

Modulation of Resting-State Brain Functional Connectivity by Exposure to Acute Fourth-Generation Long-Term Evolution Electromagnetic Field: An fMRI Study

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By now, the neurophysiological effect of electromagnetic field (EMF) exposure and its underlying regulating mechanisms are not well manifested. In this study, we aimed to investigate whether acute long-term evolution (LTE) EMF exposure could modulate brain functional connectivity using regional homogeneity (ReHo) method and seed-based analysis on resting-state functional magnetic resonance imaging (fMRI). We performed the LTE-EMF exposure experiment and acquired the resting-state brain activities before and after EMF exposure. Then we applied ReHo index to characterize the localized functional connectivity and seed-based method to evaluate the inter-regional functional connectivity. Statistical comparisons were conducted to identify the possible evidence of brain functional connectivity modulation induced by the acute LTE-EMF exposure. We found that the acute LTE-EMF exposure modulated localized intra-regional connectivity ($p < 0.05$, AlphaSim corrected, voxel size ≥ 18) and inter-regional connectivity in some brain regions ($p < 0.05$, AlphaSim corrected, voxel size ≥ 18). Our results may indicate that the approaches relying on network-level inferences could provide deeper insight into the acute effect on human functional activity induced by LTE-EMF exposure. *Bioelectromagnetics*. 40:42–51, 2019. © 2018 Wiley Periodicals, Inc.

Keywords: electromagnetic field exposure; functional connectivity; long-term evolution; regional homogeneity; resting-state fMRI

INTRODUCTION

Currently, multiple standards exist for wireless communication, which ranges from second-generation (2G, GSM) to third-generation (3G, UMTS) and fourth-generation (4G, LTE) networks in daily life. Fifth-generation (5G) networks will start to appear as a commercial infrastructure in the near future. Although we enjoy the convenience of mobile phones, the widespread use of them has raised attention about the possible health effects of radiofrequency (RF) electromagnetic field (EMF) exposure [ICNIRP, 1998].

With neuroimaging and neuropsychology tools, the effect of EMF on the human brain can be reflected as signals of electrical activity [Hamblin et al., 2006; Croft et al., 2010; Lustenberger et al., 2013; Roggeveen et al., 2015a, b], cortical excitability [Tombini et al., 2013], cerebral blood flow [Aalto et al., 2006], brain glucose metabolism [Volkow et al., 2011], and hemodynamic responses

[Volkow et al., 2011; Curcio et al., 2012]. Previous studies reported that GSM signals modulated alpha band power in resting-state electroencephalogram (EEG) [Croft et al., 2010] or some event-related

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potential (ERP) components during cognitive tasks [Hamblin et al., 2006], whereas other studies did not detect any GSM exposure-induced changes in brain activity [Curcio et al., 2012]. Although some studies showed no significant effects of 3G signals on any neurophysiological measurements [Zhang et al., 2017], recent EEG studies reported significant EEG alterations associated with 3G mobile phone radiation [Roggeveen et al., 2015a, b]. The inconsistency could partly be attributed to different exposure frequencies, modulation modes, and exposure durations [Zhang et al., 2017]. For 4G-related signals, only our two previous studies have investigated the acute effect of long-term evolution (LTE) EMF exposure on human brain function [Lv et al., 2014; Yang et al., 2016] using EEG and functional magnetic resonance imaging (fMRI). We found that 30 min of LTE-EMF exposure modulated the alpha/beta EEG bands [Yang et al., 2016] and spontaneous low-frequency fluctuations [Lv et al., 2014] in some brain regions. Since LTE networks have been widely deployed, we should make more effort to evaluate the possible effects of LTE-EMF exposure from different perspectives.

Functional magnetic resonance imaging (fMRI) can detect the localized neural activation that occurs in response to altered metabolic demands of activated neurons [Apkarian et al., 2005]. This procedure maps neural activation with a fine resolution and has been a useful tool for evaluating human exposure to EMF since the 2010s [Robertson et al., 2010]. The change in the blood-oxygen-level-dependent (BOLD) signal is the cornerstone of fMRI, which traditionally is used to construct maps indicating subspecialized brain regions that are activated by certain tasks or react to a low-frequency (0.01–0.1 Hz) stimulus [Lv et al., 2018].

