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REVIEW ARTICLE

Radiofrequency electromagnetic radiation-induced behavioral changes and their possible basis

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Abstract
The primary objective of mobile phone technology is to achieve communication with any person at any place and time. In the modern era, it is impossible to ignore the usefulness of mobile phone technology in cases of emergency as many lives have been saved. However, the biological effects they may have on humans and other animals have been largely ignored and not been evaluated comprehensively. One of the reasons for this is the speedy uncontrollable growth of this technology which has surpassed our researching ability. Initiated with the first generation, the mobile telephony currently reaches to its fifth generation without being screened extensively for any biological effects that they may have on humans or on other animals. Mounting evidences suggest possible non-thermal biological effects of radiofrequency electromagnetic radiation (RF-EMR) on brain and behavior. Behavioral studies have particularly concentrated on the effects of RF-EMR on learning, memory, anxiety, and locomotion. The literature analysis on behavioral effects of RF-EMR demonstrates complex picture with conflicting observations. Nonetheless, numerous reports suggest a possible behavioral effect of RF-EMR. The scientific findings about this issue are presented in the current review. The possible neural and molecular mechanisms for the behavioral effects have been proposed in the light of available evidences from the literature.

Keywords Mobile phone · Radiofrequency electromagnetic radiation · Brain · Behavior · Anxiety · Locomotion · Learning and memory · Blood-brain barrier

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Introduction

Radiation is generally described as the transmission of energy through space in the form of waves or particles. Electromagnetic radiation (EMR) is a type of radiation, wherein the waves of electric and magnetic energy move together through the space (Cleveland and Ulcek 1999). According to Cleveland and Ulcek (1999), the energy of radiofrequency (RF) electromagnetic waves is not sufficient to cause ionization of atoms and molecules; hence, RF energy is said to be non-ionizing radiation. Though the aforesaid fact is true and well known to everyone, the relationship between this radiation and body systems is still a major concern. The very reason for this is the uncontrollable growth of mobile phone subscribers and the mobile phone use as this technology uses RF-EMR for data transfer. While communicating with a person, it is important to consider the possible health hazards due to technological advances. Until today, the scientific community could not categorically say whether these radiations are hazardous to humans. At the same time, they could not either rule out the possible health effects of these radiations. At present, we adopt a precautionary policy (WHO 2000) while dealing with these radiations. Adding more complexity to the situation, in 2011, the International Agency for Research on Cancer (IARC) of World Health Organization (WHO 2011) has classified RF-EMR emitting from mobile phones to be carcinogenic (group 2B) to humans (IARC 2011). The effects of these radiations on body systems might depend on the frequency and power of radiation. In case of lower frequencies of RF-EMR, the damage caused to the cells is determined mainly by heating effects, and thus by the radiation power. SAR is a measure of the rate at which energy is absorbed by the human body when exposed to RF-EMR. It is defined as the power absorbed per mass of tissue and has units of watts per kilogram (W/kg). SAR is usually averaged either over the whole body or over a small sample volume (typically 1 g or 10 g of tissue). The value cited is then the maximum level measured in the body part studied over the stated volume or mass. SAR values for mobile phones always refer to the maximum possible transmission power. SAR provides a straightforward means for measuring the RF-EMR exposure characteristics of cell phones to ensure that they are within the safety guidelines set by the regulatory bodies of different countries. Although the Federal Communications Commission (FCC) limit for public exposure from cellular telephones is a SAR level of 1.6 watts per kilogram (1.6 W/kg), this value considerably varies depending on each country's regulatory bodies.

Currently, the effect of RF-EMR on humans and various other organisms is a topic of interest. Work has been extensively carried out to understand the effects of RF-EMR in single-celled organisms (Aksoy et al. 2005; Gos et al. 2000; Markkanen et al. 2004), lower model organisms (Cammaerts 2013; Chavdoula et al. 2010), in rodents (Ahmadi et al. 2018; Mokarram et al. 2017; Sienkiewicz and van Rongen 2019), and in humans (Lai 2014; Carlberg and Hardell 2017; Henz et al. 2018; Elsawy et al. 2019). Behavior is defined as the way in which an organism reacts or acts. The surroundings have great influence on behavior of the organism. A good environment is a must for normal development; a bad physical environment can adversely affect the behavior of the organism to a great extent. Attempts have been made to evaluate the RF-EMR-induced behavioral effects on various animal models and on humans. Although several reports suggest the possibility of behavioral effects of RF-EMR, several contradictory observations can be seen in many of the published reports. The objective of the current review is to evaluate the behavioral effects of RF-EMR particularly on learning, memory, anxiety, and locomotion reported in rodents. In addition, an attempt has been made to explain the possible mechanisms that attribute to these behavioral changes.

Methods

Major electronic data bases such as MEDLINE/PubMed were the primary databases selected for the search of published literatures. Key words like "mobile phone radiation" and "anxiety"/"learning memory"/"locomotion", mobile phone radiation, and "hippocampus"/"blood brain barrier"/"cortex"/"cerebellum"/"amygdala" were used to extract relevant literatures. Several publicly available sources from regulatory authorities like WHO, IARC were also referred if they contain information pertaining to biological effects of RF-EMR. All titles and abstracts identified via PubMed search relevant to the issue of current review were vetted. Those publications, which did not relate to the specific topic of current review, were excluded at this stage itself. Each and every article that discussed any behavioral, histological, or biochemical endpoints in rats/mice were retained. Articles that discussed RF-EMR effects in humans and in other lower model organisms (other than rats/mice) were excluded. Those articles in non-English were also excluded. All selected articles were those deemed to support the issue of current review. Those articles met the inclusion criteria for further review were carefully analyzed. The parameters, such as RF-EMR frequency, specific absorption rate-SAR, exposure set-up, nature of exposure and duration of exposure, and all relevant biological effects, particularly the neurobehavioral effects were extracted from each one of them and summarized. Those researches reporting behavioral effects of RF-EMR published nearly past 10 years have used in this review as they provide the latest data about the radiation effects. However, some articles which were published earlier than this were also included according to their relevance to this review.

Behavioral effects of RF-EMR

RF-EMR on learning and memory

Many research reports have been published about the effect of RF-EMR on cognition. But the results have been inconsistent (Fragopoulou and Margaritis 2010). Bouji et al. (2016) have exposed 22–24-month aged male rats to 900 MHz RF-EMR, for 1 month. They have found that RF-EMR did not induce specific cerebral functional vulnerability (in spatial, emotional memory, anxiety, and locomotor activity) to RF-EMR during senescence. Intrauterine exposure to the GSM field did not show any cognitive deficits in the offspring of RF-EMR-exposed pregnant rats when tested for operant-behavior (Bornhausen and Scheingraber 2000). Differently, Aldad et al. (2012) reported that 800–1900 MHz (SAR 1.6 W/kg) mobile phone exposure (phone on active call mode for 24 h per day throughout gestation; days 1–17) induced memory impairment, hyperactivity-like behavior in mice exposed to

RF-EMR in-utero. In a study by Nittby et al. (2008), exposure for 55 weeks induced some memory deficits in rats for objects and their temporal order of presentation. Nonetheless, detecting the place and exploratory behaviors was not affected.

In another study, a single 45-min exposure to 900 MHz radiation had induced an elevation in 5-HT level without changing blood glutamate level of rats. Increased 5-HT level might lead to learning impairment and spatial memory deficit (Eris et al. 2015). In the study by Tang et al. (2015), exposure to 900 MHz radiation had altered the neurobehavioral performance in rats. These changes were more explicit in 28-day exposed group as demonstrated by impaired spatial memory and damaged blood-brain barrier (BBB) permeability by activating the mkp-1/ERK pathway (Tang et al. 2015). Studies have also proven that exposure to 900 MHz radiation can also alter the spatial learning and reference memory and induce morphological changes in the hippocampus CA1 region (Li et al. 2012). Reports also indicate that, chronic mobile phone radiation exposure could severely interact with the consolidation phase of recognition memory in mice and it is postulated that this may be due to the effect of RF-EMR on information transfer pathway connecting the entorhinal and parahippocampal regions as they are involved in the object recognition memory task (Ntzouni et al. 2011). On the other hand, in the experiments conducted by Daniels et al. (2009), RF-EMR exposure in rats did not induce any significant changes in spatial learning and memory. However, they observed decreased locomotor activity and increased grooming tendency in RF-EMR-exposed rats. In the studies conducted by Ammari et al. (2008a, b), chronic head only exposure to 900 MHz radiation for 8 or 24 weeks did not alter the spatial learning and memory in an eight arm radial maze test. In contrary to this, Narayanan et al. (2015) have reported that 1-month exposure to RF-EMR (900 MHz) could alter the Morris water maze performance and induced dendritic changes in rat hippocampus.

