

Review

A review on the consequences of molecular and genomic alterations following exposure to electromagnetic fields: Remodeling of neuronal network and cognitive changes

Shima Abtin^{a,1}, Fatemehsadat Seyedaghamiri^{a,1}, Zahra Aalidaeijavadi^a, Amir Mohammad Farrokhi^a, Fazel Moshrefi^a, Tayebbeh Ziveh^b, Mohammad Ismail Zibaii^c, Hadi Aliakbarian^d, Mostafa Rezaei-Tavirani^e, Abbas Haghparast^{a,f,g,*}

^a Neuroscience Research Center, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

^b Laboratory of Biophysics and Molecular Biology, Departments of Biophysics, Institute of Biochemistry and Biophysics, University of Tehran, Tehran, Iran

^c Laser and Plasma Research Institute, Shahid Beheshti University, Tehran, Iran

^d Faculty of Electrical Engineering, KN Toosi University of Technology, Tehran, Iran

^e Proteomics Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

^f School of Cognitive Sciences, Institute for Research in Fundamental Sciences, Tehran, Iran

^g Department of Basic Sciences, Iranian Academy of Medical Sciences, Tehran, Iran

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ABSTRACT

The use of electromagnetic fields (EMFs) is essential in daily life. Since 1970, concerns have grown about potential health hazards from EMF. Exposure to EMF can stimulate nerves and affect the central nervous system, leading to neurological and cognitive changes. However, current research results are often vague and contradictory. These effects include changes in memory and learning through changes in neuronal plasticity in the hippocampus, synapses and hippocampal neuritis, and changes in metabolism and neurotransmitter levels. Prenatal exposure to EMFs has negative effects on memory and learning, as well as changes in hippocampal neuron density and histomorphology of hippocampus. EMF exposure also affects the structure and function of glial cells, affecting gate dynamics, ion conduction, membrane concentration, and protein expression. EMF exposure affects gene expression and may change epigenetic regulation through effects on DNA methylation, histone modification, and microRNA biogenesis, and potentially leading to biological changes. Therefore, exposure to EMFs possibly leads to changes in cellular and molecular mechanisms in central nervous system and alter cognitive function.

1. Introduction

The growing prevalence of electronic devices and the digitization of human life have sparked worries over human health (Quan et al., 2017). Electromagnetic fields (EMFs) are energy packets without mass that are categorized as ionizing and non-ionizing radiation (Tekieh et al., 2016). Humans are exposed to two categories of EMFs: extremely low-frequency (ELF-EMF) and radiofrequency (RF-EMF) (Xu, 2022; Warille MO et al., 2016; Ahmad et al., 2020; Yorgancilar et al., 2017). EMFs can cause a range of biological consequences such as alteration of cell proliferation (Lee et al., 2010), gene expression (Chen et al., 2012),

and DNA damage (Phillips et al., 2009). The key issue about EMFs is their effects in the biochemical and physical condition in cells and tissues, as well as the heat and resonance produced in the biological setting and the energy which absorbed by living tissues (Kesari et al., 2013). The precise biological mechanisms of EMFs remain incompletely known. EMFs have a major effect on the central nervous system (CNS). Numerous studies have investigated the controversial effects of EMF exposure on various aspects of neuronal patterns changes that lead to alteration of cognitive functions. Cognitive processes including memory and learning in animals and human are dependent on hippocampus neurogenesis, and this process is strongly influenced by environmental

* Corresponding author at: Neuroscience Research Center, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

E-mail addresses: Haghparast@yahoo.com, Haghparast@sbmu.ac.ir (A. Haghparast).

¹ These authors have contributed equally to the present study

stimuli. Studies have shown that EMF is involved in adult hippocampal neurogenesis by maintaining reactive oxygen species (ROS) levels (Zhang et al., 2021). Moreover, several electrophysiological and behavioral studies have shown that exposure to EMF changes memory and learning through changes in neuronal plasticity in the hippocampus (Khajei et al., 2021; Xia et al., 2021). EMF-RF Exposure during the postnatal period affects the structure of synapses and the development of hippocampal neuritis (Kim et al., 2021). EMFs decrease the production of calcium channels, leading to lower calcium levels in hippocampal neurons (Kim et al., 2018; Ahmad et al., 2020; Tekieh et al., 2016). Also, exposure to EMF during the prenatal period has inevitable effects on memory and learning through the negative effect of hippocampal neuron density and change of hippocampal histomorphology (Azimzadeh and Jelodar, 2020). In addition, EMF exposure changes the metabolism and levels of neurotransmitters, which are key factors in cognitive and emotional processes (Hu et al., 2021). Also, there are various controversies among researchers on determining the effect of EMF and its amount on apoptotic pathways and the effects of these settings on improving or weakening cognitive functions (Barati et al., 2021). Electromagnetic radiation (EMR) is interestingly able to change the structure and function of glial cells by changing the proliferation, differentiation and cell cycle distribution of the glioma cell line (Sul et al., 2006). Ion channels in the CNS are one of the main targets that are affected by EMR at different levels, including gate dynamics, ion conduction, membrane concentration, and protein expression. It has been proven that EMF causes changes in the functional levels of voltage-gated calcium channels by changing calcium homeostasis (Bertagna et al., 2021). EMF exposure has complex effects on the structure and permeability of the blood-brain barrier (BBB). There is evidence that exposure to EMF in non-thermal surfaces causes disruption in the BBB. Continued research is needed to gain an understanding of the exact biophysical mechanisms of EMF effects on the BBB and how to reduce the resulting damage (Nittby et al., 2008). Also, EMF changes the number and structure of dendritic spines (Kim et al., 2021). Furthermore, exposure to EMF changes the expression of genes related to cellular processes, including signaling and cellular metabolism. Considering that gene expression is an efficient way for cells to adapt to the changes applied by the external environment, maybe the body tries to adapt to the effects of EMF by changing the expression of genes (Zhao et al., 2007). ELF-EMF probably has the potential to change epigenetic regulation through the effect on DNA methylation levels, histone modification and microRNA biogenesis, these epigenetic changes may lead to changes in biological processes (Wydorski et al., 2024). This review focused in investigating the possible role of EMFs exposure on molecular, genetic and behavioral alteration (Fig. 1).

2. An overview at the effects of energy emitted by the electromagnetic sources on the body

Increasing use of electronic devices, the emergence of new communication systems, and people's addiction to mobile phones have raised significant concerns about human health (Quan et al., 2017; Chen and Liu, 2018; Yan et al., 2019). The steady movement of electric charge around any object creates a magnetic field around that object (Lyon, 2002). The interaction of these magnetic and electric fields perpendicular to each other generates an EMF, which is measured in units of magnetic flux density (Tesla). The electric field is received by the body (physical or biological) and is transferred across the body's surface as an electric current. However, the magnetic components are capable of penetrating tissues. EMFs exert various biological effects depending on their intensity and duration of exposure, such as cellular proliferation, gene expression, epigenetic changes, genotoxic and carcinogenic effects, and therapeutic effects on the body. Therefore, research in these fields is insert fundamental due to their widespread and rapid environmental effects and their ability to penetrate living tissues. Based on wavelength and frequency of EMFs, they are classified into ionizing and non-ionizing

radiation. EMFs refers to non-ionizing radiation (HM, 2020). Humans are daily exposed to two types of EMF: ELF-EMF, 0–300 Hz, which includes power lines and wireless phones, and RF-EMF, 3 kHz–300 GHz, such as tablets, mobile phones, and Wi-Fi (Warille MO et al., 2016; Xu, 2022). Another type of EMF is electromagnetic pulses, which, depending on the pulse duration and frequency, have various effects, including heating and electric shock (Jiang et al., 2013; Ahmad et al., 2020). The new technologies of the fifth generation (5 G) include a frequency of 3.5 GHz to 28 GHz, which is in the RF range (Choi, 2018). Although many biological activities in the body are controlled by electric currents in the nervous system (Reilly, 1989), the exact biological mechanisms of EMFs are not yet fully understood. Considering the duration of exposure and the frequency of EMFs, the use of these devices can lead to various biological effects in living organisms. Low frequencies tend to amplify the electric potentials in the body, while higher frequencies, which primarily absorb energy at the body's surface, can result in much more serious effects. EMFs can lead to various biological effects, including the generation of ROS and disruption of cellular processes (Nezamtaheri, 2022; Wang and X, 2017), ultimately leading to cell death (Kissling, 2020). Nevertheless, many studies have reported positive effects and therapeutic applications of EMFs in low-frequency and radiofrequency ranges, such as wound healing (Wang et al., 2020; Patruno, 2010), and improvements in mental and neurological disorders (Saliev et al., 2014). The most significant impact of these fields is on the CNS, with a reduction in calcium channel expression and consequently reduced calcium levels in hippocampal neurons (Tekieh et al., 2016; Ahmad et al., 2020; Kim et al., 2018). In the modern age, the biosphere and all humans are immersed in magnetic fields (Markov, 2015). Therefore, the most critical question regarding EMFs is the identification of the biochemical and physical status of cells and tissues, as well as the investigation of the heat and resonance created in the biological environment (Markov, 2015). The biological effects of EMFs are measured based on the Specific Absorption Rate (SAR). SAR measures the amount of energy absorbed by biological tissues and is expressed in watts per kilogram (W/kg) (Kesari et al., 2013). In the United States, the permissible SAR level for the frequency range of 100 kHz to 6 GHz is on average 0.08 W/kg over the entire body and 1.6 W/kg in 1 g of body tissue (daUUA, 2021). This limit is significantly lower for children. While the International Agency for Research on Cancer declared RF-EMF as a serious carcinogenic risk in 2011 (van Deventer EvR and Saunders, 2011), cognitive effects (Ishihara T et al., 2020), behavioral and neurological disorders contributing to increased disease prevalence take precedence (Ahsan et al., 2022).

3. Modification of adult neurogenesis is involved in the remodeling of neuronal network following EMF exposure

The new neuron production is a phenomenon that occurs in the hippocampus of adult rodents as well as in the brains of several species of mammals is directly related to neural plasticity. There is also strong evidence that neurogenesis occurs in the adult human hippocampus of human. In addition some factors disrupt this process in humans. However, how the neurogenesis process is carried out and the factors affecting neurogenesis in humans remain unclear. Currently, there are many questions and challenges related to this prominent field (Moreno-Jiménez et al., 2021).

EMF with different radiation patterns and frequencies have contradictory effects on the process of neurogenesis and subsequently on neural plasticity and cognitive functions (Gao et al., 2021; Chang et al., 2021; Qin et al., 2022; Singh et al., 2023). However, animal experiments in recent years have shown that low-frequency EMFs, mainly improve neurogenesis and cognitive processes (Gao et al., 2021; Chang et al., 2021; Leone et al., 2014; Sakhaie et al., 2017).