A large number of studies have demonstrated that the human brain is organized with two basic architectural principles (functional segregation and functional integration) [Sporns et al., 2004; Park and Friston, 2013]. Functional segregation (or local integration) emphasizes distributed processing within different brain regions, whereas functional integration (or global integration) stresses long-range interactions across regions [Sporns et al., 2004; Park and Friston, 2013]. Previous neurophysiological studies have observed that EMF-induced changes in brain activity occur not only in the region near the exposure site but also in remote regions and even in contralateral brain regions [Croft et al., 2010; Lv et al., 2014; Roggeveen et al., 2015a; Yang et al., 2016]. This phenomenon of remote effects inspired us to investigate whether EMF exposure modulated functional integration between different brain regions. With the

event-related coherence method, Vecchio et al. [2007] found that GSM signals emitted from mobile phones affected the interhemispheric synchronization of temporal and frontal resting EEG alpha rhythms in normal young subjects and epileptic patients [Vecchio et al., 2012]. Based on resting-state fMRI, we observed that LTE-EMF exposure modulated the interhemispheric homotopic functional connectivity around the medial frontal gyrus and paracentral lobule [Lv et al., 2014]. In fact, in addition to interhemispheric functional connectivity, functional integration from the local to global scales can be identified with other postprocessing methods on resting-state fMRI [Margulies et al., 2010]. However, the possible effects of LTE-EMF exposure have not been investigated in terms of functional connectivity.

In this study, we aimed to investigate whether acute LTE-EMF exposure could modulate brain functional connectivity using resting-state fMRI. We performed LTE-EMF exposure experiments lasting for 30 min under a controllable environment and recorded the resting-state brain activities before and after EMF exposure. Then, we applied the regional homogeneity (ReHo) index [Zang et al., 2004] to characterize localized intraregional connectivity and the seed-based functional connectivity method [Margulies et al., 2010] to evaluate interregional brain connectivity. Statistical comparisons were conducted to identify possible evidence of brain functional connectivity modulation induced by acute LTE-EMF exposure.

MATERIALS AND METHODS

Participants

Twenty-one right-handed healthy subjects (14 males and 7 females; mean age: 25.2 ± 4.1 years; age range: 19–36 years) took part in this study. None of the participants had a history of neurological or psychiatric disorders that might affect brain structure or function. Each participant completed a questionnaire survey about mobile phone usage in their daily life before the experiment. They were all identified as regular mobile phone users with less than 1 h of use per day, and no one used the mobile phone for more than 10 min during the day prior to the experiment. The study was approved by the ethics committee of the People's Liberation Army (PLA) General Hospital (Beijing, China). All subjects gave written informed consent after the experimental procedure had been fully explained.

Exposure Experiment

To eliminate study biases, we employed a double-blind, crossover, randomized, and counterbalanced

design. Each participant underwent two experimental sessions including real exposure and sham exposure, which were separated by 1 day. The order was controlled by the experimental operator and was unknown to the participants and data analysts. The only difference between the two experimental sessions was whether the power of the exposure equipment was on or off (Fig. 1). The time-division LTE signal (2.573 GHz) was produced by a signal generator (CMW500, R&S, Munich, Germany) using a standard formulation for LTE signals. The applied radio frame (total length: 10 ms) consisted of 2 half-frames of equal length. Each half-frame had 5 subframes, each 1 ms in length. We selected the maximal emission configuration (6 uplink subframes in the radio frame). The radiation duration (including the uplink subframes and uplink pilot time slot (upPTS) special subframes) accounted for 63.3% of the total frame length. The signal was augmented by an RF power amplifier (AR40S1G4, AR, Bothell, WA). A 1-cm plastic spacer was used to maintain the distance between the right ear and a standard dipole. We applied 2 power meters (E4416A, Keysight, Santa Clara, CA) to ensure constant incident power to the emission dipole [Wu et al., 2012]. The power delivered to the standard dipole of 2.6 GHz (D2600V2, Speag, Zurich, Switzerland) was 24 dBm (mean value), which was equivalent to a theoretical maximal emission by an LTE terminal. The experiments were conducted in a shielding room to avoid the influence of environmental EMF. Each exposure session lasted for 30 min. During the exposure, the participants were instructed to select a comfortable

posture on the chair and to hold the position as much as possible. The room for MRI scans was adjacent to that used for the exposure experiments, and the distance from the chair of the exposure experiment to the MRI bench was within a 10-meter walk. The subjects were instructed to move to the MRI scan room immediately after the exposure experiments with moderate speed. The interval between the exposure and fMRI scan was less than 1 min. The subjects were asked to report whether they fell asleep during the scan.