According to the reports by Kumlin et al. (2007), exposure to 900 MHz radiation can enhance spatial memory performance without affecting morphology of hippocampal morphology in rats. In a study on mice, by Fragopoulou et al. (2010), 2-h exposure to 900 MHz radiation on a daily basis had induced alterations in spatial memory performance. Another study suggests that a single exposure to 900 MHz radiation does not induce activation of astrocyte but increased IL-1β in the olfactory bulb and leads to enhance contextual emotional memory in middle-aged rats (Bouji et al. 2012). In contrast to this, another report suggests that 916 MHz, 10 w/m^2 EMF could change the learning and memory in rats to some extent in a short period during exposure; however, the rats get adapted to long-term exposures (Hao et al. 2013). In another study, RF-EMR exposure for a period of 4 weeks had induced deficits in spatial memory performance (Narayanan et al. 2009). In yet another recent study (Saikhedkar et al. 2014), exposure to 900 MHz for 4 h/day for a period of 15 days had induced deficits in learning and memory. There was also hippocampal neuronal degeneration in these rats. Conflicting reports are available on the effect of RF-EMR on emotional learning and memory. When pregnant rats were exposed to RF-EMR throughout their gestational period (900 MHz), the emotional learning and behavior in their male and female offspring were found to be drastically affected by the exposure as demonstrated by their altered learning acquisition and memory retention (Razavinasab et al. 2016). Report also suggests that RF-EMR did not induce changes in passive avoidance behavior in mid and late adolescent rats (Keleş et al. 2018). One-month exposure to 900 MHz RF-EMR induced altered passive avoidance behavior and morphological changes in the hippocampus of rats (Narayanan et al. 2010). Further, a study investigated to know whether RF-EMR induce molecular changes in amyloid precursor protein processing and amyloid beta (Aβ)-related memory impairment in the 5xFAD mouse, revealed no effect on Aβ-related memory impairment or Aβ accumulation in the 5xFAD Alzheimer's disease model (Son et al. 2016). In a recent report, Wang et al. (2017) demonstrated that exposure to 1800 MHz RF-EMR can significantly increase recognition memory in mice and can change dendritic-spine morphology and neuronal excitability in the hippocampus and prefrontal cortex. In another very recent study, Ahmadi et al. (2018) report that 4 weeks of mobile phone exposure impaired inhibitory avoidance (IA) memory performance in rats.

RF-EMR on anxiety

Anxiety can be defined as an emotional and physiological response that can influence humans as well as animals, which could be associated with a threat to their well-being (Steimer 2002). Anxiety-like behavior in animal models is often extrapolated to the anxieties that are reported in human beings. It is considered as a pliable response to a foreign environment, chiefly when the individual is exposed to any alarming situation or threat (Ohl 2005). Many studies indicate the widespread usage of mobile phones as a proven potential risk factor to human health in this era of technology boom. For investigating anxiety-like behavior in animal models over the years, researchers have developed various behavioral paradigms. Some of the commonly used strategies in testing anxiety in animal models includes elevated plus maze (EPM), open field test (OFT), and black and white box. Studies by Zhang et al. (2017), in RF-EMR-exposed mice brain, revealed significant reduction in GABA and aspartic acid (Asp) in cortex and hippocampus. The authors claim that the possible cause of anxiety in RF-EMR-exposed rat brain could be due to the reduction in GABA and Asp. Open field test, in RF-EMR-exposed mice, revealed a significant reduction in the time spent and distance traveled in the central arena in comparison with the sham group. This is considered as a behavioral indicator of elevated anxiety levels. Researchers have also reported the potential impact of RF-EMR exposure on increasing the emotionality of rodents. This was demonstrated by the exposed groups decreased open arm entries, time spent, and total distance traveled on the open arms (Narayanan et al. 2013). Similar findings were also reported by Saikhedkar et al. (2014). They noticed that the rats presented significant anxiety-like behavior in EPM and OFT when exposed to 900 MHz RF field for about 15 days. In a study conducted by Zhang et al. (2017), when mice were exposed to a radiofrequency field of 1.8 GHz for 4 weeks, induced anxiety-like behavior in the exposed animals. This was demonstrated by their decreased total accumulative distance traveled and time spent in the center area of open field. However, in contrast to this, Junior et al. (2014) found no significant effects on the anxiety-like behavior in male rats that were exposed to RF-EMR. Obajuluwa et al. (2017) investigated the impact of 4- to 8-week exposure of 2.5 GHz band radio-frequency electromagnetic wave on male rats. They found that there was increased anxiety-like behavior which was evidenced by reduction in the line crossing frequency in OFT. In a study by Narayanan et al. (2013), cell phone radiation-exposed rats showed low rearing and high grooming frequency in EPM test. This correlates positively with the enhanced anxiety-like behavior. In another study, similar behavioral pattern was noticed when animals were subjected to 10-min call per day for 4 weeks (Shehu et al. 2016). Rats exposed to 50 missed calls per day for 4 weeks from cell phone kept in a vibratory mode showed hypoactivity in EPM test (Kumar et al. 2009). This finding was supported by a later study by Saikhedkar et al. (2014). They found that when rats were subjected to mobile phone radiations for about half a month (4 h per day), the exposed group exhibited enhanced anxiety in EPM test. Mobile phone radiation of 900 MHz for 1 h/day has also induced significant changes in place preference behavior (Narayanan et al. 2018). Additionally, Sokolovic et al. (2012) have reported that GSM mobile phone exposure 900 MHz for 4 h/day induced anxiety-related behavior after 10 days of exposure. The observed changes were the most intense after 60 days of exposure.

RF-EMR on locomotor behavior

Many researchers have reported the effects of RF-EMR on locomotor behavior in animals. According to some of these studies, RF-EMR does not alter the locomotion. But some researchers have shown positive correlation between cell phone radiation and locomotor behavior in rodents (Odacı et al. 2013; Kim et al. 2017). Decreased locomotor activity was observed in rats when exposed to mobile phone radiation (4 h/day) for 15 days (Saikhedkar et al. 2014). Obajuluwa et al. (2017) reported that exposure to 2.5 GHz radiations for 4 to 8 weeks of duration reduced locomotor activity in rats indicated by reduced line crossing frequency pattern in open field test. In the meantime, a report by Narayanan et al. (2013) demonstrated that mobile phone radiation over a period of 1 month did not significantly alter the general locomotion in rats.

Possible underlying mechanisms for RF-EMR-induced behavioral changes

It is evident from the Table 1 that a substantial number of reports are available indicating the possible behavioral effects of RF-EMR. Although 900 MHz frequency band has been studied extensively, behavioral effects induced by other frequency bands have also been reported by many (Table 1). What could be the possible reason for the altered behavioral patterns seen in rodents following radiation exposure? The possible reasons for the altered behavioral patterns observed after RF-EMR exposure could be (a) the structural changes that may occur in various brain regions (blood-brain barrier, hippocampal formation, cerebral cortex, cerebellum, and amygdala), (b) impact of RF-EMR effects on glial cells, and/or (c) the modulatory role of RF-EMR on various neurotransmitter levels in different brain regions.

