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NON-THERMAL EFFECTS AND MECHANISMS OF INTERACTION BETWEEN ELECTROMAGNETIC FIELDS AND LIVING MATTER

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Is cognitive function affected by mobile phone radiation exposure?

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Abstract

Behavioral tasks, including the Morris water maze (MWM), radial arm maze and object recognition task, have been extensively used to test cognitive impairment following exposure of rodents to mobile phone (MP) radiation on various frequencies and specific absorption rate (SAR) values. Exposed animals in most of the cases revealed defects in their working memory possibly due to cholinergic pathway distraction. The only experiment on mice at very low SAR did not show statistically significant deficits by 8-arm maze, but our own data in mice exposed to GSM 900 MHz radiation, revealed memory lesions on MWM task; exposed mice had difficulties in memory consolidation and/or retrieval of the stored information. Lastly, a number of studies have been applied to volunteers showing variable results depending on the experimental setup, revealing memory improvement or deficits following MP exposure.
The recorded data from the literature are generally favouring the conclusion that EMF is affecting memory function although a more rigorous and reproducible exposure system has to be adopted in relation to the recently criticized importance of SAR.

Key words: **electromagnetic fields, Morris water maze, spatial memory, cognition**

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Note added in proofs:
A number of studies have appeared after the submission of the manuscript, dealing with EMFs and cognitive memory function. It is worth mentioning that a positive effect was found on transgenic mice for Alzheimer's disease following chronic exposure to MP radiation as reported by Arendash GW, Sanchez-Ramos J, Mori T, et al. Journal of Alzheimer's Disease 2010; 19: 191–210.

Introduction

The extended use of mobile phone technology throughout all social levels and all ages, starting from as low as 4 years old, has forced a large number of scientists to get involved in the investigation of the effects. The major issue is that unlike other forms of everyday radiation exposure, the use of the mobile phone and the wireless DECT phone takes place near the user's head and therefore direct or indirect effect on the brain function is highly possible. Thus, the elucidation of the cellular, molecular and behavioural effects has to be explored in depth, especially since the majority of life-time users will be the current teenagers.

The aim of this kind of research is to determine a specific absorption rate (SAR) value threshold below which no obvious effects are detected in any organism, any cell, in order to propose biologically based levels for exposing humans on a daily basis either through cell phones, or base stations or DECT wireless phones or even wi-fi routers and baby monitors.

To approach these questions, extensive research is being performed in various laboratories. Due to the still unknown mode of primary action at the molecular level, many approaches studying the effects of microwaves (MW) have been applied[1].

At the population level, studies deal with the effects by statistically correlating exposure conditions to health symptoms, as severe as brain tumors[2, 3], or mild well being discomforts, such as headaches or fatigue[4]. There is also a report on children exposed prenatally to mobile phone radiation showing defects on behavior[5]. In humans, the studies involve mainly volunteers and have investigated possible effects on sleeping conditions and memory function[6].

Studies on animal models involve every possible aspect of experimental approach (behavioral, molecular, biochemical, biophysical, ultrastructural, physiological). Such models used are mainly rodents and to a less degree insects. Our group has shown DNA fragmentation and induced cell death during oogenesis, along with a decrease in the offspring number in insects and a defect on osteogenesis following prenatal exposure in mice[7-9].

Due to the fact that mobile phone use affects mainly the brain tissues, special attention has been given to the study of hippocampus, cerebellum and frontal brain function and structure on rodents (mostly rats). In general there are numerous reports on the effects of electromagnetic fields (EMF) on cognitive functions. Animal learning and memory function have been tracked using mazes, such as the Morris water maze (MWM), the radial arm maze (RAM), as well as the object recognition task (ORT) and the object location task (OLT). It is well documented that these mazes are related to the spatial environment and recognition learning and memory. Extra maze spatial cues are widely applied to facilitate learning and testing any deficits following exposure to MW. Especially RAM is being used to explain hippocampal formation and function[10].

The MWM task is widely used since spatial navigation is a complex cognitive function that depends on several neural and cognitive systems for successful completion[6, 11]. Unlike the T-maze in which the animals have to make a binary decision (i.e. going left or right), in the MWM successful performance requires continuous monitoring of the animal's position in relation to extra-maze cues: a process that involves "cognitive mapping". Many reports have controversially showed impairment[12, 13], or improvement[14, 15].