An experimental study on the adult mice model of hippocampal Injury showed that an extremely low frequency (LF- EMF) stimulates new neuron production in the dentate gyrus, and improves cognitive

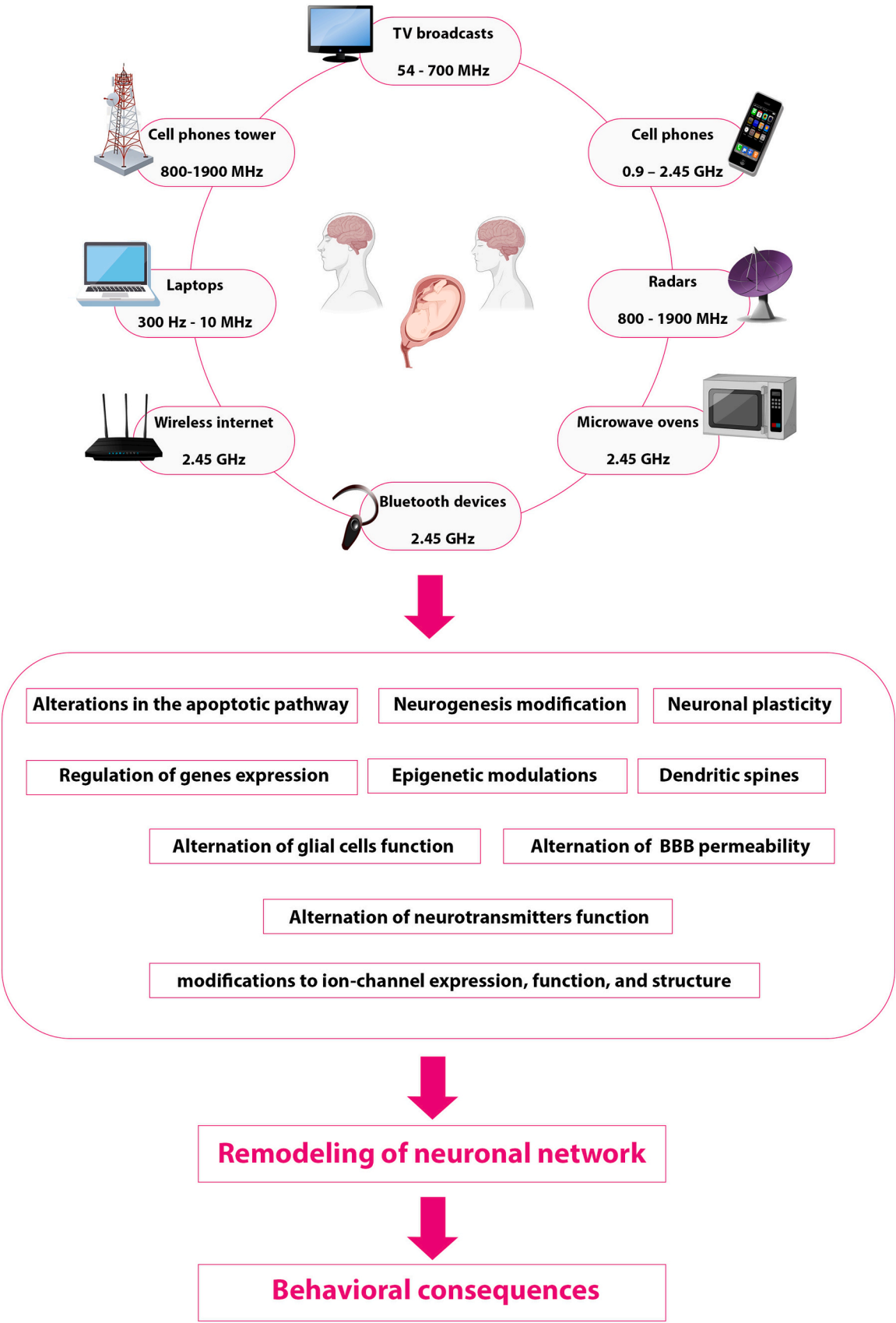


Fig. 1. Molecular and genomic alterations related to remodeling of neuronal network and cognitive changes following exposure to Electromagnetic field.

functions in these animals (Sakhaie et al., 2017). The results of a recent study have shown that LF- EMF improves neurogenesis in the hippocampus of rats with cerebral ischemia by increasing the expression of key proteins of the Notch signaling pathway including Notch1, Hes1, and Hes5 proteins (Gao et al., 2021). It is also known that the intermittent radiation of low frequency electromagnetic waves (EMW) promotes the neurogenesis of the GABAergic cortical network. Therefore, the use of electromagnetic stimulation by increasing the ratio of GABAergic neurons has a promising therapeutic potential for dementia and Alzheimer's disease (Gramowski-Voss et al., 2015).

The results of a study interestingly showed that electromagnetic stimulation of the hippocampus of aged mice using electro-magnetized gold nanoparticles through the specific activation of histone acetyltransferase Kat2a and histone H3K9 acetylation in adult NSCs, increased the numbers of neural stem cells (NSCs) and neural progenitors in the adult hippocampus, and resulting in the stabilization of memory and improving cognition in aged mice (Chang et al., 2021).

Isolating the neural stem cells of newborn mice exposed to a LF-EMF, prenatally showed that exposure to this field during prenatal time causes epigenetic modulation in favor of increased expression of pro-neuronal genes, including the pro-proliferative gene hairy enhancer of split 1, neuronal determination genes NeuroD1 and Neurogenin1. Also, increases the acetylation of HTR and binds the transcription factor phosphorylated (cAMP) response element binding protein (CREB) on the regulatory sequence of these genes. It was also found that epigenetic changes dependent on LF- EMFs are prevented by nifedipine, a Cav1 channel blocker. Nifedipine exerts its effect by increasing the occupancy of CREB binding protein (CBP) to the same sites in the promoters (Leone et al., 2014); Fig. 2.

4. Alterations in the apoptotic pathway following exposure to EMF

Neuronal apoptosis is directly related to cognitive impairments and anti-apoptotic agents can improve cognitive decline (Zhang et al., 2023; Mei et al., 2023).

In the last decades, experimental studies have been carried out to investigate the effects of radiofrequency EMF exposure on the apoptotic process. The effects of EMF on the molecular mechanisms of apoptosis,

depending on the amount and pattern of radiation, are very different (Zuo et al., 2020; Gupta et al., 2018; Zielinski et al., 2020).

Has been found pulsed EMF can decrease neuronal cell death induced by hypoxia through modulating p38, heat shock protein 70 (HSP70), CREB, brain-derived neurotrophic factor (BDNF), and B-cell CLL/lymphoma 2 (Bcl-2) family proteins. Rapid activation (30 min) of the p38 kinase cascade, and HSP70 survival chaperone molecule, causes an increase of CREB phosphorylation (24 hr). In this cascade, BDNF and the antiapoptotic pathway modulated (48 hr) via the Bcl-2 family of proteins are used to promote neuronal survival (Gessi et al., 2019). A recent study has shown that exposure to power-frequency EMF might have potential therapeutic value for Alzheimer's disease by mitochondria/caspase-dependent apoptotic pathway (Zuo et al., 2020).

However, a study in recent years has shown the destructive effects of EMR 2450 MHz on cognitive processes through related pathophysiological changes in mitochondrial and cholinergic function and also, activation of apoptosis intrinsic pathway in rat. Exposure of animals to these radiations increased the release of cytochrome c, the expression of caspase 3 and 9 and the Bcl-2/Bax ratio in the hippocampus (Gupta et al., 2018). Long-term exposure to 2450 MHz EMW disrupts the integrity of mitochondria, changes the ratio of Bax to Bcl-2, changes the apoptosis process in mitochondria and cytoplasm, and causes anxiety-like behaviors in rat (Gupta et al., 2019). Has been shown, acute exposure to 3500 MHz (5 G) Radiofrequency EMR causes ultrastructural changes such as swollen mitochondria and layered myelin sheaths, cytochrome-c delocalization, caspase-9, and cleaved caspase-3 activation in Guinea Pigs (Yang et al., 2022). Furthermore, demonstrated that 1800 MHz EMR for 48 h may cause apoptosis in NIH/3T3 cells and this apoptosis probably is related to mitochondrial injury and the increasing of p53 expression, a key molecule in apoptosis (Li et al., 2020). An another study has shown, that EMW exposure in zebrafish embryos increases p53 expression which is responsible for the execution phase of apoptosis (Sabri í-zen et al., 2020).

Anyway, a study on human neuroblastoma and murine microglial cells showed that pulse-modulated radiofrequency magnetic field exposure does not alter apoptosis, the number of living cells, and the apoptosis-inducing factor (Zielinski et al., 2020). In addition, the results of a recent study indicated EMW emitted by mobile phones with a frequency of 900–1800 MHz showed no significant change in the transcript

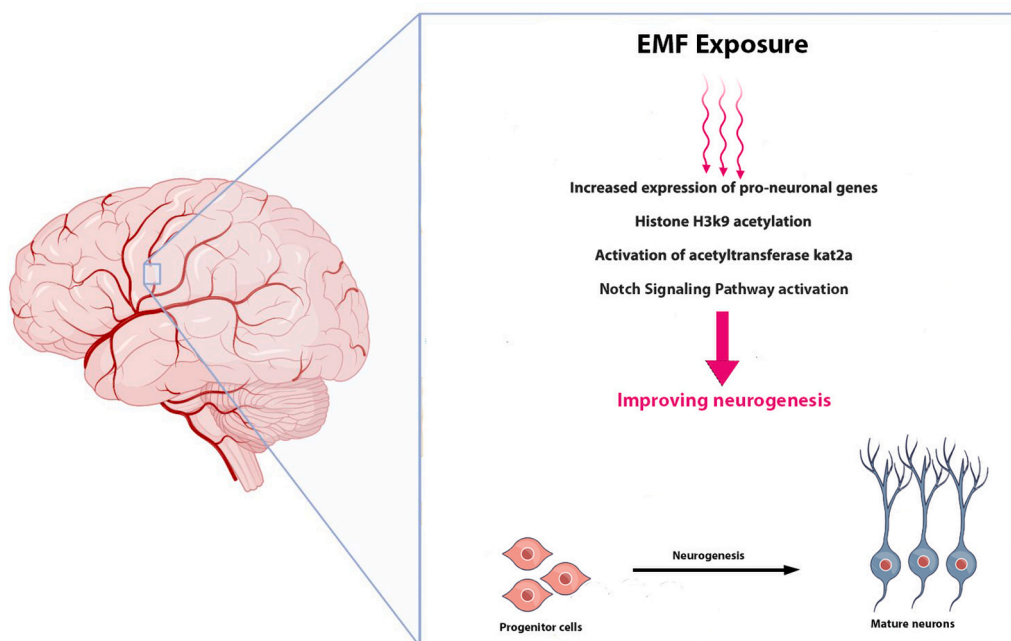


Fig. 2. Effect of EMF exposure on neurogenesis, EMF, Electromagnetic field.

level of proapoptotic and antiapoptotic genes in embryos of mice (Koohestanidehaghi et al., 2023); Fig. 3.

5. The regulation of gene expression related to cognitive processes by EMF exposure

It has been found that exposure to EMF causes genetic effects and chromatin structure changes in living organisms. The expression of various genes, including genes involved in cell cycle arrest, apoptosis and stress responses, heat shock proteins (HSP) are changed under the influence of exposure to EMR (Lai, 2021). Based on our findings, several numbers of studies have been done on the effects of EMFs on the expression of genes related to cognitive and memory processes (Win-Shwe et al., 2013; Obajuluwa et al., 2017; Kazemi et al., 2022). The first in vivo study that investigated the effect of EMR on the expression of genes related to the memory process, has shown that exposure to EMR emitted from a cooking appliance has no effect on the expression of genes and signaling molecules related to memory, including NMDA subunits NR1, NR2A, and NR2B, CaMK-IV, CREB -1, Nerve growth factor (NGF) and BDNF in the hippocampus of mice (Win-Shwe et al., 2013).

Recently, has been found that ELF-EMF waves (12 Hz) increase the expression of the N-methyl-D-aspartate (NMDA) receptors gene and improve cognitive functions, including visual learning, visual memory, and visual working memory in rhesus monkeys. There is greatest density of the NMDA receptors gene is in the hippocampus, prefrontal cortex, and amygdala. The gene expression of NMDA receptors plays a key role in learning and memory processing (Kazemi et al., 2022). A study on a cell model of Alzheimer's disease showed that ELF-EMF, through modulation of microRNAs regulating such as Beta-Secretase 1 (BACE1) gene, can modulate the neurophysiological activity of pathological circuits and produce clinical benefits in patients with Alzheimer's disease (Capelli et al., 2017). BACE1 plays an important role in the abnormal production of Amyloid beta plaques, which characterizes the pathophysiology of Alzheimer's disease (Sathya et al., 2012).

In addition, it has been found that 2.45 GHz EMFs cause different expressions of two HSP genes, (HSP27 and HSP70), in the hippocampus, especially in the pyramidal neurons of the cornu-ammonis 3 (CA3) and

granule cells of the dentate gyrus and leads an HSP-related stress response in rat hippocampus (Yang et al., 2012). Another study has shown that EMW with Wi-Fi sources, through altering the expression of the acetylcholinesterase (AChE) gene, result in reducing the activity of this enzyme, which subsequently causes inducing anxiety-like behaviors and motor incoordination related to this behavior in rat (Obajuluwa et al., 2017). Genetic studies have shown that the AChE protein controls the termination of stress-enhanced acetylcholine signaling. The activity of the AChE enzyme showed an inverse relationship with anxiety measures (Sklan et al., 2004); Fig. 4.