Structural changes in the brain after RF-EMR exposure

Altered blood-brain barrier (BBB) integrity

This has been extensively studied for several decades. Rats subjected to 915 MHz continuous and pulse modulated (8, 16, 50, and 200 s^{-1}) wave electromagnetic radiation, with 0.016 to 5 W/kg SAR for 2 h, have showed presence of albumin and fibrinogen. This confirms that there was altered structural integrity of BBB following electromagnetic radiation exposure (Salford et al. 1994). Single 20-min exposure to 1.3 GHz continuous or pulsed microwave energy can also result in an increase in permeability of BBB in medulla, cerebellum, hypothalamus, hippocampus, and cortex. In one of the studies, permeability had increased immediately following the exposure and had lasted for 4 h (Oscar and Hawkin 1977). In a study, continuous wave radio frequency radiation (RFR) exposure had significantly increased the permeability of BBB in male animals. However, this effect was not observed in female animals (Sirav and Seyhan 2009). Blood-brain barrier is usually low permeable to hydrophilic and charged molecules; an increased permeability for these molecules is detrimental to the brain. Exposure to EMF enhances the permeability of BBB for macromolecules; however, this process is reversible (Stam 2010). In addition to that, 2 h of exposure to EMR (electromagnetic radiation) emitted from GSM mobile phone resulted in albumin extravasation into the neural tissue and

Table 1 Radiofrequency electromagnetic radiation (RF-EMR) exposure effects on behavior

Author and year of publication	Frequency studied	Specific absorption rate (SAR)	Power density	Exposure system or set-up	Exposure duration	Exposure nature (whole body/head)	Animal model and age	Behavioral and other parameters studied	Behavioral and other biological effects reported
Bouji et al. 2016	900 MHz	6 W/kg	Not reported	A radiofrequency generator that emits 900 MHz	Forty-five minutes per day for 1 month	Head region	Young (4–6 months) and old (22–-24 months) adult male Wistar rats	Spatial and emotional memory, anxiety, and locomotor related behaviors. Interleukins (IL)-1β and 6, glial fibrillary acidic protein and corticosterone	Decreased anxiety-related behavior was evident in RF-EMR exposed rats Deficits in spatial learning, exploration, was found with aged rats. Increased hippocampal ILs and cortical IL-1β
Bornhausen and Scheingraber 2000	900 MHz	Ranged between 17.5 and 75 mW/kg	0.1 mW/cm^2	The EMF-generating equipment and two exposure chambers with an inner lining of 15 cm RF-absorbing, solid foam.	From day 1 to 20th day of pregnancy.	Whole body exposure	Pregnant, 3-month-old Wistar rats	Offspring's of RF-EMR exposed and sham exposed dams were tested for operant behavior	No measurable cognitive deficits were observed.
Aldad et al. 2012	800–1900 MHz	1.6 W/kg	Not reported	Mobile phone	Phone on active calling mode for 24 h/day throughout gestation	Whole body exposure	CD-1 male and female mice	Memory, anxiety and hyperactivity. Corticosterone level measurements, whole-cell voltage clamp in prefrontal, ventral medial hypothalamus to observe and study miniature excitatory postsynaptic currents (mEPSCs).	Impaired memory and hyperactive behavior in mice exposed to RF-EMR in-utero. Altered neuronal developmental programming. Glutamatergic synaptic transmission onto layer V pyramidal neurons of prefrontal cortex was impaired.
Nittby et al. 2008	900 MHz	Average SAR 0.6 and 60 mW/kg	33 mW/m^2 and 3.3 W/m^2	TEM-cells were used and a GSM test phone was connected to 4 TEM cells with no voice modulation.	2 h/week for 55 week	Whole body exposure	Male and female Fischer 344 rats, 4–6 months old	Episodic-like memory and exploratory behavior	Impaired memory for objects and their temporal order of presentation. No change in exploratory behavior.
Tang et al. 2015	900 MHz	Whole body; 0.016 and 2 W/kg (locally in the head).	1 mW/cm^2	Microwave power generator and monopole antenna	3 h/day 14 or 28 days	Whole body exposure	Male Sprague-Dawley rats	Spatial memory performance, morphological alterations in the hippocampus, cortex, and blood brain barrier.	Impaired spatial memory in 28 days exposed group compared to 14 day exposed group. Additionally, cellular edema and neuronal organelle degeneration were observed in 28 days exposed group. Increased blood brain barrier permeability in the hippocampus, and cortex
Li et al. 2012	900 MHz	0.52–1.08 W/kg	Not reported	GSM 900 MHz mobile phone	2 h/day for 1 month	Whole body exposure	Wistar rats, aged 8 weeks	Spatial learning, reference memory, and synaptic ultrastructural alterations in the hippocampus	Altered spatial learning and reference memory. Mitochondrial degenerations, fewer synapses and shorter postsynaptic densities in the hippocampal CA1 region
Ntzouni et al. 2011	1800 MHz	0.22 W/kg	Mean electrical field density averaged over 6 min to 17 V/m	Conventional mobile phone operating at GSM 1800 MHz	90 min/day for 17 or 31 days	Whole body exposure	Male *M. musculus* C57BL/6 mice, 45 days	Object recognition memory	Altered recognition memory in 17 days exposed group
Daniels et al. 2009	840 MHz	Not reported	60 µW/m^2	Radio frequency signal generator	3 h/day from post-natal days 2–14	Whole body exposure	Male and female Sprague-Dawley rats	Spatial memory, locomotion, exploratory behavior, grooming, corticosterone levels, and hippocampal morphology	No deficits in spatial memory, decreased locomotor activity, and increased grooming. Corticosterone levels did not vary significantly and hippocampal architecture was not altered.
	900 MHz	Not reported							

Table 1 (continued)

Author and year of publication	Frequency studied	Specific absorption rate (SAR)	Power density	Exposure system or set-up	Exposure duration	Exposure nature (whole body/head)	Animal model and age	Behavioral and other parameters studied	Behavioral and other biological effects reported
Ammari et al. 2008			Brain-averaged specific absorption rate (1.5 W/kg) Brain-averaged specific absorption rate (6 W/kg)	Radio frequency generator emitting 900-MHz	45 min/day 5 day a week for 8 weeks. 15 min/day, 5 days a week for 24 weeks	Head only exposure	Male Sprague-Dawley rats (6 weeks old)	Spatial learning and memory assessed using radial maze test	RF-EMR exposure did not affect spatial learning and memory on eight arm radial maze
Narayanan et al. 2015	900 MHz	Peak power density: 146.60 μW/cm^2	1.15 W/kg	Conventional mobile phone operating at GSM 900 MHz band	1 h/day (7 days a week) for 28 days	Whole body exposure	Male Wistar rats, 4 weeks old	Spatial learning and memory, hippocampal surviving neuron count, and dendritic arborization pattern in the hippocampal CA3 neurons	Deficits in spatial learning and memory consolidation. In CA3 neurons Hirano bodies and Granulovacuolar bodies were absent in the CA3 neurons, decreased viable cell count and decreased dendritic arborization pattern in the dorsal hippocampal CA3 neurons
Kumlin et al. 2007	900 MHz	Not reported	Whole body averaged SARs are 0.3 W/kg and 3.0 W/kg	Modified GSM 900 phone was used as the signal source	2 h/day, 5 days a week for 5 weeks.	Whole body exposure	Male Wistar rats, 21 days old	Spatial memory performance, locomotor and exploratory activity, anxiety, general reactivity, attention, spatial learning and memory, and hippocampal morphology	Enhanced spatial memory performance observed. No changes were found in locomotor, exploratory activity, anxiety, general reactivity and attention tests. No degenerative changes, dying neurons or leakage of BBB were observed.
Fragopoulou et al. 2010	900 MHz	Varied between 0.05 and 0.2 mW/cm^2	Ranging from 0.41 to 0.98 W/kg	GSM Mobile phone	2 h/day for 4 days	Whole body exposure	M. *musculus* Balb/c 50-day-old male mice	Spatial memory performance	Altered spatial memory performance
Bouji et al. 2012	900 MHz	0 or 6 W/kg	Not reported	Radio frequency power source emitting 900 MHz	45 min/day for 1 month.	Head only exposure	Male Sprague-Dawley rats (6 weeks and 12 months old)	Contextual emotional memory GFAP expression, brain interleukin (IL)-1β and IL-6, plasmatic levels of corticosterone (CORT), and emotional memory	Contextual emotional memory was enhanced in middle aged rats. No astrocyte activation. In middle aged rats, IL-1β was found to be increased in the olfactory bulb. Corticosterone levels were increased in the plasma of young rats
Hao et al. 2013	916 MHz	Not reported	10 W/m^2	Microwave power generator	6 h/day (in two, 3 h. sessions with 2 h and 30 min gap between the two sessions), 5 days per week for 10 weeks	Whole body exposure	Male Wistar rats aged 8 weeks	Learning and memory using eight arm radial maze and hippocampal neuronal discharge signals	Learning and memory found to be affected during weeks 4–5, indicating RF-EMR affected this process during middle period of exposure and rats gets adapted to long-term RF-EMR exposure. Neurons in the hippocampus displayed altered firing pattern; more spikes with shorter interspike interval.
Narayanan et al. 2009	GSM (900/1800 MHz)	Not reported	Not reported	GSM mobile phone	Rats were exposed to 50 missed calls (each was separated by 15 s inter call intervals)/day for 4 weeks	Whole body exposure	Male Wistar rats (10–12 weeks old)	Spatial memory performance	Poor spatial navigation and object place configurations of phone-exposed animals in Morris water maze test.
Saikhedkar et al. 2014	900 MHz	0.9 W/kg	Not reported	Mobile phone (Spice S-5110)	4 h/day for 15 days	Whole body exposure	Young adult Wistar male	Spatial learning, and memory, anxiety, effects on brain antioxidant status and neuronal damage in the brain	Poor spatial learning and memory and increased anxiety. Increased lipid peroxidation, and neurodegenerative