At the cell culture level, a number of studies have been performed in order to clarify under controllable and reproducible conditions, the actual primary damage induced by

EMFs. Thus, in cultured hippocampus neurons a decrease of excitatory synaptic activity and a reduced number of excitatory synapses was detected after exposure to GSM 1800 radiation (15 min/day for 7 days) at a SAR value of 2.4 W/kg[16].

In addition, a recent report has found that EMFs affect the endocytotic activity of murine melanoma cells[17].

Besides MW radiation effects, a limited number of studies has used extremely low frequency (ELF) EMF (50 or 60 Hz depending on the power line) revealing memory deficits on rats[18-20], which, interestingly, become less prominent upon exposure of the animals to MW[21]. A similar study but on mice showed reversible effects on cognitive functions as revealed by 8-arm RAM[22].

Given the controversial evidence existing on the occurrence or not of any effects following MW exposure, we present herein a comparative analysis of reports on cognitive effects including some of our own recently published experimental data.

Results and discussion

Several pioneer studies concerning the effects of MW on cognitive functions, that examined the short term memory of rats, are published using a 2450-MHz circular waveguide exposure system and a SAR value of 0.6 W/kg[23]. These investigators demonstrated significant deficits when exposed rats were performing at the RAM and the MWM and suggested that the reported defects in the working memory of rats are possibly due to cholinergic pathway distraction. On a later report it was shown that rats exposed to the same conditions, pulsed 2450-MHz MW (500 pulses/s, average power density 2 mW/cm^2, average whole body SAR 1.2 W/kg), for 1 hour just before each training session in a water maze, showed a deficit in their spatial "reference" memory[24].

On the other hand, Cobb and collaborators[25], replicating the experiments by Lai[23], under the same conditions of exposure, i.e. 2450-MHz, circular polarized waveguide system (CWG), SAR value 0.6 W/kg, but with minor methodological differences, did not find any effects on memory and learning in rats. Additionally, another report that appeared at the same year by exposing rats at similar conditions, did not observe any effects with RAM (Table 1)[26]. However, it had been reported earlier that MW affect specific cognitive aspects of behavior such as, attention, memory, learning, discrimination, time perception, which may occur even at very low SAR levels[27].

Also, using RAM and ORT, no evidence was found at even higher SAR values of 1-3.5 W/kg, by applying head only and not whole body exposure of rats for 45 minutes and at another frequency of 900-MHz[28]. Cosquer and collaborators on 2005 using a 12-arm maze apparatus, bordered by 30 cm high opaque walls, observed that exposed rats behaved normally. Therefore they concluded that MW exposure under those conditions (2450-MHz, circularly polarized field – Table 1) does not alter spatial working memory, when access to spatial cues was reduced[29].

In a recent report, the MWM performance of male Wistar rats was affected following exposure to 50 missed calls/day for 4 weeks by a GSM (900/1800 MHz) mobile phone in vibratory mode[30]. The phone-exposed animals had significantly (~3 times) higher mean latency to reach the target quadrant in the MWM and spent significantly (~2 times) less time in the target quadrant. Trying to understand the cellular basis of the observed behavioural deficits, Leif Salford and collaborators have reported that a 2-hr exposure of rats at GSM 915-MHz resulted in neuronal damage, 28 and 50 days later[31]. In addition,

Table 1 - Comparative studies of EMF on cognitive performance (ND=not determined, MWM=Morris Water Maze, RAM=Radial Arm Maze)