6. The consequences of EMF exposure from an epigenetic perspective

Epigenetic modulations play a key regulatory role in many cellular processes as well as pathological conditions (Kumar et al., 2021). EMFs may be associated with changes in epigenetic mechanisms, such as DNA methylation, histone modifications, and expression of micro RNAs (Giorgi and Del Re, 2021). Epigenetic studies have shown that EMW emitted from mobile phones and wireless devices can cause changes in neurodevelopment through changes in DNA structure, probably affecting childhood development and resulting in changes in neural behaviors and symptoms such as retardation of memory, learning, cognition, causing attention and behavioral impairments. Hyperactivity disorder is caused by attention deficit, as a result of epigenetic changes caused by exposure to EMR (Sage and Burgio, 2018). Also, one of the epigenetic side effects of excessive exposure to EMFs is an increase in the change of DNA structure in favor of the occurrence of autism, which is characterized by incoherence to verbal communication and repetitive movements (Ahuja et al., 2013).

Recently has been found that long-term exposure to radiofrequency EMR 2.45 GHz, reduces global DNA methylation in mice (Spandole-Dinu et al., 2023). In addition, the EMW emitted from mobile phones, with increasing frequency and duration of exposure, can cause significant epigenetic modulations in the rat hippocampus, including a decrease in global DNA methylation and an increase in histone methylation (Kumar et al., 2021). Exposure to pulsed EMFs causes epigenetic modification and leads to a significant decrease in H3

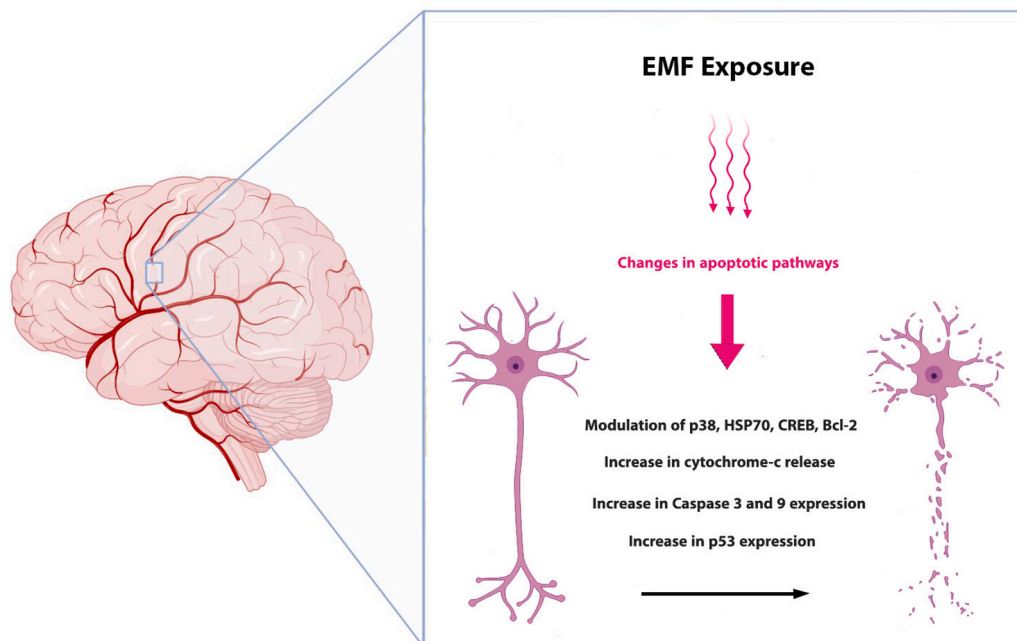


Fig. 3. Effect of Electromagnetic field exposure on apoptotic pathways, EMF, Electromagnetic field; HSP70, Heat shock protein 70; CREB, Cellular transcription factor; Bcl-2, B-cell lymphoma 2.

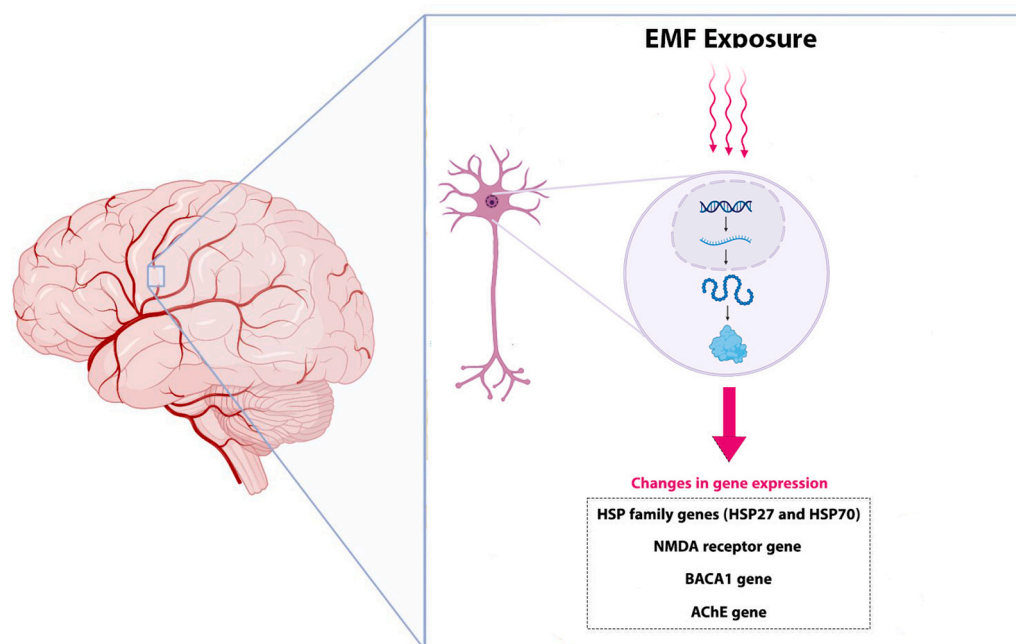


Fig. 4. Effect of Electromagnetic field exposure on gene expression; **EMF**, Electromagnetic field; **HSP**, Heat shock protein, **AChE**, Acetylcholinesterase; **BACA1**, Beta-secretase 1; **NMDA**, N-methyl-D-aspartate.

acetylation and H3 levels dependent on histone deacetylase 2 (HDAC2) acetylation, as well as a decrease in BDNF gene expression in the hippocampus. These events are associated with reduced neurogenesis, neuronal survival, and spatial memory impairment in rats (Tian et al., 2020).

Indicated that repeated electromagnetic stimulation causes structural changes and protonation in RNA. These changes help the RNA to bind and activate heat shock transcription factor 1 (HSF1). Activated HSF1 binds to DNA-expressing chaperones that regulate autophagy and remove abnormal proteins. This complicated epigenetic effect can help to improve age related diseases including Parkinson's and Alzheimer's

disease (Perez et al., 2022). The results of an experimental study have shown that exposure of mice to extremely ELF-EMF, increases the regulation of epigenetic mechanisms that lead to pro-neural gene expression. Exposure to these waves causes a notable increase in the expression of the pro-proliferative split 1 gene hair enhancer and the neuron determination genes NeuroD1 and Neurogenin1. These processes occur under the influence of increased acetylation of H3K9 and the binding of the cAMP - CREB on the regulatory sequence of these genes. Therefore, ELF-EMF waves through chromatin remodeling associated with histone acetylation may have the potential to induce epigenetic changes in favor of improving endogenous neurogenesis and

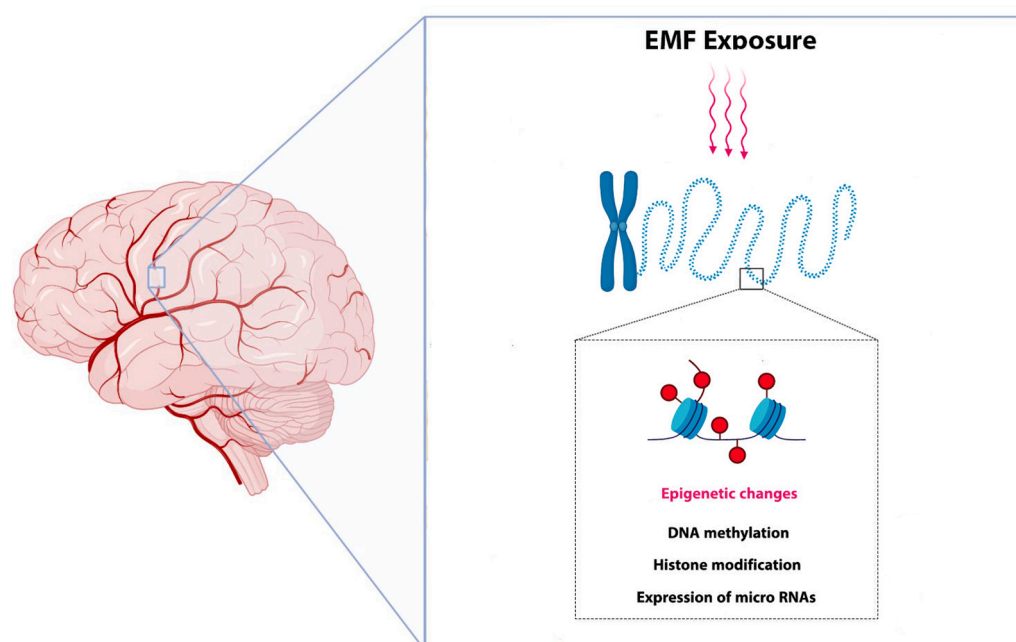


Fig. 5. Effect of Electromagnetic field exposure on epigenetic changes, **EMF**, Electromagnetic field.

promoting memory and learning (Leone et al., 2014); Fig. 5.

7. Relationship between prenatal EMF exposure and cognitive deficits

The prenatal period is known as the most sensitive period of exposure to EMR (Azimzadeh and Jelodar, 2020). EMF exposure in the prenatal period causes the production of free radicals and oxidative stress in the cellular environment, which changes cellular functions and creates changes in the antioxidant defense system. Also, depending on the amount and number of radiation, EMW cause changes in brain function and enzyme and hormonal impairments in the fetus growing in the womb. Additionally, EMFs inhibit the proliferation and differentiation of neural stem cells during the embryonic period and affect CNS development (Kaplan et al., 2016). It is recommended that pregnant women keep mobile devices away from their stomachs so that their fetuses are less affected by mobile radiation. The exposure of pregnant mothers to EMW emitted from mobile phones can cause hyperactivity and inattention problems in their children at the age of five to seven years (Birks, 2018). These concerns are so serious that the World Health Organization has started a project called the Baby Safe Wireless Project, to limit the exposure of pregnant women to EMFs (Gayathri et al., 2020).

Due to the high capacity of the immature rodent brain to differentiate, multiply, and reorganize, it can be considered similar to the developing brain of a human child. Thus, the brains of immature rodents can be used as a useful animal model to study the influences of EMFs on cognitive abilities (Sakhnini et al., 2014). The memory and learning processes of rodents in the perinatal period are disturbed under the influence of exposure to EMW emitted from mobile phones (Gayathri et al., 2020). Furthermore, it has been found that prenatal Wi-Fi radiation can cause negative effects on spatial learning and physical activity in rats (DastAmooz et al., 2018). Discriminated, exposure to EMFs (900-MHz), leads to histopathological changes and reduction of Purkinje neurons in the cerebellum in the first generation of female 32-day-old rat's during fetal life (Odaci et al., 2016). Also, has been found that exposure to EMF waves (900 MHz) during the prenatal and early postnatal periods in the first 45 days after birth causes a change in the histomorphology of the hippocampus, a decrease in pyramidal neurons in this area, and also, short-term and long-term memory impairments in rats. However, these negative side effects caused by EMF exposure in the prenatal period are more severe than in the early postnatal period (Azimzadeh and Jelodar, 2020; İkinci et al., 2013; Deniz and Kaplan, 2022). In addition, EMF exposure in the prenatal period alters the Map Kinase (MAPK) pathway and reduces the p38, and MAPK p-ERK levels in

the rat hippocampus, these changes can be the cause of cognitive deficiencies such as memory and learning decline (Tan et al., 2019). Also, indicated that the pups of pregnant rats exposed to Wi-Fi radiation during pregnancy weigh less than the normal state. Moreover, the messenger RNA expression of NMDA receptors is changed, and the NR2A and NR2B receptors expression is lower in the hippocampus of these pups. Reducing the expression of these receptors probably plays a role in the occurrence of cognitive impairments in these animals (Li et al., 2020). Interestingly, the results obtained from a study showed that male mice exposed to EMFs during fetal life have learning and memory defects, while female mice exposed to the same conditions during the prenatal period, do not show these cognitive impairments. Therefore, there are probably gender differences in the effects of exposure to EMFs during fetal life on cognitive processes (Zhang et al., 2015).