Dosimetric Study

The specific absorption rate (SAR) was estimated for each subject. We developed a segmentation framework [Li et al., 2015] that could reconstruct the individual brain model in approximately 10 min using structural MRI. The segmentation was based on atlas-based registration and morphological methods. Then, the nonbrain parts were segmented interactively with iSeg (ZMT, Zurich, Switzerland). In total, 24 tissues were identified in the head model of each participant. Consequently, we performed the Finite-Difference Time-Domain (FDTD) simulation per subject to calculate the RF power in different head tissues induced by the LTE-EMF exposure [Wu et al., 2012; Lv et al., 2014]. Dielectric properties described by Gabriel et al. [1996] were applied.

MRI Scan

During each exposure session, we performed two MRI scans; the first was performed before the EMF exposure and included the structural MRI scan

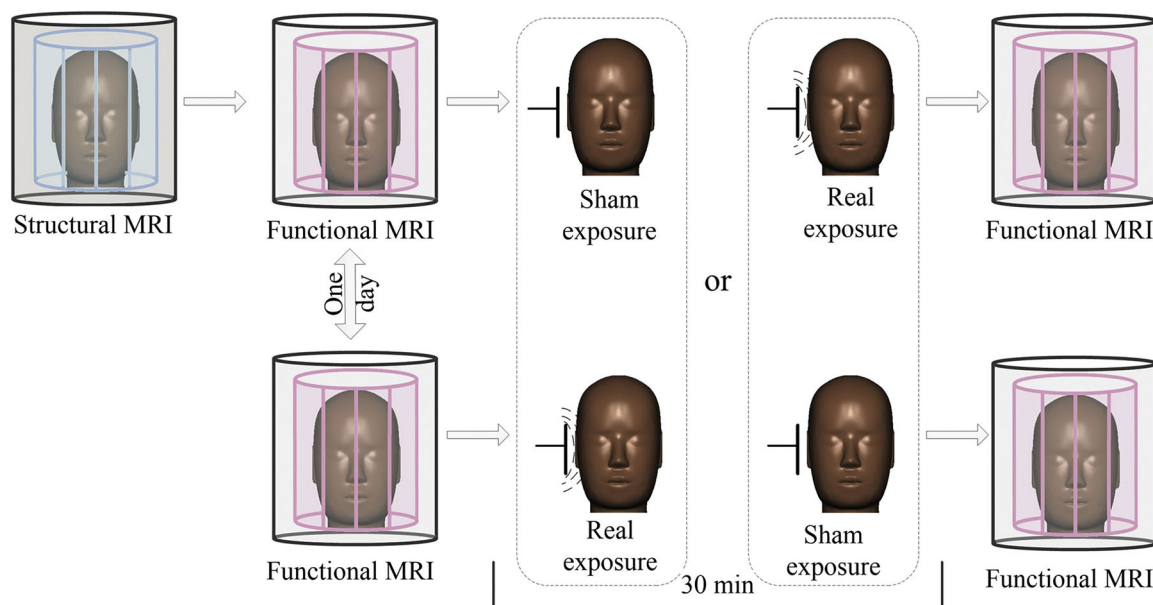


Fig. 1. Experimental procedures.

and resting-state fMRI scan, and the second was performed immediately after the exposure and only included the resting-state fMRI scan. The scans were performed on a 3.0 T MR scanner (SIGNA EXCITE, GE Healthcare, Chicago, IL) with a conventional eight-channel phased array coil. The magnetic gradient field was 40 mT/m, and the slew rate was 150 mT/m/s. The structural MRI scan was acquired with a three-dimensional fast spoiled gradient echo (3D FSPGR) sequence with the following parameters: repetition time (TR) = 6.8 ms, echo time (TE) = 2.9 ms, slice thickness = 1 mm, slice gap = 0 mm, field of view (FOV) = 22 cm × 22 cm, flip angle (FA) = 15°, matrix size = 256 × 256, in-plane resolution = 1.0 × 1.0 mm, number of excitations (NEX) = 1, and number of sagittal slices = 188. The resting-state fMRI images were collected by an echo-planar imaging (EPI) sequence with the following parameters: TR = 2 s, TE = 30 ms, slice thickness = 3 mm, slice gap = 0.8 mm, FOV = 22 × 22 cm, FA = 90°, matrix size = 64 × 64, in-plane resolution = 3.4 × 3.4 mm, NEX = 1, and 32 transverse slices. Each fMRI scan collected 180 image volumes and lasted for 6 min. The exposure experiment and MRI scan were performed at PLA General Hospital (Beijing, China).