Table 1 (continued)

Author and year of publication	Frequency studied	Specific absorption rate (SAR)	Power density	Exposure system or set-up	Exposure duration	Exposure nature (whole body/head)	Animal model and age	Behavioral and other parameters studied	Behavioral and other biological effects reported
							rats (30 days old)		cells in the hippocampal sub regions and cerebral cortex.
Razavinasab et al. 2016	900 MHz	0.3 and 0.9 W/kg	Not reported	Mobile phone	6 h/day, since the first day of pregnancy until offspring birth	Whole body exposure	Primiparous Wistar female rats	Spatial learning and memory, emotional learning and memory, brain morphology and whole cell recording of hippocampal pyramidal neurons	Altered learning and memory in male and female offspring rats. Decreased neuronal excitability in both male and female rats. Normal brain morphology
Keleş et al. 2018	900 MHz	Not reported	Not reported	The EMF-cage	1 h/day for 25 days	Whole body exposure	Male Sprague-Dawley rats (3 weeks old)	Passive avoidance, learning, memory, locomotion and motor skill learning. Histopathological evaluation of hippocampus.	No change in learning, memory and locomotion. Altered pyramidal and granular cell structure of hippocampus
Narayanan et al. 2010	GSM (0.9 GHz/1.8 GHz)	Not reported	Not reported	GSM mobile phone	Animals were exposed to 50 missed calls (each with 45 s duration with 15 s interval with the next)/day for 4 weeks	Whole body exposure	Healthy male albino Wistar rats (8–10 weeks old)	Passive avoidance behavior and hippocampal morphology	Altered passive avoidance behavior and neuronal degeneration in the CA3 region of the hippocampus.
Son et al. 2016	1950 MHz	5 W/kg	Not reported	Reverberation chamber was used. By using a microprocessor unit chip RF-EMR was generated.	2 h per day, for 3 months	Whole body exposure	5xFAD mice and RF-EMR exposure started at 1.5 months	General activity, non-spatial working memory, working memory and reference memory and hippocampus-dependent spatial memory. In the hippocampus and cortex, Ab deposition, APP, and carboxyl-terminal fragment b (CTFb) levels were evaluated. Ab peptide levels in the plasma	No significant change in spatial, non spatial memory and in locomotor behavior. No significant change observed in APP, CTFb levels or Ab deposition in the brain
Wang et al. 2017	1800 MHz	3.3 W/kg	Not reported	1800 MHz, irradiation system for live animals.	Single exposure for 30 min	Whole body exposure	Female C57/LB mice, 3–4 weeks old	Recognition memory, spontaneous locomotor activity, dendritic spine density in prefrontal and hippocampal neurons, and whole-cell recordings in acute hippocampal and medial prefrontal cortical slices	Increased recognition memory and no change in spontaneous locomotor activity. Prefrontal and hippocampal neurons showed increased dendritic spine density and length. Resting membrane potential and action potential were altered in pyramidal neurons. In addition, reduced action potential half-width threshold and onset delay was also evident in pyramidal neurons
Ahmadi et al. 2018	900 MHz	0.69 W/kg	416.9 ± 57.3 mV/m	GSM mobile phone	50 missed calls (with 35 s duration) for 4 weeks	Whole body exposure	Male Wistar rats	Inhibitory avoidance (IA) memory performance	Impaired inhibitory avoidance memory consolidation.
Zhang et al. 2017	1800 MHz	Whole body and brain SAR were, 2.7 W/kg and 2.2 W/kg	530 μW/cm^2	1800 MHz exposure system	6 h/day for 28 days	Whole body exposure	Male C57BL/6 mice (4 weeks old)	Anxiety, depression like behavior, spatial learning, and memory. Levels of amino acid neurotransmitters, and histology of the brain.	Increased anxiety, depression behavior. No change in spatial memory. Gamma-Aminobutyric (GABA) and aspartic acid (Asp) were decreased in the hippocampus. No change in brain histology
Narayanan et al. 2013	900 MHz	Mobile phone SAR	146.60 μW/cm^2	Level 4 GSM mobile phone.	1 h/day (50 unattended calls, each with	Whole body exposure	Male albino Wistar rats	Emotionality and locomotion	Increased emotionality but no change in locomotion parameters. Rearing and grooming frequency were decreased.

Table 1 (continued)

Author and year of publication	Frequency studied	Specific absorption rate (SAR)	Power density	Exposure system or set-up	Exposure duration	Exposure nature (whole body/head)	Animal model and age	Behavioral and other parameters studied	Behavioral and other biological effects reported
		specification 1.15 W/kg			45 s duration with a gap of 15 s before the next) for 28 days		(6–8 weeks old)		
Junior et al. 2014	1800 MHz	Not reported	Average electric field intensity 2.0 V/m	GSM mobile phone	25 s long mobile phone calls every 2 min, for 3 days.	Whole body exposure	Male Wistar rats, 60 days old	Anxiety patterns, locomotor activity, and working memory	No anxiety, impairment of working memory but stressful behavior patterns observed.
Obajuluwa et al. 2017	2500 MHz	Not reported	Electric field density; 11 V/m	Signal device generate 2500 MHz Wi-Fi signals	24 h/day for 4, 6, and 8 weeks	Whole body exposure	Male albino rats, 4 weeks old.	Anxiety, locomotion, acetylcholinesterace (AChE) activity in the cortex with their mRNA expression level	Increased anxiety and decreased locomotor activity. Decreased AChE activity with an increase in AChE mRNA expression levels
Shehu et al. 2016	900 MHz	Not reported	Not reported	A cell phone operates in GSM 900/1800 band	30 missed calls (20 s each)/day for a total of 10 min duration for 4 weeks	Whole body exposure	Male Wistar albino rats	Anxiety-like behavior and oxidative stress biomarkers	Increased anxiety. Decreased catalase activity, but no change in MDA concentration, SOD activity, and GPx activities.
Kumar et al. 2009	900/1800/MHz	Not reported	Not reported	GSM mobile phone	50 missed calls (with 15 s interval between each missed call) per day for 4 weeks	Whole body exposure	Male Albino Wistar rats 10–12 weeks old	Anxiety	Increased anxiety as demonstrated as deficit in open arm exploration
Narayanan et al. 2018	900 MHz	Mobile phone SAR specification 1.15 W/kg	146.60 μW/cm^2	Mobile phone	1 h/day (50 unattended calls), for 28 days	Whole body exposure	Male albino Wistar rats 4 weeks old	Place preference and locomotor activity. Surviving neuron count, dendritic arborization pattern, apoptosis in the amygdala and brain caspace-3 activity	Hyperactivity and change in place preference behavior. Decreased healthy neuron counts in basolateral and cortical amygdala nuclei but no in central nucleus. Altered dendritic arborization pattern in basolateral amygdala nucleus but not in central nucleus. Apoptosis is found in amygdala, however caspase-3 activity did not change in the brain significantly
Sokolovic et al. 2012	900 MHz	Whole body SAR; 0.043–0.135 W/kg	Not reported	GSM Mobile phone	4 h/day for 60 days	Whole body exposure	Adult male Wistar Albino rats	Anxiety related behavior, locomotor activity, rearing and grooming, body weight gain (in grams)	Anxiety-like behavior following 10 days of exposure. These changes were most intense after 60 days of exposure. A significant reduction in body mass in exposed group
Odaci et al. 2013	900 MHz	Not reported	10 V/m	Ultra-high-frequency oscillator	1 h/day from day 13 to 21 of pregnancy	Whole body	Female rats (6–8 weeks old) and pups	Anxiety, motor functions and spinal cord structure	Increased locomotor activity, no change in anxiety and pathological changes in spinal cord
Kim et al. 2017	835 MHz	4.0 W/kg	Not reported	RF-EMR generator	5 h/day for 12 weeks	Cranial exposure	C57BL/6 male mice, (6-week-old)	Autophagy pathway in the cerebral cortex, and locomotion	Autophagy in cortical neurons, myelin sheath damage and hyperactivity-like behavior