The stress of pregnant mothers can cause physiological changes in their fetuses, and these changes by affecting the stress pathways in the hippocampus can intensify anxiety-like behaviors that extend to adulthood. Has been shown, that maternal stress induced by EMF exposure causes increasing anxiety-like behavior in female rat offspring which probably is related to an increase in the pNMDAr2/NMDAr2 ratio and 24(S)-OHC in the rat hippocampus (Hosseini et al., 2022); Fig. 6.

8. EMF exposure effects on critical neurotransmitters in the cognitive functions

With the advancement of Information Technology (IT) devices becoming more and more portable, the need for wireless connectivity has increased dramatically meaning our surroundings are being filled with EMR, although this type of radiation has proved not to be ionizing, it seems to alter some of our bodily functions, more focused on CNS system (Kim et al., 2019). One of the most researched areas of this phenomenon is the brain's neurotransmitters. Our entire nervous system relies on a group of subsenses that enables the connectivity between neurons and other cell types and when this comes to cognitive functions, these subsenses become even more important as they are the key components for memory, reward, etc (Handra et al., 2019). Understanding the mechanism of the dysregulation caused by EMFs, their effect on neurotransmitters has been studied for quite a while now, and some of the results are worth mentioning. An overview of these results is listed below as they are distinguished by the type of neurotransmitters (Table 1).

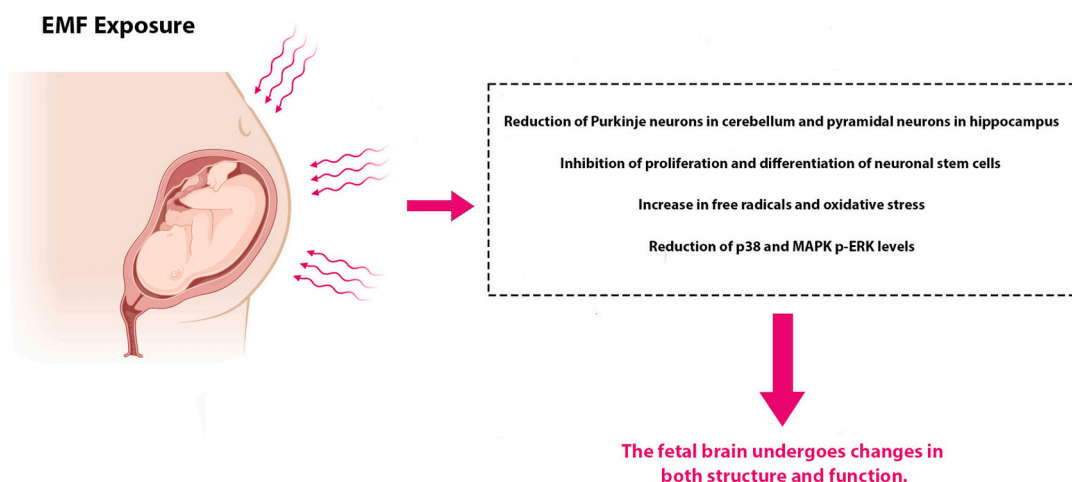


Fig. 6. Effect of Electromagnetic field exposure on fetus in prenatal period, EMF, Electromagnetic field; MAPK, Mitogen-activated protein kinases; ERK, Extra-cellular signal-regulated kinase.

Table 1
The effect of EMF on Neurotransmitters.

reference	Subject	EMF Frequency	Power density	SAR (W/kg)	Exposure Time	NT studied	Techniques used to study NT	Main results
(Ezz et al., 2013)	Adult Rats	1800 MHz	0.02 mW/cm ²	0.843	1 h	DA	High performance liquid chromatography coupled with fluorescence detection (HPLC-FD)	DA decrease in the hippocampus
(Maaroufi et al., 2014)	Rats	900 MHz	-	0.05–0.18	1 h/day for 21 days	DA	-	DA decrease in the hippocampus
(Megha et al., 2015)	Male Fischer 344 Rats	1800 MHz	1 mW/cm ²	-	2 h/day, 5 days/week for 30 days	NE & E	LC-MS/MS	NE and E decrease in the hippocampus
(Cao et al., 2000)	Male LACA Mice	900 MHz	0, 1, 2 and 5 mW/cm ²	0, 0.22, 0.44 or 1.1	1 h/day for 35 days	NE & E	-	NE increase at 1 mW/cm2
(Inaba et al., 1992)	Rats	2450 MHz	5 and 10 mW/cm ²	-	1 h	5-HT	-	5-HIAA increase in the cerebral cortex at 5 and 10 mW/cm2.
(Ishikawa et al., 1982)	Male Wistar Rats	2450 MHz	5 kW	-	0.5 or 1.5 s	5-HT	high performance liquid chromatography with electrochemical detection	5-HIAA decrease at 0.5 s; 5-HIAA increase at 1.5 s
(Li et al., 2015)	Wister Rats	2.856 GHz	5, 10, 20, 30 mW/cm ²	-	3 times per week for up to 6 weeks	5-HT	electroencephalogram (EEG) and neurotransmitter content	5-HT increase in the hippocampus from 28 days to 2 months at 30 mW/cm2
(Karri et al., 2016)	Wister Rats	-	30 mW/cm ²	-	, 10 min	Glutamate & aspartic acid	-	Glutamate and aspartic acid decrease 1 day after radiation
(Wei et al., 2019)	Male Wistar Rats	-	5,10,30, and 100 mW/cm ²	-	5 min	Glutamate & aspartic acid	regional homogeneity (ReHo) and fMRI	Glutamate and aspartic acid decrease in the hippocampus within 7 days after radiation,
(Ahmed et al., 2018)	Rats	1800 MHz	0.02 mW/cm ²	0.843 W/kg	1 h/day for 1, 2, or 4 months	Glutamate & aspartic acid	high-performance liquid chromatography	Glutamate and glutamine decrease in the hippocampus after 1 month
(Wang et al., 2016)	Male Wistar Rats	2.856 GHz	0, 2.5, 5 and 10 mW/cm ²	-	5 min/day, 5 days/week and up to 6 weeks	Glutamate & aspartic acid	-	NR2B and p-NR2B decrease in the 10 mW/cm2 group; NR2A decrease in the 10 mW/cm2 group at 1 day and 6 months
(Qiao et al., 2014)	Wistar Rats	-	30 mW/cm ²	-	5 min	GABA	western blotting and immunoelectron microscopy	GABA decrease in the hippocampus
(Wang et al., 2005)	Wistar Rats	2.856 GHz	50 mW/cm ²	-	6 min	GABA	-	GABA decrease at 6 months
(Zhang et al., 2017)	Male mice	1.8 GHz	-	-	4 weeks	GABA	liquid chromatography-mass spectrometry	GABA and aspartic acid decrease in the cortex and hippocampus
(Fujiwara et al., 1978)	Mice	2.45 GHz	-	-	-	ACh	-	Transient elevated ACh content in the brain
(Lai et al., 1989)	Rats	2.45 GHz	-	0.6 W/kg	20 min	ACh	-	Choline uptake activity increase in the frontal cortex, hippocampus, and hypothalamus
(Gupta et al., 2018)	Rats	2.45 GHz	-	-	1 h/day for 28 consecutive days	ACh	-	ACh decrease, AChE activity increased in the hippocampus
(Lai et al., 1992)	Rats	2450 MHz	1 mW/cm ²	0.6 W/kg	45 min	Peptides	-	Three subtypes of opioid receptor blocked cholinergic activity decrease in the hippocampus induced by microwave radiation
(Burlaka et al., 2016)	Wistar Rats	0.465 GHz	1.0–6.0 mW/cm ²	-	17.5 min (pulse duration 2 ms)	NO	EPR	NO synthesis increases in mitochondria of neural cells, NO synthase increases in the brain
(Hu et al., 2021)	Mice	-	0.9 V/m	-	6 h/day, 12 h/day, and 18 h/day, 30 days	NO	-	NO increase in the brain

NT: Neurotransmitter, DA: Dopamine, Ach: Acetylcholine, NE: Norepinephrine, E: Epinephrine, NO, Nitric oxide

8.1. Dopamine

When it comes to cognitive behaviors, dopamine is one of the most talked about neurotransmitters and not only it has various functions for reward, learning, emotions, motor activity and more but also its dysregulation can correlate with many neurological diseases such as Parkinson's disease, multiple sclerosis and so on (Sheffler et al., 2019; Kasture et al., 2018; Goodman, 1996; Davis et al., 1991). Many studies have shown that EMR exposure can alter dopamine function. A low-power, long-term study with an EMF frequency of 1.8 GHz, significantly decreases hippocampal dopamine levels after 2 months (Ezz et al., 2013). Another study also showed the same result after 21 days of exposure to 0.9 GHz and 1 hour per day. At 2.45 GHz and a density of 10 mW/cm² the 3,4-dihydroxyphenylacetic acid (DOPAC) content, one of dopamine metabolites, increased after an hour of exposure (Maaroufi et al., 2014). A study on 32 pregnant Wistar rats divided into 4 groups (control, low dose of 10 min, middle dose of 30 min, and high dose of 60 min exposure to mobile phone radiation) suggested that at low dose there is an increase in brain dopamine content in fetal mice and also a decrease in at high dose radiation (Jing et al., 2012). These results show that these types of radiation can lead to dysregulation of dopamine levels in the brain and cause abnormal emotional behaviors.

8.2. Norepinephrine and epinephrine

Norepinephrine, a precursor to epinephrine, plays diverse and pivotal roles in cognitive functions such as stress response, attention, sleep, and inflammation. While traditionally released as hormones from adrenal glands, emerging evidence suggests that their secretion in the brain may be subject to alteration by RF-EMF (Sheffler et al., 2019; Silverberg et al., 1978). In a long-term study, exposure to 1.8 gigahertz for two hours daily over 70 days resulted in decreased levels of both norepinephrine and epinephrine in the hippocampus region of the rat brain (Megha et al., 2015). Another experiment involving male mice exposed to 0.9 GHz at various intensities (0, 1, 2, and 5 mW/cm²) for 35 days indicated that low-intensity radiation (1 mW/cm²) could elevate brain norepinephrine content (Cao et al., 2000). Furthermore, experiments on pregnant rats during 20 days of exposure revealed that at low intensity, norepinephrine content increased in fetal rats, while high-intensity EMF caused a decrease (Jing et al., 2012). Collectively, these findings underscore the impact of prolonged EMF exposure on norepinephrine and epinephrine levels, suggesting a potential for abnormal regulation with implications for cognitive functions.

8.3. Serotonin

Serotonin, also known as 5-hydroxytryptamine (5-HT), although primarily produced outside the CNS, serves as a vital inhibitory neurotransmitter with regulatory roles in various physiological functions, including mood, feeding, cognition, memory, and pain (Charnay and Léger, 2010; Petkov and Konstantinova, 1986). The diverse functions attributed to serotonin prompt researchers to explore its interaction with RF-EMF. In a study, exposure to 2.45 GHz microwave radiation for one hour at power densities of 5 and 10 mW/cm² increased the cerebral cortex content of 5-HIAA (the primary metabolite of serotonin), while no changes were observed in serotonin content (Inaba et al., 1992). At the power density of 5 mW/cm², serotonin turnover also increased. Conversely, a long-term study involving exposure to 2.856 GHz revealed a notable increase in serotonin content in various brain areas after up to two months of exposure. This increase was associated with effects on learning, memory, and abnormal hippocampus morphology, suggesting that prolonged exposure to microwave radiation can lead to an abnormal increase in serotonin metabolism (Li et al., 2015). In a short-term, high-power experiment with 5 KW of power and a 2.45 GHz frequency, dysregulation of monoamines and their metabolites was noted. Levels of norepinephrine, dopamine, and 5-HIAA increased with

a 1.5-second exposure, while a 0.5-second exposure led to decreased levels (Ishikawa et al., 1982).

8.4. Glutamate and aspartate

Glutamate and aspartate, pivotal excitatory neurotransmitters, warrant examination for their potential interaction with EMF (Shen et al., 1999; Niciu et al., 2012). In a conducted experiment, one day post-exposure to EMF, levels of both neurotransmitters exhibited a decrease (Karri et al., 2016). Furthermore, a study involving rat exposure to 1.8 GHz for varying durations (ranging from one month to four months) reported a reduction in glutamine and glutamate levels within the hippocampus area, underscoring the potential of EMF to disrupt the balance between excitatory and inhibitory neurons (Ahmed et al., 2018). Notably, another investigation observed a decrease in memory and learning abilities following microwave exposure, coupled with an increase in hippocampal glutamine levels (Wang et al., 2016). These findings collectively suggest that microwave radiation may impair cognitive functions through the disruption of neurotransmitters. Additionally, prolonged exposure to EMF was associated with extended navigation times in the Morris Water Maze (MWM), and further investigations implicated a decrease in NR2A and 2B as a potential cause for the observed dysfunction in learning and memory (Wang et al., 2017).