Data Preprocessing

The structural data were processed with a unified segmentation algorithm in the Statistical Parametric Mapping software (SPM8, [Penny et al., 2011]). This process generated spatial normalization parameters that were used in the subsequent fMRI data analysis.

The fMRI data were preprocessed with the SPM8 and DPARSF software [Yan and Zang, 2010]. The first 10 functional volumes were discarded due to the instability of the initial MRI signal. Slice time correction and motion correction were performed on the remaining 170 volumes. The corrected functional images were spatially normalized to the Montreal Neurological Institute (MNI) space via transformation parameters between the mean functional image and T1-weighted structural image. The data were resampled to a 3 mm × 3 mm × 3 mm resolution. Finally, the linear trend was removed, and a temporal bandpass filter with 0.01 – 0.1 Hz was used to eliminate the noise of very low-frequency drift and high-frequency respiratory and heart rhythms.

ReHo and Seed-Based Analyses

We calculated the individual ReHo map from the processed functional volumes. In the ReHo maps, the value of each voxel was calculated as Kendall's coefficient of concordance (KCC, [Kendall and Babington, 1939]) of the time series of a given voxel

with its nearest 26 neighbors in a voxel-wise manner [Zang et al., 2004]. The ReHo measure is used to characterize the regional similarity of spontaneous fluctuations. To improve normality and reduce the global effects of variability across subjects, the ReHo value of each voxel was standardized by subtracting the global mean ReHo value and then dividing the standard deviation over the entire brain [Zuo et al., 2013]. The normalized ReHo maps were smoothed by convolution with an isotropic Gaussian filter (full width at half maximum = 4 mm). The ReHo maps were generated for each subject in each group.

When we detected significant differences in the ReHo values induced by EMF exposure, we selected these brain regions as the volumes of interest (VOI) to perform seed-driven functional connectivity (temporal correlation between a selected seed and all other voxels over the whole brain). The mean time series for each VOI was computed as the reference time course. Pearson's correlation coefficients were computed between the mean time series in each VOI and the time series of other voxels in the whole brain. Then, Fisher's z-transform was performed to improve the normality of the correlation coefficients [Margulies et al., 2010]. To rule out potential influencing factors, we conducted linear regression analysis with some covariates, including six head motion parameters and average time courses of the white matter, cerebrospinal fluid, and whole brain [Fox et al., 2005].

The ReHo and functional connectivity were analyzed using the Resting-State fMRI Data Analysis Toolkit (REST) v1.8 [Song et al., 2011].

Statistical Analysis

Paired *t*-tests were applied to the standardized ReHo maps generated pre- and post-exposure during each session. For the seed-based functional connectivity maps, we also applied a paired *t*-test to generate maps of significant differences. $p < 0.05$ was considered the threshold for statistical significance. We selected the Monte Carlo simulation method to correct for multiple comparisons [Yan and Zang, 2010]. This step was achieved using the AlphaSim program [Zang et al., 2007] with a combined threshold of $p < 0.01$ and a minimum cluster size of 486 mm³ (18 voxels, and the cluster connectivity criterion was edge-connected).

RESULTS

Numerical simulations that yielded spatial peak SAR averaging over 10 g tissues for the subjects was 0.98 ± 0.27 W/kg, with a maximal value of 1.52

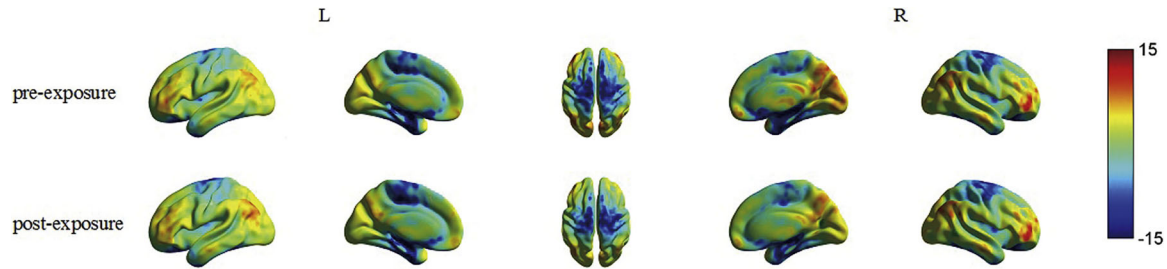


Fig. 2. Mean ReHo for before and after real exposure. L = left hemisphere and R = right hemisphere.

W/kg, which was below the safety limits [ICNIRP, 1998].