lead to neurodegeneration. Increased BBB permeability was noted immediately after the exposure and lasted for 14 days (Nittby et al. 2009). Further, in one of the studies, exposure to 900 MHz radiation for 3 h/day for 14 or 28 days at SAR between 0.016 and 2 W/kg locally in the head caused albumin extravasation in hippocampus and cortex resulting from damage to BBB. Cellular edema and cell organelle degeneration were noted in 28-day exposure group. These structural changes produced significant impairment in spatial memory (Tang et al. 2015). GSM microwave exposure for 2 h/day at 900 MHz with SAR of 0.12, 1.2, 12, or 120 mW/kg for either 14 or 28 days. Albumin extravasation and its uptake into neurons were increased in 14-day exposure group. Numbers of dark neurons were enhanced in 28-day group (Eberhardt et al. 2008), whereas 1439 MHz EMF near field exposure with SAR of 0, 2, and 6 W/kg for 90 min/day for 1 or 2 weeks did not show any pathological changes and vascular permeability of BBB in immature and young rats (Kuribayashi et al. 2005). Exposure to 1457 MHz RFR for 50 min did not show evidence of albumin leakage. This proves that there were no changes in the BBB permeability among rats of different age groups (Masuda et al. 2015).

Changes in the cytoarchitecture of hippocampal formation

There is enough scientific evidence for electromagnetic radiation causing significant neurodegeneration in brains, especially basal nuclei and hippocampus (Salford et al. 2003). Maskey et al. (2010a) exposed the rats to 835 MHz EMF with SAR of 1.6 W/kg and 4.0 W/kg for 1 h/day for 5 days: 1 day and for 1 month. This exposure for 1 month produced neurodegeneration in CA1 are of hippocampus indicating a possible detrimental effect on hippocampal functions. In a report by Altun et al. (2017), exposure to EMF for 1 h/day for 15 days showed significant neuronal loss in CA1 and CA2 areas; however, there was no significant difference in CA3 area of hippocampus. Loss of granule cells was noted in the dentate gyrus. Further, significant short entrance latency was observed in EMF-exposed group (Altun et al. 2017). However, exposure to GSM radiation for 1 h/day for 4 weeks in mobile phone-exposed animals resulted significant histopathological changes in hippocampal CA3 region and short entrance latency into the dark compartment (Narayanan et al. 2010). Animals that received 900 MHz radiation through mobile phone for 4 h/day for a period of 15 days have shown neurodegeneration in CA1, CA3, and dentate gyrus sub regions of hippocampus. This neuronal loss could be a reason for poor learning and memory (Saikhedkar et al. 2014). In another study, when pregnant mice from 0.25 and 11.25 days of gestation to till term received 10 GHz microwave radiation exposure, their offspring mice had showed histopathological changes in hippocampus (Sharma et al. 2017). Studies have also shown that prenatal and postnatal EMF exposure for 120 min/day can cause neurodegeneration in the dentate gyrus, hippocampal CA3 region, and increased GFAP (glial fibrillary acidic protein) among astrocytes in offspring and adult animals. These pathological changes may affect memory (Amal et al. 2013). The animals which received 900 MHz RFR for 1 h/day for 1 week and 1 h/day for 2 weeks have shown dark neuron in the hippocampus (Awad and Hassan 2008). Animals that were exposed to 25, 50, 75, and 100 missed calls in a day for 4 weeks have shown congestion, hemorrhage, enlarged perivascular spaces, and deformed nuclei. Electron microscopy revealed distorted cristae and swollen mitochondria in neurons of CA3 region of hippocampus. These changes in long term may lead to behavioral and cognitive deficits (Faridi and Khan 2013).

Animals exposed to 1800 MHz RF-EMR from a cell phone for 3 months showed vascular congestion and degenerative changes in pyramidal cells of hippocampus (Hussein et al. 2016). Mice that were exposed to 2G radiation (900–1800 MHz) for 48 min/day for 30–180 days resulted less density of neurons in CA1, CA2 areas of hippocampus; however, CA3 region showed high density of neurons. Further, the nuclear diameter was less in CA1, CA2, and CA3 region neurons (Mugunthan et al. 2016).

Rats that were exposed to 900 MHz microwaves from 1st to 19th day of gestation, caused neurodegeneration, and reduced pyramidal cell number in offspring's hippocampus (Bas et al. 2009). Exposure during 13–21 days of pregnancy showed significant loss of pyramidal cells in offspring's hippocampus (Bas et al. 2013). Pregnant animals exposed to 900 MHz radiation 1 h at a time, three times per day for the period of 21 days showed perivascular edema, chondriosomes in neuron and neuroglia (Gao et al. 2013).

Changes in the cytoarchitecture of cerebral cortex

Many studies have reported RMF- and EMF-induced histological changes in the cerebral cortex of animals. Significant neuronal damage in cerebral cortex was found following 2-h GSM 900 MHz exposure (Salford et al. 2003). Animals which were exposed to 900 MHz EMR for 1 to 2 weeks have shown dark neurons in the cortex. Adult male Wistar rats that received 900, 1800, and 2450 MHz microwaves about 1 h/day for the period of 2 months had shown marked degeneration such as contracted cytoplasm and pyknotic nuclei in the frontal cortex neurons (Eser et al. 2013). Rats exposed to 900 MHz radio waves by hand phone for 15 days have also shown neurodegeneration in cerebral cortex (Saikhedkar et al. 2014). A recent report demonstrates that, in neuroinflammatory conditions, acute exposure to GSM-1800 MHz can significantly affect microglia and neuronal activity in the rat primary auditory cortex (Occelli et al. 2018).

Changes in the cytoarchitecture of cerebellum

Like other regions of the brain, cerebellum is also vulnerable to RMF exposure. Prenatal (0.25 and 11.25 days of gestation till term) exposure to 10 GHz radiation for 15 days in mice showed reduction in Purkinje cell number. (Sharma et al. 2017). Radiation of 900 MHz for 28 days has also resulted in a decrease in Purkinje cell number in female rat cerebellum (Sonmez et al. 2010). Even, 900 MHz EMF for 15 days caused significant Purkinje cell loss. But no significant difference was seen in the number of granular cells (Altun et al. 2017). Rats exposed to cell phone radiation for 30 min (2 h and 8 h) showed reduction in internal granular cell population and external granular cell layer thickness (Bolbanabad et al. 2014). Adolescent and young rats from postnatal days 21 to 46 that received 900 MHz RF-EMR for 1 h/day for 25 days showed fewer Purkinje cells, altered cerebellar morphology (Aslan et al. 2017). Degenerative changes in Purkinje cells of cerebellum have also been noticed in rats exposed to 1800 MHz mobile phone radiation for 3 months (Hussein et al. 2016). However, mice exposed to 900 MHz RF-EMR for 30 days did not show any histopathological changes in the brain (Khalil et al. 2012).