8.5. GABA

In recent years, the investigation of inhibitory amino acid neurotransmitters, such as GABA (gamma-aminobutyric acid) and glycine, has revealed their pivotal roles in regulating vital cognitive functions (Stone et al., 2014). Notably, EMF have emerged as potential modulators of these neurotransmitters. Experimental studies involving rats exposed to EMF indicate a decrease in GABA levels, suggesting a modulatory effect on this inhibitory neurotransmitter. Additional experiments propose that EMF may also reduce GABA transmission (Zhang et al., 2017; Qiao et al., 2014). Moreover, extended exposure, spanning from one to four months, has revealed an increase in glycine levels in the midbrain. This extended exposure duration underscores the intricate influence of EMF on the delicate balance of brain excitation and inhibition (Noor et al., 2011).

8.6. Acetylcholine

Acetylcholine, the neurotransmitter released from cholinergic nerve endings, holds the distinction of being the first neurotransmitter measured. Given that the cholinergic nervous system is integral to cognitive functions, investigating its potential alteration by EMF becomes imperative (Li et al., 2018). Various experiments utilizing diverse methodologies have yielded conflicting results, with some indicating an increase and others a decrease in brain acetylcholine content following EMF exposure. Notably, despite variations in acetylcholine levels, subjects across experiments consistently demonstrated a decrease in learning, memory, and cognitive function (Krylova et al., 1992; Shang and Filizola, 2015). This suggests that EMF exposure may disrupt these cognitive processes by influencing the acetylcholine neurotransmitter, potentially impacting the specific receptors it activates, and underscores the complexity of the interaction between EMF and cognitive function.

8.7. Peptides and other neurotransmitters

Among the prominent peptides, opioid peptides stand out due to their involvement in diverse brain pathways and their role in regulating memory and learning (Kirichuk et al., 2011). Compelling evidence indicates that the opioid system is susceptible to the effects of EMF exposure (Lai et al., 1992). Additionally, it has been observed that EMF may contribute to a decrease in hippocampal cholinergic activity, with

the opioid system potentially playing a role in this microwave-induced effect (Lai et al., 1992). Furthermore, prolonged exposure to EMF has been associated with increased levels of nitrous oxide (NO), and this elevation may give rise to toxic effects, contributing to neural damage and further impairing learning and memory processes (Burlaka et al., 2016).

8.8. Possible mechanisms underlying neurotransmitter changes caused by EMF

While the precise mechanisms underlying the alterations induced by EMFs on neurotransmitters remain uncertain, we will examine three potential pathways through which EMF radiations may contribute to these distortions in neural interactions. Existing evidence suggests that EMR has the potential to elevate neural cortical excitability and efficiency. This implies a modification in the electrical properties of neurons, resulting in an imbalance that may subsequently lead to heightened reaction times and disruptions in sleep Electroencephalogram (EEG) patterns, among other effects (Volkow et al., 2011; Carubba et al., 2010). An additional conceivable avenue through which EMFs may impact neurotransmission properties involves alterations in cell membrane dynamics. Experimental evidence indicates that in the presence of EMFs, there is an observed increase in the number of opened calcium channels (Walleczek, 1992). Moreover, research has substantiated that EMR can modify cell membrane permeability. Scientists have asserted that exposure to EMR may up-regulate apoptosis pathways, leading to neural apoptosis. This effect is thought to be associated with the heightened generation of ROS following exposure to EMR (Narayanan et al., 2019). However, it is important to note that further research studies are imperative to elucidate the intricate effects of EMR on each type of neurotransmitter and to provide a more comprehensive understanding of the underlying mechanisms governing the alterations induced by radiofrequency.

In generally while the effects of radiofrequency EMFs have been explored in the studies and experiments mentioned earlier, additional evidence, detailed in Table 1, has not been explicitly outlined. The findings of these studies, though sometimes conflicting, collectively suggest a propensity for exposure to EMFs to induce cognitive function impairment, potentially through the alteration of neurotransmitter balance. This underscores the need for further investigation to enhance our understanding of this significant subject.

9. How do glial cells respond to EMF exposure?

By modulating synaptic transmission and plasticity, astrocytes guarantee the proper operation of neurons and synapses. They have the ability to actively modify the extracellular environment, hence affecting the diffusion of neurotransmitters in the extracellular space. Astrocytes modulate neuronal excitability and synaptic transmission by the release of neuroactive compounds like as glutamate, ATP, and D-serine. They play a vital role in both the passive and active functions of synapses. (Kim and Chung, 2023; Araque and Navarrete, 2010).

Microglia are immune cells that perform an essential part in the formation and operation of neural circuitry. They perform an important role in synapse formation, elimination, and synaptic function regulation. Microglia play multiple functions in synaptic plasticity under physiological and pathological conditions, according to studies. Neurodevelopmental disorders may be influenced by disturbances in microglia-dependent synapse elimination. Loss of synapses has been observed in neurodegenerative diseases resulting from trauma, infection, and aging. Microglia contribute to synapse creation during development and learning, as revealed by genetic techniques (Andoh and Koyama, 2021; Whitelaw et al., 2023).

Multiple studies have documented the impact of EMR on glial function. As an illustration, a 15-minute EMR exposure of 900 MHz with a modulation frequency of 217 Hz and a SAR of 6 W/kg in adult rats

resulted in a substantial enlargement of the immunoreactive Glial fibrillary acidic protein (GFAP) region in the cortex, striatum, and hippocampus. This study demonstrated that acute exposure to microwaves can cause an increase in the size and/or number of astrocytes (Mausset-Bonnefont et al., 2004). Brillaud et al. examine glial evolution two, three, six, and ten days following one exposure to 900 MHz GSM (Global System for Mobile Communications) for fifteen minutes at a brain average SAR of 6 W/kg. The extent of GFAP-stained surface area in the frontal cortex and caudate putamen increased two days after exposure. Significant increases were detected in the aforementioned regions, in addition to the cerebellar cortex, following a three-day exposure period (Brillaud et al., 2007). In primary cultured astrocytes, two hours of exposure to an RF-EMR at 1900 MHz resulted in the upregulation of apoptosis-associated speck-like protein containing a caspase recruitment domain, caspase-6 and caspase-2. Additionally, the Box gene was found to be upregulated in astrocytes (Zhao et al., 2007). In addition, Campisi et al. performed experiments on astroglial cell cultures by employing 900 MHz continuous waves or modulated 900 MHz waves with a power density of 0.26 W/m². The exposure durations were 5, 10, and 20 minutes. After 20 minutes of exposure to modulated EMF, ROS levels and DNA fragmentation increased, in contrast to continuous waves or lesser exposure times (Campisi et al., 2010). Furthermore, the impact of 935 MHz RF-EMF on, oxidative stress, autophagy, and apoptosis in N9 microglial cells was examined by Zielinski et al. at a SAR value of 4 W/kg for either 2 or 24 hours. Autophagy marker ATG5 levels increased in response to 24-hour exposure to RF-EMF, but not for 2-hours. This finding implies that autophagy may be induced by short-term exposure to EMR, contingent upon the duration of the exposure (Zielinski et al., 2020). According to the aforementioned research, even short-term exposure to radio frequencies can interfere with the activity of microglia and astrocytes.

However, other research has looked at how glial cell activity is affected by prolonged exposure to EMFs. Paulraj et al. exposed rats to 2.45 GHz EMF, 2 h/day during 35 consecutive days, with SAR 0.11 W/kg and the power density of 0.344 mW/cm². They found that glial cell population increased in the exposed group (Paulraj and Behari, 2006). Rats exposed to a chronic GSM signal at 6 W/kg at 900 MHz for a period of 24 weeks (15 or 45 minutes/day, 5 days/week) demonstrated elevated GFAP expression in the brain. Prolonged exposure to 1.5 W/kg GSM was unable to increase GFAP expression. Ammari et al. discovered that extended exposure to GSM 900 MHz microwaves (SAR 6 W/kg) can lead to permanent astroglial activation in the rat brain (Ammari et al., 2008). Moreover, Dasdag et al. applied 900 MHz microwave radiation to Wistar Albino adult male rats. The power intensity used was 0.052–0.338 mW/cm²; the SAR values were 0.17–0.58 W/kg; the rats were subjected to a 2-hour daily EMF exposure for a duration of 10 months. They observed that the rat brain's catalase and overall antioxidant capacity increased after exposure to 900 MHz radiation, but the final score for apoptosis decreased. (Dasdag et al., 2009).

According to these studies, short-term or long-term exposure to EMF can alter the number and function of glial cells, especially astrocytes and microglia, which may subsequently result in neurological dysfunction. These effects depend on the exposure time and the intensity and type of radiation waves may be different.

Nevertheless, it is also important to note that some studies have been conducted in this field that do not confirm any effects of EMF on glial cells. For example, Finnie et al. performed microwave exposure on mice for 60 min or 60 min/day on 5 days/week over a period of 104 weeks, at 4 W/kg. They found no alternation in microglial Iba1 expression in brains after short- or long-term microwave exposure (Finnie et al., 2010). Sakurai et al. exposed the human fetus-derived astroglia cell line (SVGp12) to microwave radiation, with frequency of 2.45 GHz, for 1, 4 and 24 h, with SAR 1, 5 and 10 W/kg. There were no notable modifications detected in the gene expression in SVGp12 cells (Sakurai et al., 2011). Due to variations in the parameters employed in the studies, such as exposure duration and frequency, accurate conclusions regarding the

impact of EMF on glial cell function remain elusive. Consequently, further comprehensive investigations are warranted (Table 2).

10. EMF exposure-induced modifications to ion-channel expression, function, and structure

Ion channels are fundamental integrating and regulatory apparatuses utilized to regulate the excitability of cells. Various categories of ion channels have been delineated, including those that are reactive to mechanical, electrical (voltage-dependent ion channels), or chemical (ligand-gated ion channels) stimuli. The majority of ion channels are voltage-dependent and are composed primarily of Ca^{2+} , Na^{+} , K^{+} and channels. Any alterations in ion channel function may have profound physiological consequences (Mathie et al., 2003). Numerous investigations have shown that EMF can have an impact on the structure and function of a variety of ion channels. Using a computational model, Balcavage et al. showed for the first time that PEMFs (pulsed electromagnetic fields) in the 50–60 Hz range perturb cation transmembrane movement through their respective channels (Balcavage et al., 1996). In the following years, many experimental studies were conducted demonstrating the effects of EMW on ion channels. Exposure to EMFs (1 millitesla, 50 hertz) enhances the process of neuronal differentiation in neural stem cells by increasing the expression of certain genes. Piacentini et al. showed that EMF exposure (1 mT, 50 Hz) enhances the process of neuronal differentiation in neural stem cells by increasing the expression and function of voltage-gated Ca^{2+} channels (Piacentini et al., 2008). According to He et al. exposure EMF (1 mT, 50 Hz) for 10–60 minutes significantly increased voltage-activated Na^{+} channel currents (INa) in a time- and intensity-dependent manner as well as Nav 1.2 protein levels on the cerebellar granule cells membrane. Recently, Cecchetto et al. demonstrated that EMF (268 μT and 902 μT , 20 Hz) significantly increased Kv1.3 currents in CHO-K1 cells. Following exposure, the increase reached a steady state after a few seconds, and then returned to baseline after several minutes (Cecchetto et al., 2020). An investigation was carried out to analyze the impact of high frequency EMFs on the conduction and concentration of calcium ions within voltage-gated calcium channels. Different frequencies and intensities were considered in the simulations. Simulated results illustrate the changes in conductance, ion concentration profiles, and average ion number inside the channels in response to high frequency radiation. As the ionic current increases in the channel, the residence of ions in the channel decreases, as indicated by the concentration profiles (Tekieh et al., 2016). However, Kim et al. found that high frequency EMF (4 W/Kg, 835 Hz, 5 h/day for 12 weeks) reduced calcium channel expression.