Averaged ReHo maps are shown in Figure 2 for the pre- and post-real exposure groups. The results were plotted on ICBM-152 brain template [Fonov et al., 2011]. Based on the standardized ReHo maps, we detected significant differences between pre- and post-real exposure using paired *t*-tests (Fig. 3). Table 1 provides detailed information about these brain regions. The detected clusters included cluster 1, which was located in the posterior part of the right inferior and middle temporal gyrus (ITG_R and MTG_R); cluster 2, which was located in the junction of the right calcarine sulcus and dorsal posterior cingulate area (CS_R and PC_R); and cluster 3, which was located in the caudal portions of the left middle and superior frontal gyrus (MFG_L and SFG_L). Compared with the pre-exposure condition, these brain regions had decreased ReHo values post-real exposure. All results were corrected by AlphaSim at $p < 0.05$. We did not find any significant differences

in the ReHo values induced by EMF exposure for the sham exposure.

Three VOI spheres were created according to the detected clusters of EMF-induced differences on the ReHo maps. The radius of the VOI sphere was set to 8 mm to cover the significant clusters, and the MNI coordinates of their centers were (63, -60, -3), (-18, -69, 15) and (-24, 3, 63). The VOI names refer to the order of the clusters from 1 to 3. Figures 4–6 demonstrate significant differences in seed-based functional connectivity between pre- and post-real exposure (VOIs 1–3, respectively), and Table 2 provides detailed information about the detected brain regions. All results were corrected by AlphaSim at $p < 0.05$. The red hue illustrates brain regions with lower functional connectivity after exposure, whereas the blue hue shows increasing functional connectivity after exposure. The statistical results showed that VOI1 had significantly increased functional connectivity to the left parahippocampal gyrus (PHG_L) and the anterior portions of the left inferior and superior temporal gyrus (ITG_L and STG_L) at post-real exposure. Compared to that of pre-exposure, VOI2 had significantly increased functional connectivity to the posterior part of the left inferior temporal gyrus (ITG_L), left inferior occipital gyrus (IOG_L), and bilateral superior and middle occipital gyrus (SOG and MOG) post-real exposure but significantly decreased functional connectivity around the left inferior frontal gyrus (IFG_L) and posterior part of the left middle and inferior temporal gyrus (MTG_L and ITG_L). After real exposure, VOI3 had significantly increased functional connectivity to the right inferior occipital gyrus (IOG_R) and right precuneus (PC_R) and significantly decreased functional connectivity to the junction of the right precuneus and cuneus (PC_R and CUN_R).

In order to assess the restorability after exposure, we analyzed the data from the subjects who received real exposure in the first day of experiment. The qualified data were from 9 subjects. No obvious change in term of ReHo was detected by MRI scan on

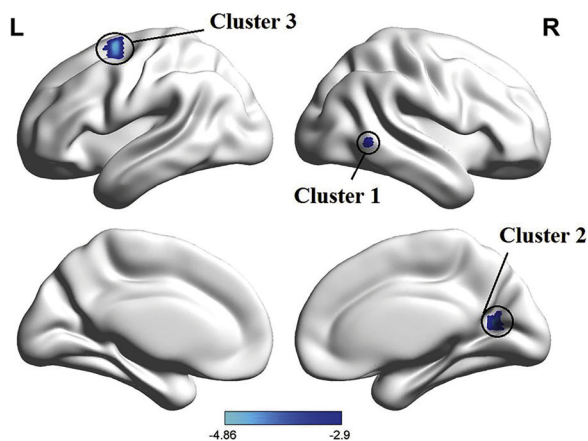


Fig. 3. The ReHo differences between pre- and post-exposure during real exposure ($p < 0.05$, AlphaSim corrected). The maps are colored according to the bar at the bottom. L = left hemisphere and R = right hemisphere. More details of these regions were described in Table 1.

TABLE 1. Brain regions showing significant difference in standardized ReHo values between pre- and post-exposure condition during real exposure.

Cluster	Brain region	BA	MNI coordinate			Peak t-value	Cluster size(mm ³)
			x	y	z		
1	MTG_R, ITG_R	37, 21	63	-60	-3	-4.23	594
2	CS_R, PC_R	31, 17	18	-69	15	-4.63	675
3	MFG_L, SFG_L	6	-	3	63	-4.86	621

Note: BA = Brodmann area, AAL = Anatomical Automatic Labeling, MNI = Montreal Neurological Institute, MTG_R = right middle temporal gyrus, ITG_R = right inferior temporal gyrus, CS_R = right calcarine sulcus, PC_R = right posterior cingulate, MFG_L = left middle frontal gyrus, SFG_L = left superior frontal gyrus

the second day. The results are shown in Figure 7. There was no significant difference for the sham group before and after the sham exposure.

