed of their right to withdraw from the study?

Participants will be briefed fully before any testing takes place. They will be informed verbally of their right to withdraw, and this will also be contained on the consent form they will be required to sign. If for any reason the participant does not wish to continue his/her participation, s/he is free to leave the experiment at any time without having to explain his/her reason. The participant will be paid for his/her participation minus completion bonus.

21. Will the investigation include the use of any of the following?

Audio recording	**Yes**		**No**	*
Video recording	**Yes**		**No**	*
Observation of participants	**Yes**		**No**	*

If yes to any, please provide detail of how the recording will be stored, when the recordings will be destroyed and how confidentiality of data will be ensured?

22. What steps will be taken to safeguard anonymity of participants/confidentiality of personal data?

All of the data collected in this study will be encoded using the participants assigned subjects' ID, which normally consists of subject number and condition. So the participant remains anonymous and only those involved in this research will have access to the data.

23. What steps have been taken to ensure that the collection and storage of data complies with the Data Protection Act 1998? Please see University guidance on Data Collection and Storage and Compliance with the Data Protection Act.

All data will be encoded to ensure participants remain anonymous. All data will be referred to by a subject ID of which the participants' identity is not able to be established. In addition, all of the data will be stored in locked cupboards, on the premises of the centre.

24. INSURANCE COVER:

It is the responsibility of investigators to ensure that there is appropriate insurance cover for the procedure/technique.

The University maintains in force a Public Liability Policy, which indemnifies it against its legal liability for **accidental** injury to persons (other than its employees) and for accidental damage to the property of others. Any **unavoidable** injury or damage therefore falls outside the scope of the policy.

Will any part of the investigation result in **unavoidable** injury or damage to participants or property? **Yes** [ ] **No** [*]

If yes, please detail the alternative insurance cover arrangements and attach supporting documentation to this form.

The University Insurance relates to claims arising out of all **normal** activities of the University, but Insurers require to be notified of anything of an unusual nature

Is the investigation classed as **normal** activity? **Yes** [*] **No** [ ]

If no, please check with the University Insurers that the policy will cover the activity. If the activity falls outside the scope of the policy, please detail alternative insurance cover arrangements and attach supporting documentation to this form.

25. Declaration

I have read the University's Code of Practice on Investigations on Human Participants and have completed this application. I confirm that the above named investigation complies with published codes of conduct, ethical principles and guidelines of professional bodies associated with my research discipline.

I agree to provide the Ethical Advisory Committee with appropriate feedback upon completion of my investigation.

Signature of applicant: .....

Signature of Head of Department: .....

Date 4/3/2005

PLEASE ENSURE THAT YOU HAVE ATTACHED COPIES OF THE FOLLOWING DOCUMENTS TO YOUR SUBMISSION.

1 Participant Information Sheet
2 Informed Consent Form
3 Health Screen Questionnaire
4 Advertisement/Recruitment material*
5 Evidence of consent from other Committees*

*where relevant

10.2 APPENDIX B: SUBJECT'S CONSENT FORM

Sleep Research Centre
Participant Consent Form

I _____ consent to taking part in a Sleep Research Centre experiment. An explanation of the nature and purpose of the procedure has been given to me by _____.

I understand that I may withdraw from the experiment at any time, and that I am under no obligation to give reasons for such withdrawal. I understand also that I may feel sleepy during some parts of the experiment, and undertake to obey the instructions of the experimenter for safety purposes.

I understand that any information about myself which I have given will be treated as confidential by the experimenter.

Signed _____
Dated _____
Signature of experimenter _____

Loughborough
Sleep Research Centre

http://sleep.lboro.ac.uk
Tel: 01509 228814
E-Mail: C.Hung@lboro.ac.uk

10.3 APPENDIX C: SCREENING QUESTIONNAIRE

SLEEP RESEARCH CENTRE
Screening Questionnaire: CONFIDENTIAL

PERSONAL INFORMATION

Name: .....
Address: .....
.....
.....
Phone Number: .....
National Ins: .....

