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Acute effects of radiofrequency electromagnetic field emitted by mobile phone on brain function

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Abstract

Due to its attributes, characteristics and technological resources, mobile phone (MP) has become one of the most commonly used communication devices. Historically, ample evidence has ruled out the substantial short-term impact of radiofrequency electromagnetic field (RF-EMF) emitted by MP on human cognitive performance. However, more recent evidence suggests the potential harmful effects associated with MP EMF exposure. The aim of this review is to readdress the question of whether the effect of MP EMF exposure on brain function should be reopened. We strengthen our argument focusing on recent neuroimaging and electroencephalography studies, in order to present a more specific analysis of effects of MP EMF exposure on neurocognitive function. Several studies indicate an increase in cortical excitability and/or efficiency with EMF exposure, which appears to be more prominent in fronto-temporal regions and has been associated with faster reaction time. Cortical excitability might also underpin disruption to sleep. Notably however, several inconsistent findings exist, and conclusions regarding adverse effects of EMF exposure are currently limited. It also should be noted that the crucial scientific question of the effect of longer-term MP EMF exposure on brain function remains unanswered and essentially unaddressed.

Keywords: mobile phone; radiofrequency electromagnetic field； neuroimaging；brain function；addiction

Introduction

The total number of mobile phone (MP) users is forecasted to reach 5 billion worldwide by 2019 and most of this growth is due to the increasing popularity of smartphones [Statista Inc, 2015]. Historically, concerns have been raised regarding the acute effects of radiofrequency electromagnetic field (RF-EMF) emitted by MP on brain function, particularly given that MPs are often used in close proximity to the human head. Although there are some inconsistent findings, e.g., some suggest impaired or facilitating cognitive effects due to mobile phone use, whereas others found no effects (for a review, see [Kwon and Hamalainen, 2011; Barth et al., 2012], previous reviews do not support short-term impact of high frequency EMF by MPs on human cognitive performance [Valentini et al., 2010; Barth et al., 2012]. It is argued that the heterogeneity of results may be due to methodological differences, statistical power and interpretation criteria [Valentini et al., 2010].

However, more recently, several large population-based cohort studies have reported negative effects of RF-EMF. For example, Byun et al. [2013], examined attention deficit hyperactive disorder (ADHD) symptoms and MP use of 2,422 children at 27 elementary schools over 2 years. MP use was measured using questionnaires administered to parents or guardians in 2008 and 2011, including the ownership of a MP by children, age at first ownership of a MP, monthly MP bill, average time of daily use, etc. ADHD symptom risk was positively associated with MP use in a dose-response manner. In research by Guxens et al. [2016], the relationship between exposure to RF-EMF source and cognitive function was examined in 2354 children aged 5-6 years. They report reduced visuomotor coordination with exposure to RF-EMF from mobile phone base stations, but improved speed of information processing, inhibitory control, and visuomotor coordination with residential RF-EMF indoor sources [Guxens et al., 2016]. Thus the effect of RF-EMF exposure on the brain might vary qualitatively and quantitatively depending on the source.

Greater understanding of neurocognitive mechanisms associated with RF-EMF would lend support against such relationships being due to chance or other residual confounding variables (e.g., socioeconomic status, geographical position) [Guxens et al., 2016]. Neuroimaging methods such as Functional Magnetic Resonance Imaging (fMRI) which detects regional changes in blood oxygen utilisation during neuropsychological performance, positron emission tomography (PET) which measures the signal from a radioactive ligand and electroencephalographic (EEG) techniques that measure changes in the extracellular electrical potential of the cortex are useful in this respect. Brain imaging techniques complement behavioral measures (e.g., neuropsychological assessment) by providing important information about biological substrates that might be affected by RF-EMF. Previous review papers have examined the evidence published up to February 1, 2011 on **e**ffects of electromagnetic fields (EMF) from MPs on human behavioral and psychomotor performance, and concluded that MP EMF do not induce any effect [Valentini et al., 2010; Barth et al., 2012]. Thus the focus of the current review is to determine whether, based on previous reviews and more recent studies (from 2011-Oct 2016), the effect of MP use on brain function should be reopened.