DISCUSSION

To attain maximal repeatability and to eliminate the possible heating conduction caused by a mobile phone operating against the ear, we selected a standard dipole as the exposure source instead of a commercial mobile phone. The emitted power was comparable to the maximum emission from a real mobile phone. Our experimental paradigm was a double-blind, crossover, randomized and counterbalanced design, which could avoid subjective bias during experimental data collection and processing. In terms of safety, we established the head anatomical models based on structural MR images and calculated the EMF-induced power distribution in the head tissues with dosimetric stimulation. We confirmed

that the spatial peak SAR averaged over 10 g tissue in each subject was less than the safety limit (2 W/kg) in the ICNIRP guidelines [ICNIRP, 1998].

In our previous studies, we found that LTE-EMF exposure depressed the amplitude of spontaneous low frequency fluctuations (ALFFs) in some brain regions [Lv et al., 2014], such as those surrounding the left superior temporal gyrus and middle temporal gyrus (STG_L and MTG_L), right superior temporal gyrus (STG_R), right medial frontal gyrus, and right paracentral lobule (MFG_R and PCL_R). In the present study, we found new evidence that acute LTE-EMF exposures lasting for 30 min modulated brain functional connectivity including not only localized intraregional connectivity, but also interregional connectivity. With the ReHo index, we detected decreased localized intraregional connectivity surrounding three clusters (ITG_R and MTG_R, CS_R and PC_R, and MFG_L and SFG_L) after real exposure. Since the exposure source was located near

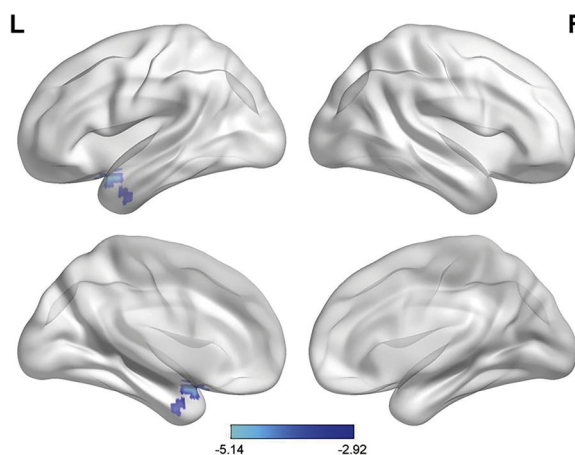


Fig. 4. The difference of seed based functional connectivity with cluster 1 between pre- and post- exposure during real exposure session ($p < 0.05$, Alpha simulation corrected). The maps are colored according to the bar at the bottom. L = left hemisphere and R = right hemisphere. Details could be referred to Table 2.

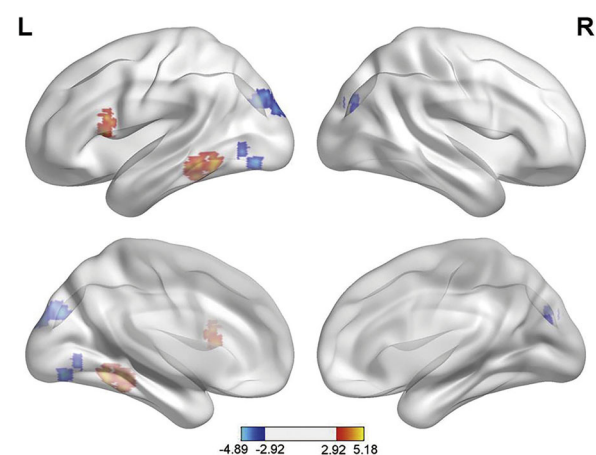


Fig. 5. The difference of seed based functional connectivity with cluster 2 between pre- and post- exposure during real exposure session ($p < 0.05$, Alpha simulation corrected). The maps are colored according to the bar at the bottom. L = left hemisphere and R = right hemisphere. Details could be referred to Table 2.