Odaci et al. (2016) exposed pregnant rats from 13 to 21 days of gestation to 900 MHz EMF for 1 h/day. These rats had shown pyknotic neurons and reduction in total number of Purkinje cells in the offsprings (Odaci et al. 2016). In one of the earlier studies, pregnant Swiss albino mice were subjected to GSM radiation at 890–915 MHz. These mice had also shown significant decrease in Purkinje cell number whereas an increased number of granule cells was observed (Ragbetli et al. 2010). In one of the studies, rats from 16 to 21 days of gestation and their young ones were subjected to 100 MHz radiation at 46 mW/cm for 97 days. In another study, pregnant rats were irradiated with 2450 MHz continuous microwave at 10 mW/cm^2 21 h/day from 17 to 21 days of gestation. In yet another study, 6-day-old rat pups were exposed to 2450 MHz radiation at 10 mW/cm^2 for 5 days. In both these studies, there was decrease in the number of Purkinje cells in fetal or early post-natal life irradiated animals. Post-natal irradiated animals showed less number of Purkinje cells; however, it was reversible after the recovery period of 40 days (Albert et al. 1981).

Changes in the cytoarchitecture of amygdala

Studies on changes occurring in the amygdaloid nucleus due to exposure to RF-EMR are scanty. According to a report by Narayanan et al. (2014), on rats, 900 MHz RF-EMR exposure for the period of 4 weeks had resulted in oxidative stress in rat brain. But the magnitude of this varied from one region to the other. Additionally, according to a very recent report, RF-EMR exposure (900 MHz) for 28 days had resulted in apoptosis in the amygdala. It had also changed dendritic arborization pattern in basolateral part of amygdala (Narayanan et al. 2018).

Impact of RF-EMR effects on glial cells

It is now well known that not only neurons but glial cells too help in information processing with regards to animal behavior (Laming et al. 2000; Laming 1989). Hence, poor performance of rats related to behavioral parameters could also be due to the damage to glial cells caused by RF-EMR. This damage, in turn, could alter the neuronal activity in various regions of the brain. Acute exposure to GSM 900 MHz radiation for 15 min and the glial reaction was evaluated at 2, 3, 6, and 10 days after exposure. GFAP showed a remarkable increase in frontal cortex, caudate nucleus, cerebellum, and putamen (Brillaud et al. 2007). Chronic exposure to GSM 900 MHz microwaves with SAR of 1.5 W/kg for 45 min/day for 5 days/week for 24 weeks and 15 min/day at a SAR of 6 W/kg. Results showed chronic exposure to GSM at 6 W/kg increased GFAP-stained areas and astroglia activation in the brain. (Ammari et al. 2008a, b). However, one recent report has shown that long-term exposure of murine brains to 900 MHz RF-EMR at 4 W/kg, 5 days a week for 104 weeks does not produce any astrogliosis (Court-Kowalski et al. 2015).

Modulatory role of RF-EMR on various neurotransmitter levels in the brain

RF-EMR exposure can potentially alter the neurotransmitter levels in various brain regions. It is well understood that no brain region works in isolation. Similarly, it is well known that behavioral functions are controlled by the interplay of various brain regions and many neurotransmitters. Therefore, the modulatory effect RF-EMR on various neurotransmitter levels (in various brain regions) is a serious concern. According to many studies, there exists a clear relationship between exposure to RF-EMR and amino acid neurotransmitters imbalance in various parts of the brain of young and adult rats (Noor et al. 2011) and in humans too (Ferreri et al. 2006). A study on fetal rats also indicates that chronic short-term exposure to cell phones can result in marked increase of norepinephrine and dopamine. Moreover, both neurotransmitters were reduced in group that was subjected to radiation for a longer period (Jing et al. 2012). Furthermore, disturbances in the hypothalamic (Radwan et al. 2007), thalamic, and striatal (Ahmed et al. 2007) neurotransmitters after long- and short-term exposure to RF-EMR have been documented earlier. Additionally, it was also found that the RF-EMR can induce changes in the cortical excitability which eventually can lead to changes in cortical amino acid neurotransmitters (Khadrawy et al. 2009). Probably, this might be another reason for behavioral changes found with RF-EMR-exposed rats.

Possible underlying mechanism for structural changes in the brain after RF-EMR exposure

As discussed earlier, the structural changes in various brain regions could be one of the main reasons for the behavioral alterations. However, the mechanisms that attribute to altered structures should be considered. It could be the direct effect of radiation on various brain structures or and aftereffect of stress induced by the radiation. A number of mechanisms have been proposed to explain the harmful effects of cell phone RF-EMR on the brain. The effects of RF-EMR on body systems could be thermal effect, non-thermal effect, or cumulative effect. Thermal effect is due to the heating up of the living tissue by rotations of polar molecules induced by the electromagnetic field. Thermal effect is mainly on the superficial structures of the head. Whether it will cause a change in brain function is a subject of debate as calculation of maximum temperature increase on the surface of the head after exposing to mobile phone radiation is found to be only 0.1 °C (Tahvanainen 2007). A biological effect due to this rise in temperature is a subject to debate. Specific effects (non-thermal effects) of RF-EMR are not very well understood. However, the ensuing mechanisms have been postulated to explain these effects on neurons.

Increased generation of reactive oxygen species (ROS)

Oxygen-free radicals could influence in the mechanisms of the biological effects induced by mobile phone radiation (Narayanan et al. 2014; Phillips and LeDoux 1992; DeIullis et al. 2009; Kesari et al. 2012; Alkis et al. 2019). In one of the earlier studies, 900 MHz radiation had increased the serum SOD activity and decreased the serum nitric oxide (NO) in radiation-exposed animals. No change was found in the levels of NO and MDA and activities of adenosine deaminase, xanthine oxidase, catalase, myeloperoxidase, glutathione peroxidase in the serum and brains of either group (Irmak et al. 2002). In a study on guinea pigs, 890- to 915-MHz radiation for 30 days had increased the MDA levels. But the glutathione levels and CAT enzyme activity were decreased. Vitamins A, E, and D(3) levels did not change in the brain tissues of RF-EMR-exposed group. Furthermore, increased levels of vitamins A, E, and D(3) levels, MDA, and CAT enzyme activity had increased. Blood GSH level had decreased in RF-EMR-exposed group (Meral et al. 2007).

Neurons are largely dependent on oxidative phosphorylation for energy, and this makes them vulnerable for oxidative stress compared to other cells. The metabolic activity of the brain is very high and the demand for oxygen is also high. Approximately 2% of the oxygen gets converted to hydrogen peroxide and superoxide anion radicals ($O^{2\cdot-}$) (de Moura et al. 2010). During RF-EMR exposure, oxidant-antioxidant imbalances in the brain lead to oxidative stress. As a chain reaction, it would have induced structural and later behavioral alterations in rats. Oxidative stress-inducing effect of RF-EMR is a concern due to the following reasons.

a. Interference with the learning and memory processes (Alzoubi et al. 2013).
b. Acceleration in various neurodegenerative diseases (Fridovich 1999).
c. Leading to anxiety-like behaviors (Hovatta et al. 2005).
d. Impairment and oxidization of sugars, proteins, lipids, DNA, consequently leading to malfunction of these molecules within the cells causing their death in various organs (Mohsenzadegan and Mirshafiey 2012).
e. A possible tumor promoter behavior (Kamendulis et al. 1999; Aravalli et al. 2013).