Methods

Studies were identified using searches of MEDLINE, EMBASE, PsycINFO, and Cochrane CENTRAL. Search terms were a combination of free-text, and thesaurus terms (phone AND cognition), such as "phone", and "mobile phone", combined with cognition-related terms such as "cognition", "cognitive function" "cognitive defect" "cognitive impairment", "memory", "attention", "executive function", and "perception". Different search strings were used to maximise the relevance of the returned results when searching in different databases. Peer-reviewed journals, and English language limits were used. Studies were selected if they met the following criteria: 1) the study had to assess direct effects of mobile phone use on human neurological functioning; 2) neuroimaging and

electrophysiological techniques, including MRI, EEG, and Positron emission tomography (PET), were used; and, 3) information on brain function related to mobile phone was clearly presented.

Results

A total of 16 studies met the inclusion criteria, and are included in this review. Checking the references of the articles did not result in inclusion of further articles. Of the 16 studies, two studies used MRI for data acquisition [Curcio et al., 2012; Lv et al., 2014], one used PET scans [Volkow et al., 2011], and the rest utilised EEG. The studies primarily investigated the potential physiological effect induced by RF-EMFs. It should be noted that one study assessed not only the effect of phone use, but also the mix effect of caffeine, and simultaneous MP exposure. Typically, double/single blind randomised counterbalanced crossover design was used [Lowden et al., 2011; Volkow et al., 2011; Curcio et al., 2012; Schmid et al., 2012a; Schmid et al., 2012b; Vecchio et al., 2012b; Loughran et al., 2013; Lv et al., 2014; Ghosn et al., 2015; Roggeveen et al., 2015b; Yang et al., 2016], in which the participants were exposed to two different conditions. In the sham condition, the MP was switched "on" but without global system for mobile communication (GSM) radiofrequency (RF); in the real condition, the phone was switched "on" with GSM RF. EMF exposure were primarily defined based on exposure intensity and time, and frequency-domain characteristics. The participants of the included studies were healthy adults, apart from two studies. The one included adolescents aged from 11 to 13 [Loughran et al., 2013], and another included epileptic patients who typically exhibit abnormal brain activity [Vecchio et al., 2012b]. Detailed information on the included studies is shown in Table 1.

MRI findings

MRI is a noninvasive technique that utilises a powerful magnetic field and radio frequency pulse to produce detailed images of the body. It measures multiple physiologic parameters, including blood oxygenation, blood flow, and volume, and has been integrated effectively into neuroscience to investigate brain activity, e.g., energy is required for activation of neurons. With increased demand for oxygen and other nutrients, there is increased cerebral blood flow (CBF). Therefore, brain activation can be measured using blood-oxygen-level dependent (BOLD) signals [Logothetis and Wandell, 2004]. Curcio et al. [2012] were the first research team to investigate the possible effects induced by brain exposure to GSM emissions using functional MRI (fMRI). BOLD signals were recorded while performing a go/no-go task in either sham or real conditions. Participants were required to refrain from using MP for 12 h preceding the experimental session. The results showed that there was no acute effect of MP exposure to GSM mobile phone signal on either BOLD response or behavioral performance in a sensorimotor cognitive task. It was suggested that if MP emissions affect the excitability of neurons, that this would be at a relatively restricted local level undetectable using traditional fMRI techniques.

In comparison, Lv et al. [2014] found decreased amplitude of low frequency fluctuations (ALFF) in the BOLD signal in several regions (left superior temporal gyrus, left middle temporal gyrus, right superior temporal gyrus, right medial frontal gyrus and right paracentral lobule) during rest after real exposure. ALFF was calculated as the total power within the frequency range between 0.01 and 0.1 Hz, and thus indexes the strength or intensity of low frequency oscillations [Lv et al., 2014]. Whilst the cognitive significance of these changes remains unclear, similar reductions in ALFF and fALFF activities in the medial prefrontal cortex and lateral prefrontal regions have also been found in patients with mild cognitive impairment [Han et al., 2011].