Study	Experimental Animal	Exposure source	Frequency	SAR or density	Duration of exposure	Task	Findings
Lai *et al.*, 1994	Rats	Circular polarized generator	2450 MHz	0.6 W/kg	45' before each trial	12-arm RAM	Deficit in working memory
Wang B, Lai H, 2000	Rats	Circular polarized generator	2450 MHz	1.2 W/kg	1 h before each training	MWM	Deficit in spatial reference memory
Cobb *et al.*, 2004	Rats	Circular polarized generator	2450 MHz	0.6 W/kg	45' before each trial	12-arm RAM	No effect
Dubreuil *et al.*, 2003	Rats	RF generator Head only	GSM 900 MHz	1 W/kg 3.5 W/kg	45' before each trial	12-arm RAM ORT	No effect
Cassel *et al.*, 2004	Rats	Circular polarized generator	2450 MHz	0.6 W/kg	45' before each trial	RAM	No effect
Cosquer *et al.*, 2005	Rats	Circular polarized generator	2450 MHz	0.6 W/kg	45' before each trial	RAM reduced access to cues	No effect
Nittby *et al.*, 2008	Rats	TEM cells	GSM 900 MHz	0.6 mW/kg 60 mW/kg	2 hr/week for a year	ORT episodic-like memory test 3 weeks after exposure	Effect
Narayanan *et al.*, 2009	Rats	Mobile phone	GSM 900/1800 MHz	ND	~ 50'/day (50 missed calls/day for 4 weeks)	MWM	Spatial memory impairment
Lai, 1996 Lai *et al.*, 1998	Rats	Sinusoidal magnetic fields	60Hz	1 mT	1 hr	12-arm RAM	Effect
Jadidi *et al.*, 2007	Rats	Sinusoidal magnetic fields	50 Hz	8 mT	20'	MWM	Spatial memory impairment
Sienkiewicz *et al.*, 2000	Mice	GTEM cells far field	GSM 900 MHz	0.05 W/kg	45'/day for 10 days	8-arm RAM	No effect
Fragopoulou *et al.*, 2010	Mice	Mobile phone	GSM 900 MHz	0.41-0.98 W/kg	1 hr before each trial and between the trials	MWM	Spatial memory impairment, learning lesions

(continued)

Table 1 - *continued*
(ND=not determined, MWM=Morris Water Maze, RAM=Radial Arm Maze)

Study	Experimental Animal	Exposure source	Frequency	SAR or density	Duration of exposure	Task	Findings
Sienkiewicz *et al.*, 1998	Mice	Sinusoidal magnetic fields	50 Hz	7.5 μT to 7.5 mT	45' before each trial	8-arm RAM	Reversible effects
Preece *et al.*, 1999	Humans	Local brain exposure analog phone	915 MHz	1 W power	ND	Working memory	Improved performance
Koivisto *et al.*, 2000	Humans	Local brain exposure by mobile phone	GSM 902 MHz	0.25 W mean power	On and off	Working memory	Improved performance
Edelstyn and Oldershaw, 2002	Humans 20-22 years old	Local brain exposure by mobile phone	GSM 900 MHz	1.19 W/kg	30'	Cognitive neuropsycho-logical tests subtraction and verbal fluency	Improvement
Maier *et al.*, 2004	Humans	Local brain exposure by mobile phone	GSM 915 MHz	1.0 mW/m^2	50'	Auditory discrimination	Impairment
Besset *et al.*, 2005	Humans	Local brain exposure by mobile phone	GSM 900	ND	2 hr/day, 5 days/week for 45 days	Cognitive tasks	No effect
Russo *et al.*, 2006	Humans	Local brain exposure by mobile phone	GSM 888 MHz Modulated CW-un-modulated	1.4 W/kg	40' prior to test	Cognitive tasks	No effect
Krause *et al.*, 2006	Children	Local brain exposure by mobile phone	GSM 902 MHz	1.4 W/kg	On and off	Auditory memory task	Effects on brain oscillatory responses
Regel *et al.*, 2007	Humans	Local brain exposure by mobile phone	GSM 900 MHz	1.0 W/kg	30' prior to test	Cognitive tasks	Increased accuracy in a working memory test
Haarala *et al.*, 2007	Humans	Signal generator and dummy phone	GSM 902 MHz	1.1 W/kg	On and off	Cognitive tasks	No effects
Luria *et al.*, 2009	Humans	Local brain exposure by mobile phone	GSM Nokia 5110	0.54-1.09 W/kg	On and off	Spatial working memory	Delay on reaction time

(continua)

Table 1 - *continued*
(ND=not determined, MWM=Morris Water Maze, RAM=Radial Arm Maze)

Study	Experimental Animal	Exposure source	Frequency	SAR or density	Duration of exposure	Task	Findings
Wiholm *et al.,* 2009	Humans	Headset with a fixed antenna placed on the left side of the head	884 MHz	1.4 W/kg	150' prior to test at 10 p.m.	Spatial memory and learning	Symptomatic group improved their performance

Reports have been ordered according to date published, species exposed and type of radiation

the same group has reported that the blood brain barrier (BBB) has been disrupted in irradiated rats[32].