Age/D.O.B. .....
Sex: .....
Weight: .....
Height: .....
Occupation: .....
BMI: .....

Participation YES/NO

If Yes.....
Subject No:
Suitable Times
.....
.....
.....

If No...
Reason for Rejection
.....
.....
.....

GENERAL QUESTIONS

1. Do you smoke?

Yes	1
Sometimes	2
No	3
Don't Know	0

1a. If yes, How many cigarettes per day?

1-5	1
5 or more	2
Don't Know	0

2. How many cups of tea/coffee do you usually drink in a day?

None	1
1-2	2
3-4	3
5-6	4
Over 6	5
Don't Know	0

HEALTH QUESTIONS

4. In general would you say your health is:

Excellent	1
Very Good	2
Good	3
Fair	4
Poor	5

5. Have you ever experienced any of the following medical conditions, and if so when?

No = 1 **Yes in the past = 2**
Yes, sometimes = 3 **Yes, at present = 4**

(a)	Asthma	.....	(b)	Hay fever	.....
(c)	Eczema	.....	(d)	Allergies	.....
(e)	Thyroid Problems	.....	(f)	Undue anxiety	.....
(g)	Sleepwalking	.....	(h)	Loud snoring	.....
(I)	Nightmares	.....	(j)	Bruxism	.....
(k)	Difficulty reading/writing	.....	(l)	Arthritis/Rheumatism	.....
(m)	Depression	.....	(n)	Heart problems	.....
(o)	Stomach problems	.....	(p)	Waking up with a jolt	
(q)	Waking up excessively early	.....	(r)	Difficulty falling asleep	.....
(s)	Stress/anxiety at home/work	.....	(t)	Epilepsy	.....
(u)	Migraine	.....	(v)	Colour blindness	.....
(w)	Hearing Problems	.....	(x)	Diabetes	.....

6. Do you regularly task pills or medicines from the chemist or by prescription?

Yes	1
No	3
Don't Know	0

If so can you tell me what they are?

.....
.....

SLEEP QUESTIONS

7. What time do you normally go to bed? .....

8. What time do you normally get up? .....

9. How long does it normally take you to fall asleep?

0-5 minutes	1
5-10 Minutes	2
10-20 Minutes	3
20-30 Minutes	4
Over 30 Minutes	5
Don't know	0

10. Do you ever miss a night's sleep or have much sleep than usual?

No	1
Yes, sometimes	2
Yes, regularly	3
Don't know	0

10a) If yes, can you tell me what is the reason for this?

.....
.....

11. How much does your quality of sleep vary from one night to the next?

Very much	1
Moderately	2
Slightly	3
Not at All	4

12. How many times do you wake , on average, a night?

Never	1
Hardly Ever	2
Once or Twice	3
Once a month	4
Never	5
Don't know	0

12a) If volunteer wakes up:
How long does it take you to get back to sleep again?

Less than 10 minutes	1
10 – 30 Minutes	2
30 – 60 Minutes	3
Over 60 Minutes	4
Don't know	0

13. Are you a Morning Person or Evening Person?

Morning	1
Evening	2
Neither	3
Don't know	0

14. Do you ever have difficulty staying awake during the day?

Yes every day	1
Yes, several times a week	2
Yes, several times a month	3
Yes, once a month	4
Never	5
Don't know	0

14a) If yes, At about what time does this sleepiness usually start?

.....
.....

15. Do you ever nap during the day?

Yes	1
No	3
Don't Know	0

15a) If yes, how often on average?