Inconsistent findings in fMRI studies may in part be due to small sample size (e.g. n=12 in Curcio et al; n=18 in Lv et al) and findings therefore need to be interpreted with caution. Methodological differences also exist in terms of task parameters and dependent variables. Also typical basic GSM

signal with a carrier frequency of 902.40 MHz was used in Curcio et al.' s study, while Lv et al used the standard dipole antenna to emit a LTE signal at 2.573 GHz. Furthermore, the choice of exposure site differed between the two studies. The left side of brain was chosen in the study by Curcio et al. [2012], while the right side of brain was selected by Lv et al. [2014]. Thus, the effect of RF-EMF on BOLD signal remains unclear, and requires further investigation.

PET findings

PET uses nuclear imaging to detect gamma rays indirectly emitted by a radioactive trace that is introduced to the body to measure blood flow, metabolism, and neurotransmission [Berger, 2003]. Volkow et al. [2011] used PET to study brain glucose metabolism in humans over 50 min during MP activated, relative to MP deactivated conditions. Means of (^{18}F) fluorodeoxyglucose (^{18}FDG), a more proximal marker of neuronal activity compared to regional Cerebral blood flow (rCBF), was used to examine the cumulative effects of MP exposure on resting metabolism. Increased metabolism was observed in the orbitofrontal cortex and temporal pole (i.e. those regions that were close to the MP antenna) during acute EMF exposure. Under normal condition, metabolism is closely related to regional blood oxygenation and flow, reflecting current level of brain activation e.g. blood flow increased is associated with increases metabolic demand. However, the authors did not investigate whether such changes manifest in any behavioural response.

EEG findings

EEG is a non-invasive measure of the brain's electrical activity. It records the synchronised activity of gross extracellular excitatory and inhibitory post-synaptic potentials from predominantly pyramidal cells in cerebral cortex, and displays the activity as voltage amplitude changes over time [Gevins, 1998]. This electrical activity is recorded as brain waves or oscillations that vary as a

function of arousal (e.g., sleep-wake cycle), and cognitive function (e.g., learning [Ray and Cole, 1985], memory [Klimesch et al., 1999], and attention [Wang et al., 2015a]). The EEG recorded from the human scalp ranges in frequency (<1-100Hz) with typical bands including delta (0−4 Hz), theta (4−8 Hz), alpha (8−13 Hz), beta (15−30 Hz), and gamma (30-100Hz). EEG can be recorded during sleep and awake states, and its functional significance is likely state dependent.

Sleep EEG

A study by Lowden et al. [2011] investigated the effect of 3 h of EMFs exposure on subsequent night sleep, and found an increased spectral power in alpha and delta frequency bands during stage 2 sleep, within the first two hours. The presence of alpha and delta waves during stage 2 sleep is defined as alpha-delta sleep EEG pattern, and was first observed and reported in a study with a group of patients with psychiatric disorders [Hauri and Hawkins, 1973]. It has since been frequently observed in individuals with fibromyalgia [Olsen et al., 2013]. Although the clinical implication of this sleep EEG pattern remains controversial [Mahowald and Mahowald, 2000], it has been suggested that alpha/delta sleep interferes with sleep function, resulting in nonrestorative sleep, daytime fatigue, and musculoskeletal pain [Roizenblatt et al., 2001]. A positive correlation between alpha-delta sleep and perceived shallow sleep has been reported [Perlis et al., 1997]. The appearance of alpha-delta sleep is considered to be related to reduced serotonergic activity which is significantly involved in regulation of sleep and wakefulness [Philipsen et al., 2005], and this could potentially act in competition with non-rapid eye movement (NREM) sleep system, impairing the presumed restorative function of NREM sleep [Moldofsky et al., 1975]. An initial study by Schmid ad colleagues [Schmid et al., 2012a] suggested that the effect of EFM on sleep function and awake behaviour may depend on the emission frequency. They found that exposure to 14Hz EFM for 30 min prior to an 8-h sleep period caused a greater increase EEG power in the spindle frequency range (13.75–15.25 Hz) during NREM sleep than exposure to 217 Hz [Schmid et al., 2012a]. Furthermore,