Research have generally shown that prolonged exposure to ELF-EMF increases ion transport through voltage-gated sodium channels, high-threshold calcium channels, and calcium-activated potassium channels, as well as their expression (Guleypoglu et al., 2013; Marchionni et al., 2006). As a result of exposure to RF-EMF, calcium channel genes and proteins are altered as well as the conductance of the calcium channels changes (Kim et al., 2018). It is thought that EMF exerts these effects by affecting their voltage-sensing and pores-forming domains (Sun et al., 2016). Considering the importance of voltage-dependent ion channels in neuronal processes, there are not enough studies in this field. This is especially since most of these studies have been conducted on the effect of ELF-EMF on calcium channels and on the other frequencies and channels of few other studies have been done.

On the other hand, a number of studies have demonstrated that EMF also affects the expression and activity of ligand-gated channels. NMDA receptors are glutamatergic ion channels characterized by high Ca^{2+} permeability, regulating neuronal processes such as synaptic plasticity through Ca^{2+} -dependent cascades. (Iacobucci and Popescu, 2017). NMDA receptors have been reported to be altered in the binding of ligand, to exhibit transient elevations in expression of subunits, and also to show effects on their activation by EMF (Kazemi et al., 2018;

Manikonda et al., 2007; Li et al., 2014; Mausset-Bonnefont et al., 2004; Bodera et al., 2017). It should be emphasized that these effects differ based on the frequency and length of exposure. Bonnefont et al. observed that when rats were subjected to GSM 900 MHz radio-frequency fields for a short period of time, there was a drop in glutamate binding activity and a reduction in the expression level of various NMDA receptor subunits (Mausset-Bonnefont et al., 2004). While repeated daily exposure to an 1800 MHz RF-EMR for 15 minutes did not have any effect on the expression of NMDA receptors in brain tissue. Furthermore, Manikonda et al. found that 90 days of exposure to 50 Hz magnetic fields at 50 and 100 μT intensities decreased the binding of NMDA receptors (Manikonda et al., 2007). Also, Duan et al. showed that ELF-EMF (50 Hz, 8 mT, 28 days) caused NMDA receptors to become overactive and increased the number of NR2B subunits on these receptors (Duan et al., 2014). According to these results, frequency plays a significant role in determining the effects of EMF on the expression and activity of NMDA receptors. Moreover, Li et al. demonstrated that Following 14 days of ELF-MF (50 Hz, 0.5 mT) exposure, GluN2A and GluN2B levels in the hippocampus were significantly elevated. After two weeks of exposure, glutamate NMDA receptor subunit zeta-1 (GluN1) and glutamate NMDA receptor subunit 2A (GluN2A) levels were elevated. NMDA receptor subunit expression patterns were different after 28 days of ELF-MF exposure. In the hippocampus and prefrontal cortex, increased GluN2A expression was recovered after prolonged ELF-MF exposure. Decreases in GluN2A levels were seen in the entorhinal cortex, and enhanced expression of GluN1 reached control levels (Li et al., 2014). The results of their study show that different effects can be produced by changing the duration of exposure. EMF can affect neuronal processes such as plasticity by influencing voltage-dependent ion channels and ligand-dependent ion channels, which will be described in detail in the next section (Table 3).

11. Neuronal plasticity: a link between EMF Exposure and cognitive changes

After various forms of brain damage, synaptic plasticity, the capacity of neurons to alter the strength of their synaptic connections, is involved in the remodeling of brain networks (Stampanoni Bassi et al., 2019). Recent studies suggest that EMF may affect brain circuits through its effects on synaptic plasticity. Different aspects of synaptic plasticity are examined in these studies. Among them are the study of changes in the expression of related proteins and the direct study of synaptic plasticity through electrophysiological methods. An electrophysiological study conducted by Xu et al. on culture of hippocampal neurons demonstrated a selective decrease in AMPA miniature excitatory synaptic current (mEPSC) amplitude following chronic exposure to 1800-MHz microwaves at 2.4 W/kg for 8 days, while the amplitude of NMDA mEPSCs did not change and the frequency of AMPA mEPSCs. As well, the GSM microwave treatment reduced post-synaptic density 95 (PSD95) expression in cultured neurons. Their findings indicate that microwaves operating at a frequency of 1800 MHz and with a power density of 2.4 W/kg resulted in a decrease in both the excitatory synaptic activity and the number of excitatory synapses in cultured rat hippocampus neurons (Xu et al., 2006). Karimi et al. found that rats exposed for 2 hours a day over a period of 40 days to microwave radiation at 2.45 GHz with a power density of 0.016 mW/cm² and a SAR of 0.017 W/kg decreased learning and memory performance as a result of reduced long-term potentiation induction and excitability of CA1 neurons. Despite this, microwave radiation had no effect on short-term plasticity or the paired-pulse ratio as an indirect indicator of glutamate release likelihood (Karimi et al., 2018).

Prochnow et al. performed experiments on male Wistar albino rats by exposing them to microwave radiation 2 GHz at SAR of 2 or 10 W/Kg for 120 min. SAR (10 W/kg) but not 2 W/kg resulted in significant reductions in Long-term potentiation (LTP) and Long-term depression (LTD) (Prochnow et al., 2011). Also, exposure to a 2.856 GHz pulsed

Table 2
Changes in glial cells following EMF exposure.

Reference	Subject	EMF frequency	Power density	SAR	Exposure time	Techniques used	Main results
(Fritze et al., 1997)	Male Wistar rats	890–915 MHz and with a repetition frequency of 217 Hz or a CW signal of 900 MHz	–	brain averaged SAR 0.3 W/kg, 1.5 W/kg and 7.5 W/kg	4 h	Immunocytochemistry	Neither the levels of the microglia-specific antibody OX–6 nor GFAP messenger RNAs increased.
(Mausset-Bonnefont et al., 2004)	Male Wistar rats	A 900-MHz carrier frequency with a 217-Hz pulsed modulation frequency (head-only exposure)	–	6 W/kg	15 min	Autoradiography Binding experiments Western blotting	Microwave exposure significantly increased the immunoreactive GFAP region in the hippocampus, striatum, and cortex, leading to astrocyte hypertrophy or hyperplasia.
(Lee et al., 2006)	Human T-lymphocyte Jurkat cells and rat primary astrocytes	1763 MHz	–	2 or 20 W/kg	30 min or 1 h	Western Blotting	Nothing alternation was observed in HSP90, HSP70, HSP27 expression, ERK1/2, or JNK1/2 phosphorylation status, and no stress response was induced.
(Paulraj and Behari, 2006) (Thorlin et al., 2006)	Male Wistar 35-day-old rats Astroglial and microglial cell cultures	2.45 GHz 900 MHz with the normal GSM repetition rate of 217 Hz	0.344 mW/cm ² –	0.11 W/kg 3 W/kg GSM MW or 27 W/kg CW	2 h/day for 35 days 4, 8 or 24 h for mw or 24 h for cw or 8 h for microglial cell cultures	Calcium-dependent protein kinase assay Morphology Immunocytochemistry Gfap measurements Determination of protein concentration Tnfa and Il6 analyses SDS-PAGE and western blotting	The exposed group had more glial cells. The morphology of microglia and astroglial cells, as well as damage-related markers like GFAP, IL6, TNF- α , and ED–1, were not affected by microwave radiation.
(Brillaud et al., 2007)	Male Sprague–Dawley rats	900 MHz	–	brain averaged SAR 6 W/kg	15 min	Immunohistochemistry	GSM exposure to 900 MHz significantly increased GFAP expression in the frontal cortex and caudate putamen, and glial reactivity in the cerebellum cortex.
(Höytö et al., 2007)	Murine L929 fibroblasts, rat C6 glioblastoma cells, human SH-SY5Y neuroblastoma cells, and rat primary astrocytes	872 MHz CW or a GSM type signal pulse modulated at 217 Hz	–	1.5, 2.5 or 6 W/kg	2, 8 or 24 h	ODC activity assay	Rat primary astrocyte cellular ornithine decarboxylase activity significantly decreased with exposure to GSM modulated or CW radiation, while secondary cell lines exhibited unaffected activity.
(Zhao et al., 2007)	primary cultured neurons and astrocytes	1900 MHz	–	–	2 h	Real-time RT-PCR Array analysis	Radiofrequency radiation from cell phones can induce upregulation of apoptotic pathway components in neurons and astrocytes, including caspase–2, caspase–6, Asc, and Bax gene in astrocytes.
(Ammari et al., 2008)	Sprague-Dawley rats (6 weeks old)	900 MHz (head only exposure)	–	1.5 W/kg Or 6 W/kg	45 min/day Or 15 min/day, 5 days in a week for 24 weeks	Immunohistochemistry	Prolonged exposure to GSM 900 MHz microwaves could potentially cause gliosis in rats by activating astroglia persistently.
(Dasdag et al., 2009)	Male Wistar rats	900 MHz	0.052–0.338 mW/cm ² Average power density around the brain	0.17–0.58 W/kg	2 h/ day, 7 days in a week for 10 months	Immunohistochemistry Semi-quantitative scoring of protein expressions Determination of	The experimental group showed a reduced apoptosis score and a higher antioxidant

(continued on next page)

Table 2 (continued)

Reference	Subject	EMF frequency	Power density	SAR	Exposure time	Techniques used	Main results
(Ammari et al., 2010)	Sprague-Dawley rats	900 MHz pulse modulated at 217 Hz		1.5 or 6 W/kg	45 or 15 min/day 5 day/week For 8 week	catalase activity Measurement of antioxidative capacity Measurement of oxidant status Immunohistochemistry	capacity and catalase levels. Exposed rats exhibited elevated levels of GFAP in their brains 3 and 10days following the exposure.
(Campisi et al., 2010)	Astroglial cell cultures	900 MHz CW or 900 MHz waves modulated in amplitude at 50 Hz	0.26 W/m ²		5, 10, or 20 min	MTT test Spectrophotometric analysis Comet assay	Astrocytes were susceptible to the production of reactive oxygen species (ROS) and DNA breakage following a brief exposure to EMF.
(Finnie et al., 2010)	Mice	900 MHz modulated at a pulse repetition frequency of 217 Hz and a pulse width of 0.6 ms		4 W/kg	60 min or on 5 days/week for 104 weeks	Immunohistochemistry	Iba1 immunostaining revealed no detectable microglial activation.
(Sakurai et al., 2011)	The human fetus-derived astroglia cell line, SVGp12	2.45 GHz CW		1, 5, and 10 W/kg	1, 4, and 24 h	Semi-quantitative RT-PCR Oligonucleotide microarray data acquisition	Exposure to radiofrequency fields did not change the gene expression levels in SVGp12 cells.
(Watilliaux et al., 2011)	Wistar rats on postnatal day 35	1800 MHz		brain average SAR 1.7–2.5 W/kg	2 h head-only exposure	Western blot Immunocytochemistry	The expression levels of HSP90, HSC70, HSP60, serine racemase, glutamate transporters (GLT1 and GLAST), and GFAP were not significantly affected by the GSM signal.
(Liu et al., 2012)	rat astrocytes and C6 glioma cells	1950-MHz TD-SCDMA		5.36 W/kg	12, 24 and 48 h	Immuno-fluorescence staining Flow cytometric analysis Observation of cell morphology and ultrastructure Cell apoptosis assays Cell proliferation assay Semi-quantitative RT-PCR and real-time PCR Western blotting Tumorigenicity assays in nude mice	Exposure to EMF may not lead to tumor development but cause mitochondrial damage in astrocytes and trigger apoptosis through a caspase–3-dependent pathway involving bax and bcl–2.
(Barthélémy et al., 2016)	Sprague-Dawley male rats	900 MHz RF EMF pulse modulated at 217 Hz		1.5 or 6 W/kg	15 min at 0, 1.5, or 6 W/kg or for 45 min at 6 W/kg.	Enzyme-linked immunosorbent assay ELISA assay	RF EMF-induced astrogliosis was shown by an elevation in GFAP levels.
(Borovkova et al., 2017)	C6 rat glial cell line	0.12–0.18 THz	3.2 mW/cm ²		1,2,3,4 and 5 min	Assessment of changes in mitochondrial membrane potential Cell labeling procedure Flow cytometry	An increase in the proportion of cells undergoing apoptosis was detected after being exposed to THz radiation.
(Zielinski et al., 2020)	N9 microglial and	935 MHz pulse-modulated rate at 216.7 Hz		4 W/kg	2 and 24 h	Apoptosis and autophagy assay Oxidative stress assay Cytochrome c oxidase activity assay	Brief exposure to RF-EMF induced autophagy marker ATG5 levels. The magnitude of this effect was influenced by the duration of exposure.
(Salari et al., 2023)		10-Hz, 10-mT			3 days (3 h per day)	Nissl staining Immunohistochemistry Real-time PCR	The coadministration of ketamine with ELF-EMF resulted in a decrease in the number of GFAP-positive cells in the CA1 area and mPFC.