Concerning the long term effects, Salford's group has shown in rats that whole body SAR values, as low as 0.6 and 60 mW/kg, significantly alter the performance during an episodic-like memory test after 55 weeks of 2-hr exposure once a week[33].

Studies on the effects of MW radiation on mice' cognitive functions are very limited. In one of them the animals were exposed within GTEM (Gigahertz Transverse Electromagnetic) cells at GSM 900-MHz frequency but at very low SAR of just 0.05 W/kg. No statistically significant deficits were resolved by 8-arm maze[34]. Expanding the exploration on the effects of radiation on mice, our group has performed a series of experiments to test spatial memory and learning in mice *Mus musculus* Balb/c using primarily the MWM task. The exposure setup consisted of a commercially available mobile phone, as firstly introduced by our group in insects[7, 8] and applied recently as well in mice[9, 35]. In these experiments free moving mice were irradiated within their home plastic cages, as also reported by other studies in rats[30, 36]. The animals were exposed to a 2-hr daily dose of pulsed GSM 900-MHz voice modulated at a SAR level of 0.41 to 0.98 W/kg, for four consecutive days during the MWM task protocol. Extended analysis of the data revealed that the animals exposed to the near field of a commercially available mobile phone could not transfer the learned information across the training days. Moreover, the data of the memory probe trial showed that the exposed animals had difficulties in memory consolidation and/or retrieval of the stored information of the position of the hidden platform, since they showed no preference for the target quadrant. Before each set of experiments the mean power density of the radiation emitted by the mobile phone handset in the RF range at 900-MHz was measured with the field meter's probe placed inside the cage with the animals. The measured exposure values were in general within the established exposure limits by ICNIRP on 1998[37]. We used commercially available digital mobile phone handsets, in order to analyse effects of real mobile telephony exposure conditions. Thus, instead of using simulations of digital mobile telephony signals with constant parameters (frequency, intensity, etc.), or even "test mobile phones" programmed to emit mobile telephony signals with controllable power or frequency, we used real GSM signals which are never constant since there are continuous changes in their intensity[35].

The SAR was approximately calculated according to the formula[37, 38]:

$$SAR = \sigma E^2/\rho$$

where **E** is the root mean square value of the electrical field, **σ** is the mean electrical conductivity of the tissues and **ρ** is the mass density. The SAR is a parameter widely used by many authors to compare the absorbed energy in different biological tissues. Thus, the parameters used for mice and rats were calculated according to Peyman *et al.*[39].

Another very promising and significant set of approaches involves experimental studies on volunteers and have focused on human cognitive function following exposure to mobile phone radiation (Table 1). One category of reports has shown memory improvement, i.e. facilitation in attention following exposure to mobile phone[14]. In another case, 915-MHz mobile phone exposure improved performance in a working memory task[13], and in the same direction another study found improvement in cognitive tasks, i.e. verbal memory capacity, sustained attention and visuospatial working memory[40].

Also, DeSeze' group has studied on 2005 the outcomes from the daily use of mobile phones GSM 900 on cognitive function[41]. Fifty-five subjects (27 males and 28 females) were divided into two groups: a group with mobile phone switched on and a group with mobile phone switched off. The two groups were matched according to age, gender, and IQ. This double blind study lasted for 45 days and the neuropsychological test battery composed of 22 tasks, screened four neuropsychological categories: information processing, attention capacity, memory function, and executive function. This neuropsychological battery was performed four times, on day 2, day 15, day 29, and day 43. The results indicated that daily mobile phone use had no effect on cognitive function after a 13-hr rest period.