reaction time during various cognitive tasks, performed over the 30 min exposure period, tended to be faster for 14 Hz than 217 Hz pulse modulation. Accuracy was nevertheless, largely unaffected. However, an extension to this study revealed that specificity of the pulse modulation was not the most important factor in inducing effects on EEG, but limiting pulse modulation to low frequencies and eliminating higher harmonics were more critical [Schmid et al., 2012b]. It was suggested that any pulse-modulated RF EMF scheme in a frequency range that is close to biologically relevant rhythms, i.e. 2, 8, 12 or 217 Hz, may be sufficient to induce changes in the spindle frequency range of the EEG [Schmid et al., 2012b].

Wakeful EEG

In a study by Ghosn et al [2015], resting EEG was recorded while the participants underwent GSM RF exposure or a sham condition (blind to experimental condition). Each recording session lasted 61 min 15 seconds, and included three experimental conditions: pre-exposure (17 min 30 seconds), exposure (26 min 15 seconds), and post-exposure (17 min 20 seconds). Confounding factors that are known to affect alpha band, such as electrode impedance, salivary cortisol, and caffeine, were controlled for. The study found a significant decrease in alpha band power (eyes closed: lower alpha 8-10 Hz and upper alpha 10-12 Hz) during exposure to EMF, which persisted in the post-exposure period. In contrast, however, Roggeveen et al. [2015b] measured resting EEG while the participants were exposed to a 3G dialling MP which was in mute setting with vibration off using the similar experimental design, and found increased power of alpha band, along with higher frequencies (beta, gamma) over almost all brain regions. This effect was stronger when the MP was placed on the ear compared to chest. It was believed that using a real phone could better reflect the reality of MP exposure compared to a GSM module or other method to stimulate MP radiation. High resting alpha power reflects deactivation or inactivity in the underlying cortex [Hummel et al., 2002; Sauseng et al., 2009], while low resting alpha power correlates with greater cortical excitability [Neuper et al.,

2006]. Increases in beta and gamma power would also suggest greater cortical excitability. Thus, although apparently discrepant findings with regard to alpha, together these studies indicate greater cortical excitability during exposure. Inconsistencies between Ghosn et al [2015] and Roggeveen et al. [2015b] in alpha activity point to the importance of measuring this frequency band relative to other higher frequencies in addition to its absolute value. Nevertheless, neither of these studies examined the behavioral or health effects of changes in alpha activity. Thus interpretations of the functional significance of changes in alpha power are limited.

Interestingly, exposure related effects on the resting EEG observed in healthy adults was absent in adolescents [Loughran et al., 2013]. Whilst it is unclear whether such findings reflect greater brain plasticity in adolescents or an effect on brain networks that develop later in adulthood, they nevertheless suggest that individual differences may exist in response to EMF exposure. A study by Zentai et al. [2015] did not find any measurable effects of acute EMFs generated by wireless fidelity on either spectral power of EEG or sustained attention measured by psychomotor vigilance test.

Event-related desynchronization (ERD) and event related potentials (ERPs)

According to internal or external demands, EEG activity can change from a synchronized (high amplitude) into a desynchronized (low amplitude) mode and vice versa, whereby various frequency bands can show different reactivity patterns [Graimann et al., 2002; Wang et al., 2015b]. These changes can be either time and phase-locked or time-locked but not phase-locked alone. The former are represented by the ERP and the later are ERD [Graimann et al., 2002]. The voltage difference (amplitude) and time course of the waves are thought to reflect the dynamics of sensory and cognitive processing [Graimann et al., 2002]. For example, the N200 is a negative deflection occurring around 200-350 milliseconds (ms) after the eliciting stimulus, and the P300 is a positive wave occurring on average at 300 ms post-stimulus. The N200 is related to stimulus identification

and distinction, and reflects the efficiency of pre-conscious sensory processing. The P300, on the other hand, is related to the amount of attentional resources required for a given task and reflects a widely distributed network including frontal, parietal and temporal regions that responds to novelty, subjective probability, salience and task relevance [Polich, 1997; Wang et al., 2015b].