Table 3
Consequences of Ion Channel Function Changes caused by EMFs.

Reference	Subject	EMF frequency	Power density	SAR	Exposure time	Ion channel studied	Techniques used to study ion channel	Results and discussion
(Balcavage et al., 1996)		50–60 Hz				cation channel	A computational model	Pulsed electromagnetic fields (PEMFs) at frequencies between 50 and 60 Hz can disrupt the transport of positively charged ions across cell membranes.
(Piacentini et al., 2008)	neural stem/progenitor cells	50 Hz, 1 mT			for up to 12 days	Ca channel	Immunocytochemistry Confocal Ca ²⁺ imaging Patch-clamp recordings	Through the increase of Cav1-channel activity and expression, exposure to ELF-EMF induced the neural differentiation of NSCs.
(He et al., 2013)	rat cerebellar granule cells	50 Hz, 1 mT			10–60 min	voltage-activated Na ⁺ channels	Patch-clamp Recordings western blotting Immunocytochemistry	ELF-EMF exposure to cerebellar GCs significantly increased Nav currents, shifted the steady-state activation curve towards hyperpolarization, and elevated membrane expression of Nav 1.2 protein.
(Cui et al., 2014)	HEK293 (human embryonic kidney cells) cells	50 Hz, 0.2 mT			0.5 h, 1 h, 2 h and 3 h	low-voltagegated T-type calcium channels	Western blot Patch-clamp Recordings	ELF-EMF blocked all T-type channels (Cav3.1, Cav3.2, and Cav3.3) through the arachidonic acid/leukotriene E4 signaling pathway.
Li et al., 2014)	cultured dorsal root ganglion neurons	50 Hz, 1 mT pulsed electromagnetic field			2 h	L-type voltage-gated calcium channels	standard microscopic fluo–4 acetoxymethylester digital imaging	BDNF mRNA expression and [Ca2+]i increased after exposure to ELF-EMF, mediated by increased [Ca2+]i through L-type voltage-gated calcium channels.
(Liu et al., 2014)	rat cerebellar granule cells	50 Hz, 1 mT			60 min	Na _v channels (transient I _{Na})	Patch-clamp recordings Intracellular Ca2+ levels were detected by single cell fura–2 AM fluorescence intensity	ELF-EMF application markedly increased the densities of Nav currents and induced a considerable alteration to the steady-state activation curve of the Nav channel towards hyperpolarization.
(Luo et al., 2014)	Primary EC neuron culture	50 Hz,1 mT or 3 mT			24 h	high-voltage activated and low voltage activated calcium channels	whole-cell recording calcium imaging	Exposure to ELF-EMF did not have an impact on voltage-gated calcium channels. However, it did lessen the amplitude of the high-K ⁺ stimulation-induced calcium elevation, which thapsigargin can reverse.
(Çiğ and Nazıroğlu, 2015)	MCF–7 human breast cancer cell lines	900, 1800 and 2450 MHz at different distances (0 cm, 1 cm, 5 cm, 10 cm, 20 cm and 25 cm)	1.2, 12 or 120 µW/cm ²	0.36 ± 0.02 mW/kg	1 h	TRPV1	Cytosolic free Ca2+ ([Ca2+]i) concentration analysis with fura–2/AM	Wi-Fi and mobile phone electromagnetic radiation triggers oxidative stress and apoptosis in cancer cells by activating TRPV1, depending on the radiation source's distance.
(Sun et al., 2016)	Postnatal day 8–10 (p8 – p10) old C57 mice	50 Hz, 1 mT			8–10 days	calcium channels, including the P/Q, N, and R subtypes	Western blot Real-time PCR Whole cell voltage clamp recordings	Exposure to ELF-EMF increased calcium channel expression at the presynaptic nerve terminal.
(Tekieh et al., 2016)	The simulations are performed for different frequencies and intensities					voltage-gated calcium channels	They use a three-dimensional Brownian Dynamics approach, coupled with electrostatic calculations.	The simulation findings reveal changes in conductance, ion count, and concentration profiles in channels due to high frequency radiation
(Kim et al., 2018)	C57BL/6 mice	835 MHz		4.0 W/kg	4 weeks	voltage-gated calcium channels	Western blot analysis	By lowering the expression of calcium channels in the hippocampus, RF-EMF exposure may upset the calcium balance inside cells.
(Kim et al., 2019)	C57BL/6 mice	835 MHz		4.0 W/kg	5 h/day for 12 weeks	calcium channel	Western blotting	There was a significant decrease in calcium channel expression.
(Cecchetto et al., 2020)	CHO-K1 cells	20 Hz, 268 µT and 902 µT				Kv1.3	whole-cell patch-clamp	The Kv1.3 current in CHO-K1 cells showed a significant increase upon exposure to ELF-EMF.
(Zheng et al., 2021)	CA1 pyramidal neurons of rat hippocampal slices	15 and 50 Hz, (0.5, 1 and 2 mT)			10, 20 and 30 min	Sodium channel, transient outward potassium channel and delayed rectifier potassium channel	whole-cell patch clamp	ELF-EMFs increased INa densities but decreased IA and IK densities, suggesting regulation of ion channels' structure and function.
(Ding et al., 2023)		4 THz, 10 THz, 15 THz, and 20 THz				Kv1.2 voltage-gated potassium ion channel	The combined model of the “Constant Electric Field-Ion Imbalance” method by molecular dynamics.	The study discovered that the application of a terahertz electric field to a selective filter (SF) in a channel has an impact on the stability of electrostatic bonds and hydrogen bonds, which in turn changes the permeability of the channel.
(Zhao et al., 2023)		6, 15, and 25 THz				Kv1.2 potassium channel	molecular dynamics simulations	The permeability of the Kv1.2 potassium ion channel was greatly enhanced by a 15 THz electromagnetic field

microwave field with power density of 5, 10 and 50 mW/cm² for only 6 min led to a decrease in population spike amplitudes after microwave exposures of 10 mW/cm² and 50 mW/cm². Furthermore, rats exposed to microwaves of 10 mW/cm² and 50 mW/cm² had various degrees of degeneration of hippocampal neurons, reduced synaptic vesicles, and distorted synaptic clefts. In the above tests, the rats exposed to 5 mW/cm² microwaves showed no difference from the sham group (Wang et al., 2013). In cultured primary hippocampal neurons, Echchgadda et al. found that RF-EMF exposure (3 GHz at a SAR of 1 W/kg for 60 min) reduced action potential amplitudes, depolarized resting membrane potentials, and increased neuronal excitability and synaptic transmission (Echchgadda et al., 2022). According to these studies, even short-term exposure to EMW can affect synaptic plasticity. In contrast, some studies have found that long-term or short-term exposure to EMW has no effect on synaptic plasticity (Rui et al., 2022; Pakhomov et al., 2003). For example, Rui et al. showed that exposure to 5.8 GHz microwave with power density of 74.25 W/m² and SAR of 2.33 W/kg for 6 weeks (6 min per day, 5 days per week) could not affect the hippocampal synaptic plasticity of rats (Rui et al., 2022).

Similar to RF-EMF, most studies indicate that ELF-EMF reduces synaptic plasticity induction. For example, a study by Zheng et al. exposed slices of rat hippocampal tissue to different frequencies (15, 50, and 100 Hz), intensities (0, 1, and 2 mT), and durations (10 s, 20 s, 40 s, 60 s, and 5 min). A decrease in LTP amplitudes was observed after exposure to magnetic fields, and the decrease was dose- and duration-dependent, suggesting that ELF-EMFs are capable of inhibiting LTPs in a dose- and duration-dependent manner (Zheng et al., 2019). Also, Dong et al. found that ELF-EMF decreases the slope of field excitatory postsynaptic potentials (EPSPs) (Dong et al., 2018). Interestingly, a number of studies have demonstrated that ELF-EMFs may not directly induce plasticity, but rather act as modulators of endogenous synaptic plasticity (Dong et al., 2018; Zheng et al., 2019). Zheng et al. added ELF-EMF (15, 50, and 100 Hz) with intensities (0, 1, and 2 mT) to rat hippocampal slices before plasticity induction to determine the most effective magnetic stimulation parameters. They found that an ELF-EMF value of 15 Hz and 2 mT, was the most appropriate value among test parameters. Then, they examined the influence of magnetic stimulation added before, during and after plasticity induction. Synapses with weak activity or those containing blocked NMDA receptors were not affected by ELF-EMFs. These results suggest that ELF-EMFs play a metaplastic role as modulators of synaptic activity processes (Zheng et al., 2019).

However, what mechanisms are responsible for altering synaptic plasticity when a magnetic field is present? 1. It has been suggested that magnetic fields may affect genes involved in synaptic plasticity and synaptic function (Kazemi et al., 2018; Fragopoulou et al., 2012). 2. EMFs affect a variety of voltage-gated channels (Tekieh et al., 2016; Zheng et al., 2021). 3. EMW change the concentration of different neurotransmitters in the brain (Hu et al., 2021). 4. There is a possibility that the EMF may have an effect on the removal of magnesium ions that block the NMDA receptors. This may affect calcium and sodium ion neural levels in the postsynaptic regions (Kronberg et al., 2017).

In general, the body of literature concerning alterations in neuronal plasticity subsequent to exposure to EMFs underscores the intricate dynamics that exist between EMFs and the nervous system. An extensive body of research has examined the impact of EMFs on neuronal plasticity. Some studies indicate that EMF exposure can enhance neuronal plasticity and promote cognition, while other studies indicate that EMF exposure may negatively impact synaptic plasticity and neurodevelopment. Thus, to fully understand the implications of EMF exposure on neuronal plasticity, more comprehensive and standardized research is needed (Table 4).

12. Alterations in the structural organization of neural circuits following EMF exposure

12.1. Permeability of BBB

There are tight junctions between vascular endothelial cells in the BBB, which create a hydrophobic barrier. This barrier protects mammalian brains against potentially harmful blood compounds. A bilayer basal membrane as well as perivascular structures like astrocytes and pericytes contribute to maintaining the BBB. Normally hydrophilic molecules don't enter the brain tissue when the BBB is intact, whereas when it is dysfunctional, these molecules are allowed to enter the brain tissue. As a result, cerebral edema may develop, intracranial pressure may increase, and irreversible brain damage may result (Daneman and Prat, 2015).

Tang et al. found that exposure to 900 MHz radiation for 3 h/day for 14 or 28 days at a power density of 1 mW/cm² results in damage to the BBB in the hippocampus and cortex. As a result of 28 days of EMF exposure, rats developed cellular edema and neuronal organelle degeneration (Tang et al., 2015). In a study conducted by Parson et al. the effect of continuous and pulsed radio-frequency radiation (915 MHz for 2 hours) on the permeability of the BBB was examined. According to their findings, radio-frequency radiation increased the BBB permeability. Pulsed radio-frequency radiation at 8–215 Hz had a more pronounced effect than continuous radiation (Persson et al., 1992). The effect of radio-frequency radiation exposure (915 MHz at SAR of 0.12 mW/kg, 12 mW/kg and 120 mW/kg for 2 hours) on the permeability of the BBB was studied by Eberhardt et al., 14 and 28 days after exposure to radio-frequency radiation. They have shown that EMF exposure causes focal albumin extravasation and albumin uptake into neurons 14 days after exposure, but not after 28 days. Interestingly, significant neuronal damage is present after 28 days but not after 14 days. This shows that the long-term increase in BBB permeability has damaged neurons (Eberhardt et al., 2008). There is also evidence that only 20 min exposure to continuous or pulsed microwave radiation at 1.3 GHz can be associated with an increase in the permeability of the BBB in the medulla, cerebellum, hypothalamus, hippocampus, and cortex (Oscar and Hawkins, 1977). Nevertheless, some studies have shown that exposure to EMW does not affect permeability of BBB. Masuda et al. have shown that exposure to RF-EMF at 1439 MHz at SAR of 0.6, 2.4, 4.8 W/kg for 10 min did not change permeability of BBB (Masuda et al., 2007). Also, Tsurita et al. found that RF-EMF at 1439 MHz at SAR of 2 W/kg in the brain 0.25 W/kg in the whole body 1 h/day for 5 consecutive days for 2 or 4 weeks did not induce observable changes in the BBB permeability (Tsurita et al., 2000). We found only one study that examined ELF-EMF effects on permeability of BBB. There was no Evans-blue albumin extravasation in the brains of the control, diabetic, and ELF-EMF (50 Hz, 5 mT for 8 hours a day, for 21 consecutive days) groups in this study. However, in the group with diabetes and ELF-EMF, the permeability of BBB increased (Oztaş et al., 2004). Consequently, even though ELF-EMF alone does not affect the permeability of the BBB, it increases the vulnerability of the BBB in streptozotocin-induced diabetes.