In a very interesting study Krause and collaborators assessed the effects of EMF emitted by mobile phones on the 1-20 Hz range by event-related brain oscillatory electroencephalogram (EEG) responses in children performing an auditory memory task (encoding and recognition)[42]. What they found was that EMF emitted by mobile phones has effects on brain oscillatory responses during cognitive processing at least in teenagers. Also in an attempt to test MW effects on human attention Russo and collaborators studied on 2006 a large sample of volunteers (168) using a series of cognitive tasks apparently sensitive to RF exposure (a simple reaction task, a vigilance task, and a subtraction task)[43]. Participants performed those tasks twice, in two different sessions. In one session they were exposed to RF, with half of subjects exposed to GSM signals and the other half exposed to continuous waves (CW) signals, while in the other session they were exposed to sham signals. No significant effects of RF exposure on performance for either GSM or CW were found. On the other hand, it has been shown that in humans, exposure at 1 W/kg, to pulse-modulated radio frequency electromagnetic field 900 MHz, reduced reaction speed and increased accuracy in a working-memory task[44]. The same study showed that exposure prior to sleep alters brain activity. For a summary of the available literature see Table 1.

The possible effects of CW and pulse modulated (PM) EMF on human cognition in 36 healthy male subjects were studied by Haarala and collaborators on 2007. They performed cognitive tasks while the volunteers were exposed to CW, PM, and sham EMF. They found no differences between the different EMF conditions[45].

In a just recent report, Bengt Arnetz' group investigated the effects of a 2 hr and 30 min RF exposure (884-MHz) on spatial memory and learning, using a double-blind repeated measures design[6]. The exposure was designed to mimic a real-life mobile phone conversation, at a SAR value of 1.4 W/kg. The primary outcome measure was a ''virtual'' spatial navigation task modelled after the commonly used and validated MWM. The distance travelled on each trial and the amount of improvement across trials

(i.e., learning) were used as dependent variables. The participants were daily mobile phone users, with and without symptoms attributed to regular mobile phone use. The symptomatic group improved their performance during RF exposure while there was no such effect in the non-symptomatic group (Table 1).

Conclusions

In the presented studies the effects of MW radiation deriving either from RF generator providing continuous or modulated mobile phone-like signal, or from conventional mobile phone either computer controlled or under normal communication, were investigated at various carrier frequencies, 900, 1800 and 2450 MHz on the spatial learning and memory of rodents and humans. Several investigators have demonstrated the commonality between the performance of humans on real time spatial navigation tasks as compared to rats, mice and most other mammals studied so far[46]. The role of hippocampus, in particular, in navigation is concordant with neuronal response in rats and we assume in mice as well.

In our experiments using the MWM, Balb/c mice were required to find a submerged platform in the circular pool after 4 days of training by creating a "reference map" (reference memory)[47]. Exposed mice to the near field of a conventional mobile phone showed difficulty in finding the position of the hidden platform during training and could not transfer the learned information across the days. The recorded data from the probe trial indicated that exposed mice had difficulty in memory consolidation and/or retrieval of the stored information[35].

A number of studies have used a range of SAR values, from 0.02 mW/kg up to 4 W/kg in order to induce and detect memory deficits in rodents and especially in rats. In the vast majority of the studies the Transversal Electromagnetic Mode (TEM) cells were used, exposing the animals at a given power density from an RF generator. Similar learning and memory deficits revealed with the MWM following exposure to pulsed circularly polarized 2450-MHz MW at 2 mW/cm^2 power density, have been also reported in rats[25]. Some studies failed to reveal any effects whereas others have demonstrated that according to the radiation set up used (frequency, power density and duration of exposure) the animals' memory function is somehow affected by EMF (Table 1). In a very recent study Narayanan and collaborators using similar to ours exposure setup protocol irradiated male Wistar rats, 10-12 weeks old, which are developmentally comparable to human teenagers[30]. The rats were exposed to 50 missed calls/day for 4 weeks from a GSM (900/1800-MHz) mobile phone in vibratory mode (no ring tone). After the experimental period, the animals were tested for spatial memory performance using the MWM test. Both phone exposed and sham exposed animals showed a significant decrease in escape time with training. In the probe trial phone exposed animals had significantly (~3 times) higher mean latency to reach the target quadrant and spent significantly (~2 times) less time in the target quadrant than age- and sex-matched controls. It is crucial to note that this work has used similar to ours experimental protocol having the mobile phone within the cage, but with longer exposure. It seems therefore that mice and rats respond similarly to the radiation stress by exhibiting deficits in their spatial memory operation. Some investigators (including our group) have chosen to perform experiments in animals allowed to move freely in their home cages during exposure to radiation[9, 30, 35, 36]. Doing so, any possible confounding effects of restraint stress are minimized, since it is well known