A few studies have begun to examine the EMFs-related effects on event-related desynchronization (ERD) [Vecchio et al., 2012a; Vecchio et al., 2012b] and event related potentials (ERPs) [Trunk et al., 2013; Trunk et al., 2014]. In line with an increase in fronto-temporal blood flow reported by Volkow et al. [2011] in their PET study, a positive waveform over frontal and central electrode sites was seen time-locked to peaks in MP radiation (ERP 240-500 ms) [Roggeveen et al., 2015a]. This would suggest increased cortical activity induced by the presence of an active MP, which is also in line with a reduction (Ghosn et al [2015]), rather than increase (Roggeveen et al. [2015b]) in alpha power; and an increase in fast frequency bands (Beta, Gamma). In comparison, no measurable effects of EMFs exposure were observed on the ERPs elicited by either the auditory oddball task [Trunk et al., 2013] or the visual oddball paradigm [Trunk et al., 2014].

According to Klimesch et al. (2007), ERD reflects the gradual release of inhibition associated with the emergence of complex spreading activation processes. Decreased ERD of higher alpha rhythms in response to go stimuli in a visual go/no-go task was reported by [Vecchio et al., 2012a]. This effect was more prominent at frontal and left temporal scalp regions, in line with aforementioned fMRI and PET studies that show fronto-temporal effects, and was accompanied by faster reaction times. Thus, it was suggested that short term exposure to GSM-EMFs (e.g., 45 min) may enhance human cortical neural efficiency and simple cognitive–motor processes in healthy adults [Vecchio et al., 2012a]. Following their earlier work showing modulation by short-term exposure to GSM-EMFs of inter-hemispheric coupling of resting fronto-temporal alpha rhythms in healthy young adults (Vecchio et al., 2007), Vecchio and colleagues, have further investigated this effect as a function of aging and in people with epilepsy. Elderly subjects showed an increment in inter-hemispheric

coherence of frontal and temporal alpha rhythms following GSM exposure compared to younger adults, which was explained hyper-excitability possibly provoked by an age-related physiological reduction of the cholinergic tone. Similarly an increase in inter-hemispheric coupling of resting EEG rhythms, predominantly in the alpha band was also found in people with epilepsy [Vecchio et al., 2012b].

Discussion

The current review reopens the question of whether MP EMF exposure affects brain function. Previous reviews of studies prior to 2011 have suggested that there is no effect of short-term exposure to MP EMFs on human cognitive performance [Valentini et al., 2010; Barth et al., 2012]. Several studies in the current review point to an increase in cortical excitability and/or efficiency during exposure that may persist for several minutes post-exposure. Corroborating evidence for this idea is shown by an increase in cerebral metabolism (PET), a decrease in alpha activity, an increase in high frequency (Beta, Gamma) activity, increased reaction time, and disrupted sleep EEG. Based on several methodologies (fMRI, PET, EMF elicited ERPs, ERD and interhemispheric synchronisation), frontal and temporal regions appear to be more susceptible. Several factors have been proposed for the EMF-induced alterations in cortical excitability and efficiency, including modulation of dependent NA-K trans-membrane ionic channels, the alteration of cellular homeostasis of Ca++ ion, increased cellular excitability, and the activation of cellular response to stress [Vecchio et al., 2012a, b]. Whilst increased cortical excitability may have some beneficial effects during the waking state (e.g. faster reaction times), adverse effects may result from disruption to restorative sleep, which might be expected to impact on cognitive function and health. Changes in sleep architecture (e.g., increased alpha-delta activity during stage II; increased spindle activity) could reflect modulation of neurotransmission (e.g., serotonin) induced by MPs.