Activation of apoptotic pathway

Apart from other reasons for cell death in various parts of the brain after the RF-EMR exposure, programmed cell death could be another reason for the same. It has been shown that short-term exposure to radio-frequency emissions (GSM 1900 MHz, for 2 h) have up-regulated the elements belonging to apoptotic pathways in neurons. The neurons were more sensitive to this effect than the glial cells (Zhao et al. 2007). In one of the studies, cultures of rat neurons were exposed to 900 MHz radiation field. They showed apoptosis with apoptosis-inducing factor (Joubert et al. 2008). But in a study by Maskey et al. (2010a) apoptosis was seen in CA1 and CA3 regions of hippocampus and dentate gyrus of mice. Their study involved several groups with several exposures, which resulted in complete pyramidal neurons in CA1 region of hippocampus in 1 month of exposure group. The authors also suggest that this might affect the cell viability in the hippocampus. Ertilav et al. (2018) have reported that RF-EMR exposure (900 and 1800 MHz) induced increases in transient receptor potential vanilloid 1 (TRPV1) channel currents, intracellular free calcium influx (Ca^{2+}), reactive oxygen species (ROS) production, mitochondrial membrane depolarization (JC-1), apoptosis, and caspase 3 and 9 activities in the hippocampus and dorsal root ganglion of rats. Kesari et al. (2010) have investigated the effect of exposure to 2.45 GHz frequency. In their study, 35-day exposure affected the DNA of rat brain cells. Researchers also reported RF-EMR effects in human cells (Aitken et al. 2005; Tice et al. 2002) and its possible role in programmed cell death (apoptosis). The probable mechanism has been outlined and it shows that the signal transduction processes induce apoptosis in response to DNA damage due to deep penetration of radiation in the brain (Fig. 1). These

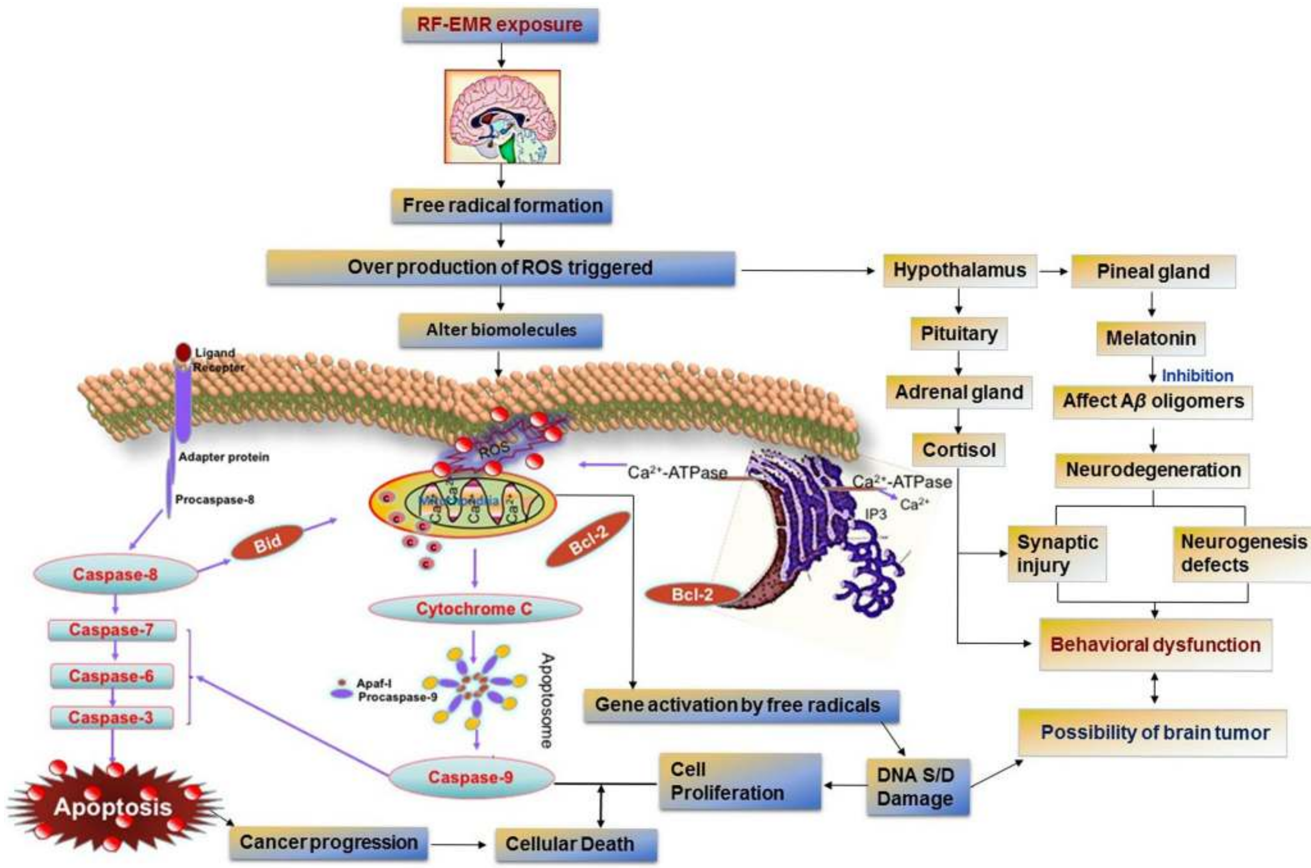

Fig. 1 Possible pathways leading to behavioral dysfunction and other biological effects in the brain following RF-EMR exposure

are mainly attributed to increased ROS generation following RF-EMR exposure.

Effects on DNA

Evidences suggest that RF-EMR and continuous waves are capable of inducing single-strand DNA breaks (Lai and Singh 1995). A recent study has demonstrated that short-term exposure (15 and 30 min) to 900 MHz RF-EMR from a mobile phone had resulted in remarkable surge in DNA fragmentation in the hair root cells of human situated near the ear, where the phone was placed while making a call (Cam and Seyhan 2012). Another recent report on Japanese Quails demonstrated that exposure to GSM 890–915 MHz RF-EMR markedly changed the number of differentiated somites. In embryos exposed to radiation during intermittent 38 h, there was increase in the number of differentiated somites, while in embryos exposed to radiation during intermittent 158 h, this number had decreased. The exposure for a shorter duration had resulted in a remarkable decrease in the DNA strand breaks in cells of 38-h embryos. But the exposure for higher duration had resulted in an increase in the damage of DNA when compared to the control (Tsybulin et al. 2013).

Effect on calcium influx/efflux across the membrane

One of the important signaling substances in the cell is calcium and an imbalance in its homeostasis in the cell can alter many functions of the cell. Previous experiments have demonstrated that amplitude-modulated RF electromagnetic fields and low-frequency electric and magnetic fields can influence transport of calcium ions over the cell membrane (Baureus et al. 2003). It was clear that the number of opened calcium channel had increased with the presence of magnetic fields. However, the applied magnetic fields were unable to affect the current of single calcium channel. The increased number of opened calcium channel might be the reason for increased intracellular calcium concentration under RF-EMR exposure (Yu-Hong et al. 2007). Additionally, report indicates that intracellular calcium oscillations can be influenced by extremely low frequency (ELF) magnetic fields which lead to series of cellular responses (Zhao et al. 2008).

The entry of calcium into hippocampal neurons (especially in CA3 neurons) leads to devastating results in CA3 neurons as they are selectively vulnerable to increased intracellular calcium ion concentrations (Sloviter 1989). Increased intracellular calcium disassembles cytoskeletal proteins, especially microtubules (Shankaranarayana Rao et al. 2001). In addition to this, increased intracellular calcium causes the dendritic cytoskeleton to depolymerize or undergo proteolysis (Black et al. 1984). In addition, it is proven that changes in intracellular calcium levels can trigger unusual synaptic action or cause neuronal apoptosis. This in turn can exert an influence on learning and memory in the hippocampus (Maskey et al. 2010b). Hippocampal CA3 region of mice exposed chronically to RF-EMR (CDMA 835 MHz, electric field strength 59.56 V/m, power density 2.5 W, and SAR 1.6 W/kg) showed weak calbindin D28-k immunoreactivity (calcium binding protein responsible for maintaining and controlling calcium homeostasis) in the cells of stratum pyramidale and stratum radiatum. Calbindin D28-k immunoreactive neurons displayed morphological changes with loss of dendritic arborization. Decrease of pyramidal cells and loss of D28-k immunoreactivity of mossy fibers were also reported in RF-EMR-exposed group (Maskey et al. 2010b). A probable mechanism for atrophy of hippocampal CA3 neurons and associated behavioral changes could be due to RF-EMR-induced impaired calcium homeostasis in CA3 neurons.