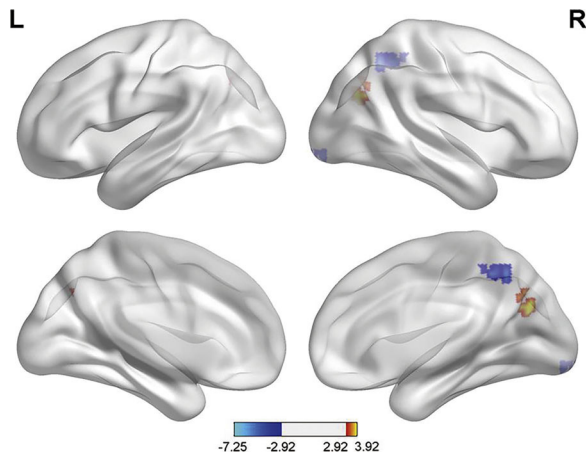


Fig. 6. The difference of seed based functional connectivity with cluster 3 between pre- and post- exposure during real exposure session. ($p < 0.05$, Alpha simulation corrected). The maps are colored according to the bar at the bottom. L = left hemisphere and R = right hemisphere. Details could be referred to Table 2.

the right ear, cluster 1 (ITG_R and MTG_R) was close to the exposure site, whereas cluster 2 (CS_R and PC_R) was on the ipsilateral hemisphere, and cluster 3 (MFG_L and SFG_L) was on the contralateral hemisphere. Compared to the ALFF results [Lv et al., 2014], cluster 1 was similar to the affected brain region caused by EMF exposure, whereas clusters 2 and 3 were newly detected brain regions. Although ALFF and ReHo are regional indexes for resting-state fMRI, they characterize different brain activation attributes. ALFF measures the amplitude of regional

activity [Zang et al., 2007], whereas the ReHo index focuses on similarities in intraregional activity [Zang et al., 2004]. Therefore, we need to integrate these results instead of comparing the findings directly. We found decreased ALFF and ReHo values near the exposure site after real exposure, which indicated that the most significant EMF effects occurred mainly in these brain regions. For the two newly discovered brain regions, we inferred that EMF exposure might have an acute effect on the corresponding human cognitive function in these brain regions. For example, the calcarine sulcus (cluster 2) is considered to be the primary visual cortex [Engel et al., 1997], and the left superior frontal gyrus is thought to contribute to working memory [Boisgueheneuc et al., 2006]. Previous studies provided evidence for electromagnetic hypersensitivity, which includes visual disturbances [McCarty et al., 2011] and acute EMF exposure, which could affect human working memory [Zubko et al., 2017]. Our results provided more support for these phenomena. Our seed-based functional connectivity results demonstrated that the alternations were significantly increased (red hues) and decreased (blue hues) in the areas surrounding the temporal and frontal cortex (Fig. 4–6), respectively. These brain regions also had altered brain activation characterized by regional measures [Lv et al., 2014, 2015; Yang et al., 2016]. However, we could not draw any conclusions about chronic exposure to EMF in light of our experimental design.

Positron emission tomography (PET) and fMRI are noninvasive brain imaging techniques. PET eval-

TABLE 2. The difference of seed based functional connectivity between pre- and post- exposure during real exposure session

Seed	Brain region	BA	MNI coordinate			Peak t-value	Cluster size(mm ³)
			x	y	z		
VOI1	IFG_L, STG_L, PHG_L	28, 34, 38	−24	15	−21	−5.14	1080
VOI2	MTG_L, ITG_L	20, 21	−60	−54	−9	5.18	1485
	ITG_L, IOG_L, MOG_L	19, 37	−42	−78	−9	−4.45	513
	IFG_L	44, 45	−51	15	9	4.60	729
	SOG_R, MOG_R	19	27	−90	33	−4.23	513
	SOG_L, MOG_L	19	−21	−90	36	−4.89	1242
VOI3	IOG_R	18	33	−96	−12	−7.25	621
	PC_R, C_R	7	−3	−75	36	5.64	1323
	PC_R	7	0	−57	48	−5.96	1944

Note: BA = Brodmann area, MNI = Montreal Neurological Institute, IFG_L = left Inferior Frontal Gyrus, STG_L = left Superior Temporal Gyrus, PHG_L = left Parahippocampal Gyrus, MTG_L = left Middle Temporal Gyrus, ITG_L = left Inferior Temporal Gyrus, IOG_L = left Inferior Occipital Gyrus, MOG_L = left Middle Occipital Gyrus, IFG_L = left Inferior Frontal Gyrus, SOG_L = left Superior Occipital Gyrus, SOG_R = right Superior Occipital Gyrus, MOG_R = right Middle Occipital Gyrus, IOG_R = right Inferior Occipital Gyrus, PC_R = right Precuneus, C_R = right Cuneus