Nevertheless, apparent inconsistencies between studies exist that limit conclusive statements in this area. These inconsistencies may in part be due to methodological factors including differences in the signal type, the modulation, the exposure frequency, the exposure intensity, individual anatomy, age of the subjects, exposure duration and presence of rigorous experimental designs. Individual differences in age appear to affect vulnerability to effects of EMF exposure, as does the presence of epilepsy. Determination of an absorbed dose is also complex and depends on many external and internal factors and thus adequate dosimetry measurement tools for evaluation of exposure is critical for quality of study results [Thomas et al., 2008]. Differences exist across studies in pre-evaluation of exposure dose. Some applied standard 1528 IEEE recommended practice for determining the peak spatial-average specific absorption rate (SAR), i.e. [Lv et al., 2014], while others used personal computer to control the exposure system, i.e. Ghosn et al. [2015]. In addition, variations of signals both in time and space have to be taken into account. RF-EMFs have been generated by either commercial mobile phone, e.g., Nokia 6650 [Ghosn et al., 2015], 3G smartphone [Roggeveen et al., 2015a] or special devices, e.g., A CMW 500 (R&S) and an RF amplifier [Lv et al., 2014]. The SAR distributions could be different among phones and these devices. For example, SAR distributions of phones of 3rd generation differ from that of 2nd generation phones [Taki and Wake, 2012]. To further understand inconsistent findings, future studies will need to explore these interactions (and other possible confounding variables e.g. sex) across neuroimaging methodologies.

Furthermore, possible interference between radio frequencies emitted by the mobile phone and EEG signals recorded during exposure, and the history of EMFs prior to the study are not always controlled for. Clearly further work is needed to delineate the interaction between these potentially confounding factors and the effect of MP use on MRI and EEG signals.

It should be noted that effects of MP EMF on brain function are primarily examined using lab-based studies. Although laboratory studies have good control of exposure factors as well as possible confounding factors, however, relevance to real life condition can be less clear. Recent evidence

shows that individuals with MP overuse experience several biopsychosocial symptoms and consequences, including stress and sleep disturbances, insomnia, anxiety, and addiction [Billieux et al., 2015]. Characteristic symptoms which have often been related to various forms of addictive behaviors (e.g., substance-related addictions and gaming addiction) have been observed in people with massive use of and dependence on MP. This is reflected in high economic cost, numerous calls and messages, a gradual increase in use to obtain the same level of satisfaction, as well as emotional alterations when phone use is impeded [Choliz, 2010]. Addiction is suggested to induce progressive changes in brain regions affecting reward, memory, learning, cognitive control and motivation [Gardner, 2011]; and it has been proposed that MP addiction or overuse might also affect these networks [Griffiths, 2000]. It is necessary to clarify whether the symptoms observed in people with MP use are related to MP EMF exposure. However, none of the studies included in this review have investigated the longer-term effects of MP EMF exposure, and further research is warranted.

This review is limited by applying English and time limits to the initial search, and then limited to the published academic literature. Furthermore, given that the aim of the review is to readdress the question of whether the effect of MP EMF exposure on brain function should be reopened, the presented literature includes only those studies since the last review (i.e. in the last 6 years) which stated that "there is no evidence for any short term effects of EMFs emitted by MP on human cognitive performance" [Barth et al., 2012]. To our knowledge, there are no systematic reviews investigating the neurophysiological changes induced by MPs.

Conclusion

Whilst several studies suggest an effect of EMF exposure on brain function there is little evidence of the harmful nature of these effects and greater understanding is needed of their functional significance. To date, the crucial scientific question of the effect of longer-term MP EMF exposure

on brain function remains unanswered and essentially unaddressed. The potential health effects of MP EMF exposure in children and adolescents have been identified by the World Health Organisation (WHO) as a high priority research area since they have a longer lifetime exposure to MP [van Deventer et al., 2011]. Prior to establishing a clear picture of a cause-effect relationship on MPs, it is safer to minimise the MP use. It has been suggested to reduce the potential harm induced by MPs by restricting call length, or by using hands-free devices [Valentini et al., 2010]. Furthermore, there is an increased number of population having problems with MP use [Billieux et al., 2015], and presence of addictive consumption styles and problematic behavior have been observed. In order to minimise possible negative consequences caused by excessive usage, further research is required to clarify the neurophysiological changes associated with long-term MP EMF exposure, and the impact of different behavioral characteristics of MP use on cognitive function.

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