A probable combined effect

Though we narrow down to biochemical imbalance in various brain regions to simplify explanation for structural and behavioral changes, the possibility of combined effects cannot be excluded (Fig. 1). It is also possible that the various behavioral effects the researchers have reported following RF-EMR exposure in animals might be due to combined effects of all that could be happening in various brain regions such as

1. Increase in ROS and thereby cell membrane damage/integrity.
2. ROS-induced DNA strand break and thereby apoptosis.
3. Imbalance in calcium homeostasis in neurons led to dendritic remodeling/cell death.
4. Increase in ROS-induced inflammation followed by cell death (necrosis).
5. Altered glial cell physiology.
6. Neurotransmitter level imbalance in different brain regions.

Chronic RF-EMR exposure may firstly produce the free radicals in the brain and later they are converted to ROS, which may include oxygen ions, inorganic and organic peroxides. Elevated levels of ROS are capable of attacking various biomolecules in the cell. This raised ROS triggered calcium release may activate the genetic factors and may lead to DNA damage. Perhaps, this is mainly through p53 gene and caspase-3 activations. Any alteration in gene and enzyme levels, particularly activation of caspase-3 (Liu et al. 2012), may cause apoptosis of neurons (neurodegeneration) which would lead to several altered behavioral manifestations. This neuronal degeneration is a fundamental feature in certain diseases like Parkinson's and Alzheimer's diseases. Reactive oxygen species generated due to exposure to RF-EMR may also react with intracellular DNA and lipoprotein, which may lead to altered cellular function and genotoxic effects (Shahin et al. 2013).

Microwave exposure (2.45-GHz pulsed MW), 3 h/day up to 30-day induced elevated ROS, may also trigger cognitive dysfunctions by altering the functioning of hypothalamic-pituitary-adrenal (HPA) axis (Li et al. 2008). It may also alter the normal melatonin secretion. In normal concentrations, melatonin scavenges ROS and inhibits the Aβ oligomer-induced toxicity in neurons. Alteration in this would lead to accumulation of Aβ oligomers which would further lead to synaptic injury, cell death, and behavioral dysfunction (Fig. 1). In fact, this seems to be one of the major causes for the disease progression in patients with Alzheimer's disease (AD).

RF-EMR can alter the intracellular signaling pathways like changes in calcium and ionic distribution and also ion permeability at the cellular level (Hossmann and Herman 2003; Adey 1981). It is proposed that RF-EMR exposures alter the calcium channels and receptors on the cell membrane, which play an important role in signaling pathways, which in turn may affect the response of mitochondrial calcium reaction (Walleczek 1992) (Fig. 1).

Fragopoulou et al. (2012) have reported that, RF-EMR exposure triggered the synthesis of 143 proteins, like glial fibrillary acidic protein heat shock protein etc. These change are attributed to the over production of ROS following RF-EMR exposure. It may modify the neuronal proteins and structural components in the brain and participate in various disorders of nervous system, that lead to neuro-inflammation and cognitive impairments. Sharma et al. (2014) have also reported that exposures to RF-EMR (10 GHz microwaves, power density 0.25 mW/cm^2, SAR 0.179 W/kg for 2 h/day for 30 days) may reduce the protein levels in the brain. Interestingly, a very recent report demonstrates that GSM irradiation alters amyloid precursor protein (APP) metabolism along with changes in monomeric α-syn accumulation, multimerization, oxidative stress, and cell death in cultured SH-SY5Y cells. The authors have concluded that, GSM radiation seems to contribute to the Alzheimer's and Parkinson's disease pathogenic mechanisms (Stefi et al. 2019). It is apparent from the above discussions that, RF-EMR exposure does increases the formation of ROS and this may alter the cellular functions eventually leading to numerous biological effects (Fig. 1).

Conclusions and scope for future research

Mobile phone safety recommendations depend mainly on 'sinusoidal wave' emitted from the cell phone when it is idle. At idle mode, the RF-EMR exposure is negligible, hence, it might not be that detrimental at this level. However, chronic exposure to the 'carrier signal' emitted when phone is in 'ON' mode (when the phone is ringing/call receiving mode) would be responsible for biological effects. Exposure to RF-EMR induces an imbalance in the oxidant/antioxidant defense system in the brain indicating that the internal environment of each brain cell was getting disturbed by the insult from RF-EMR. This therefore does not favor the nerve cells to function appropriately. Whenever the threshold is reached, the cell either stops functioning, functions abnormally, or dies. We call it structural change or morphological change. Most of the time, what happens at the cellular level is indicated at the behavioral level. It is highly difficult to join up biochemical change, morphological change, and then behavior. An imbalance in the biochemical homeostasis would itself alter the behavior which might not be structurally represented and vice versa. This is due to the mechanisms, which prevent or resist the insult from external stressors. Currently, we are not sure about this fact as there are no solid evidences which pin point or demonstrate this innate preventive/restrain mechanisms present in neurons under RF-EMR exposure. Further study in this regard will reveal much clearer picture of body's (especially brain) innate mechanisms which would withstand the potential threat caused by RF-EMR.

It is evident from earlier discussions that a possible behavioral effect does exist following RF-EMR exposure in rodents. However, caution should be taken while extrapolating these findings into humans. It is worth noting that an adult uses mobile phone approximately 4 to 5 h per day and this may be even more in teenagers. However, reports that analyze the behavioral, psychological, and health variables following RF-EMR exposure in sensitive population like young adults are scanty. Furthermore, it would be interesting to study the effect of RF-EMR exposure in early developmental stage and see what the effects of such exposures are on the critical and sensitive periods of development using animal models. Although the current review focused principally on RF-EMR-induced effects on cognition, anxiety, and locomotion, RF-EMR have been attributed to induce other behavioral effects in rodents as well as in humans. After witnessing the uncontrollable growth of this technology, everyone believes that it is high time to evaluate the health risks of continuous and chronic RF-EMR exposure effects on humans and for which further studies are warranted.

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Abbreviations *RF-EMR*, Radiofrequency electromagnetic radiation; *IARC*, International Agency for Research on Cancer; *WHO*, World Health Organization; *SAR*, Specific absorption rate; *MHz*, Megahertz; *GSM*, Global System for Mobile communication; *BBB*, Blood-brain barrier; *MWM*, Morris water maze; *Aβ*, Amyloid beta; *EPM*, Elevated plus maze; *OFT*, Open field test; *Asp*, Spartic acid; *EMR*, Electromagnetic radiation; *CA1*, Cornu Ammonis 1; *CA2*, Cornu Ammonis 2; *CA3*, Cornu Ammonis 3; *GHz*, Gigahertz; *GFAP*, Glial fibrillary acidic protein; *GSH*, Glutathione; *MDA*, Malondialdehyde; *PD*, Parkinson's disease; *AD*, Alzheimer's disease; *RFR*, Radiofrequency radiation; *EMF*, Electromagnetic fields; *EMR*, Electromagnetic radiation; *GFAP*, Glial fibrillary acidic protein; *2G*, Second generation; *RMF*, Radiomagnetic field; *RF*, Radio frequency; *SOD*, Superoxide dismutase; *NO*, Nitric oxide; *MDA*, Malondialdehyde; *GSH*, Glutathione; *CAT*, Catalase; *AIF*, Apoptosis-inducing factor; *DNA*, Deoxyribonucleic acid; *ROS*, Reactive oxygen species; *ELF*, Extremely low frequency; *CDMA*, Code Division Multiple Access; *HPA axis*, Hypothalamic-pituitary-adrenal axis; *TRPV1*, Transient receptor potential vanilloid 1 channel; *DECT*, Digital Enhanced Cordless Telecommunications; *APP*, Amyloid precursor protein

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