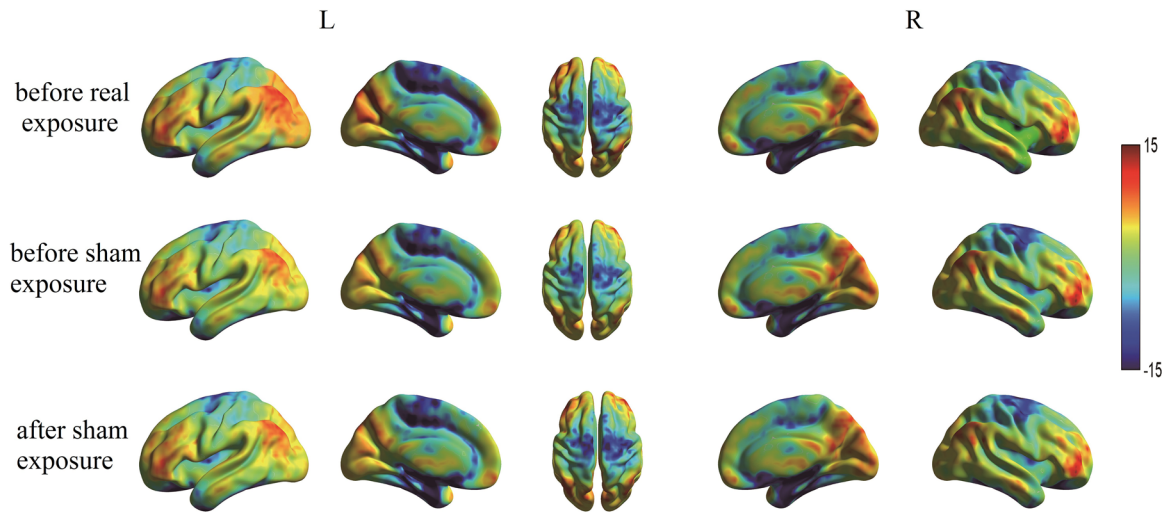


Fig. 7. Mean ReHo for 9 subjects who received real exposure → sham exposure experimental sequence. The results were from the cases of before real exposure for the first day, before sham exposure for the second day and after sham exposure for the second day.

uates brain activity via blood flow volume, whereas fMRI examines the amount of oxygen in the blood [Varvatsoulas, 2013]. One previous PET study on 2G signal exposure reported that exposure to an active mobile phone produced a decrease in regional cerebral blood flow bilaterally in the auditory cortex, but no regional cerebral blood flow alterations were revealed in the area of the maximum electromagnetic field, which was probably caused by noise from the battery of the active mobile phone [Haarala et al., 2003]. However, a subsequent PET study [Aalto et al., 2006] that eliminated noise revealed that a mobile phone in operation induced a local decrease in the regional cerebral blood flow beneath the antenna in the inferior temporal cortex and a more distant increase in the prefrontal cortex. We used the dipole as the exposure source and thus eliminated the confounding effect of auditory noise. Although we used a different exposure signal, our result was partially consistent with the PET studies. This finding is reasonable, because a lower cerebral blood flow may result in temporal desynchronization of BOLD signals across a cortical patch, resulting in a decreased ReHo [Bernier et al., 2017]. Actually, the correlation between ReHo and cerebral blood flow has been stated by a number of studies [Zou et al., 2009; Huisman et al., 2012; Li et al., 2012].

Although none of the subjects reported falling asleep, completely ruling out the possibility that subjects fell asleep or experienced sleepiness during the MRI scan was difficult. In future studies, we will use MRI-compatible physiological monitors to eliminate the possibility of falling asleep.

Although the SAR values by LTE-EMF exposure indicated no obvious temperature increase during the exposure experiments and the brain was excellent in terms of thermal regulation, we could not preclude that thermal changes, even minute changes, could be responsible for the instantaneous changes in neural firing. SAR is a metric averaging over 6 min, and its applicability for neurological studies should be discussed.

Studying restoration of the exposure effect would be preferable. In that case, multiple MRI scans should be conducted at different time points following real exposure. Nevertheless, the experimental protocol was not approved by the ethics committee. We used 9 subjects (the only subjects who underwent the real exposure → sham exposure experimental sequence) to evaluate the effect immediately after and one day after the LTE-EMF exposure. The results showed that the detected effect was restored one day after LTE-EMF exposure.

CONCLUSION

Our results may indicate that approaches relying on network-level inferences can provide deeper insights into the acute effects of LTE-EMF exposure with intensities below the current safety limits on human functional connectivity. In the future, we need to investigate the evolution of the effect over time.

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