that stress affects learning and memory[48]. Exposure conditions were carefully selected in order to simulate as close as possible ordinary mobile phone use (duration and signal strength). EMF with changing parameters are found to be more bioactive than fields with constant parameters[44, 49, 50]. That is probably because it is more difficult for living organisms to get adapted to them. Experiments with constant GSM or DCS signals can be performed, but they do not simulate actual conditions. International guidelines limit the local SAR to a maximum of 2 W/kg[37], or 1.6 W/kg[38]. Since the maximum SAR value as calculated in our experiments was at most 0.98 W/kg and since this SAR value does not affect the mice's body temperature[37], the exposure conditions used in our experiments can be considered nonthermal.

Furthermore, some investigators (including us) selected the age of the experimental animals (50-day-old) to correspond approximately to that of late adolescence in humans, a population in which mobile phone use is particularly prevalent. Similar to our exposure conditions have been used by other investigators[51]; they have irradiated rats with conventional mobile phone operating at a maximum power of 0.607 W. They found by mRNA analysis an effect on injury associated proteins leading to cellular damage to the rat brain.

Since it is well known that performance in the MWM is dependent on the hippocampus, it is plausible to assume that MW radiation exposure affected this brain area. Such a notion may be supported by the observation that apoptotic cells have been detected in the hippocampus of rats after a 2 hr for 50 days GSM radiation[31, 32]. Furthermore, the function of the hippocampus could be affected by the GSM irradiation possibly due to disruption of the blood-brain barrier, which has been reported to occur as a result of GSM irradiation[52, 53]. However, other investigators using 915-MHz at power levels resulting in whole-body specific absorption rates of 0.0018-20 W/kg failed to reveal such a relationship[54].

Considering that memory functions are similar in mice and humans with respect to the involvement of the hippocampus[55], we may assume that upon using the mobile phone in contact with the head, a person may experience cognitive deficits. Interestingly, it has been reported that exposure to GSM 890-MHz radiation results in deficits of human cognitive function[56]. The same research group reported recently using a spatial working memory task that the average reaction time (RT) of the right-hand responses under left-side exposure condition was significantly longer than those of the right-side and sham-exposure groups[57]. These results confirmed the existence of an effect of exposure on RT, as well as the fact that exposure duration (together with the responding hand and the side of exposure) may play an important role in producing detectable radiofrequency radiation (RFR) effects on performance. It is notable that right and left hemispheres did not show similar patterns of activation. Differences in these parameters might be the reason for the failure of certain studies to detect or replicate RFR effects. The question whether the memory impairment is reversible is open for exploration by further experiments which are in progress. Finally the actual molecular impact of the EMF is being studied at the proteomics level in our lab, in an attempt to explain the molecular events underlying the brain cells' malfunction after irradiation.

It has been suggested that behavioral alterations induced by EMF are thermally mediated[58]. That is because in most studies these effects derive from SAR values beyond the reference standard of 2 W/kg. The effects reported at very low SAR values may be explained by free radical formation as suggested[59]. It could also be due to protein conformation changes[60]. It might be possible that these changes cause alterations in cognitive function-related proteins, such as androgen receptors and apolipoprotein A[61].

Finally, as questioned in a recent study by Philips and collaborators[59]: "Are studies unable to replicate the work of others more credible than the original studies? In other words, can negative studies cancel positive studies or may studies showing effects be less valid because no explanation is provided?" The answer is that given the different frequency and modulation and in general the exposure set up conditions used in different studies, the issue remains open as to which of the parameters used in the "exposure cocktail", is crucial to alter brain cells' function. Is it the RF itself or the modulation? Or may be the ELF component of the battery switching mode of the cell phone. This issue is more complex than it seems when trying to compare animal studies with human clinical or experimental findings, possibly due to the differences in exposure conditions. Till the final elucidation of the effects, this research task is open for investigation requiring probably more sophisticated approaches and experimentation procedures.

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