Every Day	1
2-3 Times per week	2
Once per week	3
Once per month	0
Don't know	

16. Do you ever experience 'poor sleep'?

Yes	1
Sometimes	2
No	3
Don't know	0

17. If you had a poor nights sleep, does it affect:

How you feel	1
How you perform	2
Both of these	3
Neither of these	4
Don't know	0

18. If you had a poor night's sleep, when do you feel the consequences?

The next day	1
The day after	2
Both of these days	3
Neither of these days	4

19. Please Complete the Following:

How likely are you to fall asleep in the following situations? Please indicate, using the following scale, which is most appropriate given the situation.

0 = Would *never* doze

1 = *Slight* chance of dozing

2 = *Moderate* chance of dozing

3 = *High* chance of dozing

Situation	**Chance of Dozing**
Sitting and Reading	.....
Watching TV	.....
Sitting inactive in a public place (e.g. theatre/meeting)	.....
As a passenger in a car for an hour without a break	.....
Lying down in the afternoon when circumstances permit	.....
Sitting and talking to someone	.....
Sitting quietly after lunch without alcohol	.....
In a car, while stopped for a few minutes in the traffic	.....
ESS	

User Behaviours of the Mobile Phone

20. At what age do you have your first mobile phone? _____ y/o

Younger than 10 y/o	1
10-15 y/o	2
15-20 y/0	3
20-25 y/0	4
Older than 25 y/0	0

21. How many hours do you keep your mobile phone switched-on, on average, a day?

24 hours	1
20-24 hours	2
15-20 hours	3
10-15 hours	4
5-10 hours	5
less than 5 hours	0

22. Do you use a hand-free handset?

yes	1
no	2

23. How much time do you normally spend on using your mobile phone a day?

More than 5 hours	1
3-5 hours	2
1-2 hours	3
0.5-1 hour	4
less than 0.5 hour	0

24. What main function do you use your mobile phone?

Talking	1
Texting	2
Taking pictures	3
Download pictures / phone rings / games / MP3 / other applications	4
Browsing web information	5
E-mail	6
Shopping	7
Financial transection	8
Alarm	9
Other function: _____	0

25. Do you turn "off" your mobile phone during your sleep at night?

Yes (always turn it off every night)	1
Yes, regularly (turn it off 3-6 nights per week)	2
No, not quite often (only turn it off 1-2 nights per week)	3
No, never (always turn it on every night)	0

25(a).If Not, why don't you turn off the mobile phone during the night sleep?

Receiving text messages	1
Using alarm functions	2
Receiving calls	3
Listening to downloaded MP3	4
Other reason: _____	0

THANK YOU, THAT IS THE END OF THE QUESTIONNAIRE

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10.4 APPENDIX D: SLEEP DIARY

Sleep Research Centre
Sleep Diary

Subject's Name: _____ Subject's No:_____

This diary will be complementary to your Actiwatch data. Please note down the exact time of the following activities and **wear the Actiwatch all the time even when you go to sleep!!!** To make a maker of your bed time and getting-up time, please **press the button on the actiwatch when you go to sleep and get up**.

Here, please note down the time and the duration of the following activities when you remove your Actiwatch during the day longer than 5 minutes:

	Example (24/Feb)	Day 1 (/)	Day 2 (/)	Day 3 (/)	Test day (/)
Shower	22:00-22:15				
Sports	15:30-16:30				
Others	20:34-20:45 (washing)				

Please answer these questions in 5 minutes immediately after you get up in the morning:

	Example	Day 1	Day 2	Day 3	Test day
At what time did you go to bed last night?	23:00				
How long did it take you to fall asleep?	5 mins				
How many times did you wake up during the night after falling asleep?	1				
At what time did you wake up during the night	3:30				
For what reason did you wake up during the night?	toilet				
At what time do you get up this morning?	8:30				
How alert do you feel this morning? **0 1 2 3 4** **not at all moderately very**	3				
How enjoyable was your sleep last night? **0 1 2 3 4** **not at all moderately very**	4				
Nap time during the day	14:30-15:00				

Please bring this diary with you when coming for the test. Thank you very much for your help!