One mechanism for increasing permeability of BBB is through the increase in pinocytosis caused by electromagnetic exposure, as proposed by Neubauer et al. (Neubauer et al., 1990). Leszczynski et al. propose that the induction of HSP27 phosphorylation and increased expression by RF-EMF exposure stabilize endothelial cell stress fibers due to increased actin polymerization and might be the molecular signaling event that triggers the cascade of events leading to the increase in pinocytosis and permeability of BBB (Leszczynski et al., 2002; Fig. 7).

12.2. Structural plasticity of dendritic spines

There are small dynamic protrusions on the dendritic shafts of principal neurons called dendritic spines. Many glutamatergic synapses

Table 4
Changes in Neuronal Plasticity Following EMF Exposure.

Reference	Subject	EMF frequency	Power density	SAR	Exposure time	Techniques used to study	Results and discussion
(Pakhomov et al., 2003)	Isolated rat hippocampal slice	9.3 GHz		500 mW/kg		Field potential recording	The process of long-term potentiation (LTP) remained unaffected by EMF. Prolonged exposure to GSM reduced the amplitude of AMPA mEPSCs and postsynaptic density 95 in rat hippocampal neurons, potentially decreasing excitatory synaptic activity.
(Xu et al., 2006)	Cultured hippocampal neurons of rats	1800-MHz		2.4 W/kg	15 min per day for 8 days	whole cell patch-clamp	
(Prochnow et al., 2011)	Male Wistar rats	2 GHz		2 or 10 W/Kg	120 min	Field potential recording	At the SAR of 10 W/kg, there was a significant decrease in both long-term depression (LTD) and LTP.
(Wang et al., 2013)	Male Wistar rats	2.856 GHz pulsed microwave field	5 mW/cm ² , 10 mW/cm ² and 50 mW/cm ²		6 min	Field potential recording	EMF exposure reduced population spike amplitudes and caused degeneration in hippocampus neurons, reduced synaptic vesicles, and indistinct synaptic clefts.
(Komaki et al., 2014)	Male Wistar rats	50 Hz, 100 μ T			2 h/day for 90 days	field potential recording	Exposure to ELF-EMFs over an extended period of time boosted LTP induction.
(Xiong et al., 2015)	Male Wistar rats and PC12 cells	2.856 GHz	30 mW/cm ²		10 min every other day for 3 times	Hematoxylin and Eosin (H&E) staining Transmission electron microscope Scanning electron microscopy Immunocytochemistry and laser confocal microscopy Atomic force ficroscopy High performance liquid chromatography (HPLC) Laser confocal microscopy and flow cytometry Western blot RT-PCR, and real-time PCR Patch-clamp	Microwave radiation changed synapses structure, release of neurotransmitters, and influx of calcium, which decreased synaptic plasticity.
(Dong et al., 2018)	Male Sprague–Dawley rats	15 Hz, 50 Hz, and 100 Hz, 0.5, 1, 2 mT			20 min		The fEPSPs slope significantly decreased when exposed to priming through continuous or pulsed sinusoidal ELF-EMF stimulation.
(Karimi et al., 2018)	Sprague Dawley rats	2.45 GHz	0.016 mW/cm ²	0.017 W/kg	for 2 h/day over a period of 40 days	Field potential recording Giemsa staining	Microwave radiation reduced CA1 neurons' long-term potentiation and excitability, but did not affect short-term plasticity or paired-pulse ratio.
(Zheng et al., 2019)	Male Sprague-Dawley rats	15, 50, and 100 Hz, 0.5, 1, and 2 mT			10 s, 20 s, 40 s, 60 s, and 5 min	Field potential recording in-vitro	Exposure to ELF-EMFs reduced LTP amplitudes, directly proportional to dosage and duration.
(Zheng et al., 2019)	Male Sprague-Dawley rats	15 Hz, 2 mT			20 min	Patch clamp	The study found that ELF-EMFs, when combined with a plasticity induction approach, significantly affect synaptic plasticity.
(Khajei et al., 2021)	Male Wistar rats	100 Hz	10 mT		1 h/day for 1 week	Field potential recording	Findings suggest that EMF can potentially treat seizure-induced learning and memory deficits by returning synaptic potentiation to the hippocampal CA1 area and induced LTP.
(Xia et al., 2021)	Male Wistar rats	15 Hz, 2 mT				Field potential recording in hippocampal slices	ELF-EMF reduces LTP induction and increases LTD, but not when calcium channels and Calcineurin are blocked with cadmium chloride and Cyclosporin A.
(Echchgadda et al., 2022)	Cultured primary hippocampal neurons	3 GHz		< 1 W/kg	60-min	Patch-clamp	RF-EMF exposure reduced action potential amplitude, resting membrane potential, and increased synaptic transmission and excitability of neurons.
(Rui et al., 2022)	Male Sprague–Dawley rats	5.8 GHz	74.25 W/m ²	2.33 W/kg	2 or 4 h for 15 days	Immunofluorescence staining Western blot Golgi staining	The hippocampal synaptic plasticity was unaffected by the microwave radiation exposure.

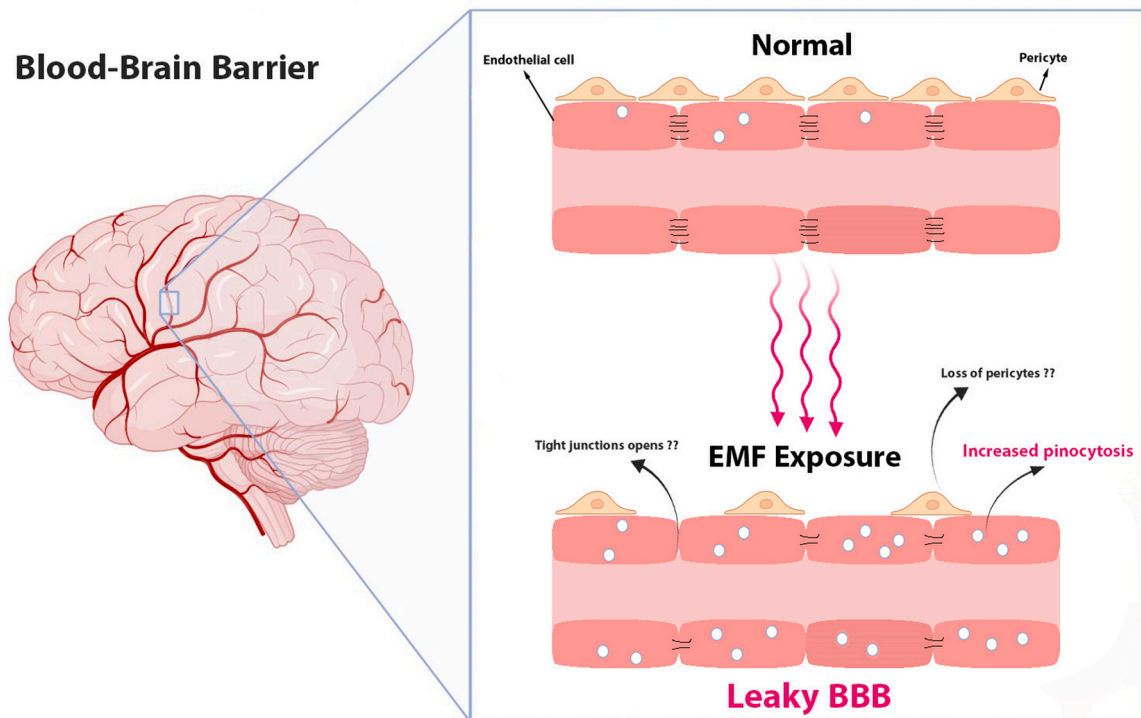


Fig. 7. Effect of Electromagnetic field exposure on blood-brain barrier permeability, EMF, Eletromagnetic field; BBB, Blood-Brain Barrier.

in mammalian brains are located in these postsynaptic compartments (Lamprecht and LeDoux, 2004). The morphology of the spine is modified by neuronal activity and affects synaptic transmission and plasticity. The enlargement or shrinkage of the spine correlates with the induction of long-term potentiation (LTP) or depression (LTD) (Bosch and Hayashi, 2012).

Xiong et al. examined the dendritic spine density and shape of the medial entorhinal cortex (MEC) after chronic exposure (14 and 28 days) to 0.5 mT 50 Hz ELF-EMFs. It was found that both 14 day and 28 day exposure to ELF-EMF decreased the spine density in the dendrites of both stellate neurons and pyramidal neurons. The authors propose that this finding may explain the impairment of cognitive function associated with ELF-EMF exposure (Xiong et al., 2013). Also, Zhao et al. demonstrated a time-dependent decline in novel object associative recognition memory and a reduction in hippocampal dendritic spine density upon exposure to ELF-EMF (50 Hz, 1 mT, 12 h/day for 7–10 day). It is noteworthy that mice exposed to ELF-EMF for 14 or 21 days had similar spine densities to mice in the control group (Zhao et al., 2015). In a recent study, Narayanan et al. found that dendritic arborization of CA3 pyramidal neurons and recognition memory reduced after exposure to RF-EMR (900 MHz; power density of $146.60 \mu\text{W}/\text{cm}^2$) for 1 h/day for 28 consecutive days (Narayanan et al., 2015). Furthermore, microwave exposure (30 mW/cm² for 6 minutes, 3 times per week for 6 weeks) caused shrinkage and even loss of dendritic spines in the hippocampus by the SNK-SPAR pathway, causing memory impairments (Zhi et al., 2018). Ning et al. reported that exposure to GSM 1800 MHz microwaves at SAR of 2.4 W/kg for 15 min each day from 6 days led to a significant decrease in the mobility of dendritic filopodia and the density of mature spines in the neurons (Ning et al., 2007). Also, Shahin et al. found that exposure to 2.45 GHz microwave radiation with power density of $0.0248 \text{ mW}/\text{cm}^2$ and whole body SAR of $0.0146 \text{ W}/\text{Kg}$ for 2 h/day over a period of 15, 30, and 60 days decreased dendritic spines in hippocampal neurons (Shahin et al., 2015).

These studies indicate that EMF decreases the density and arborization of dendrites, which may result in a decrease in cognitive abilities. Nevertheless, Wang et al. have shown that single exposure to 1.8 GHz

RF-EMR at SAR of 3.3 W/kg for 30 min increased recognition memory and dendritic spine density and length in hippocampal and prefrontal cortical neurons (Wang et al., 2017). There is still a lack of understanding as to how EMF induces spine plasticity. Despite this, Zhi et al. suggested that microwave radiation may alter spine plasticity through the SNK-SPAR pathway. Synaptic activity induces activation of the SNK-SPAR pathway, which depletes PSD-95 and results in loss of mature dendritic spines (Sui et al., 2010). Also, some studies have shown that EMF can affect actin filaments and microtubules (Yamazaki et al., 2020; Gholami et al., 2019). As these structural proteins play an important role in the plasticity of dendritic spines (Bosch and Hayashi, 2012), EMF may affect the plasticity of spines in this manner.

In general, there have been very few studies conducted in this field, and considering the importance of structural changes in dendritic spines to neuronal circuit function, it is urgent that more research be conducted here (Table 5).

13. Behavioral consequences of remodeling of neuronal network following EMF exposure

13.1. learning and memory

A large body of research has been done to date on the impact of EMW on learning and memory. The effects of 1.5-GHz microwave exposure on spatial memory and the NMDAR pathway were studied by Wang et al. in a dose-dependent manner, using average power densities of 5 mW/cm², 30 mW/cm², and 50 mW/cm². Rats exposed to electromagnetic fields (EMF) for a duration of 6 minutes, with power densities of 5, 30, and 50 mW/cm², had impaired spatial memory, alterations in the structure of the hippocampus, and changes in the subunits of NMDAR. These effects were observed to be dependent on the dosage of exposure (Wang et al., 2023). In addition, Wang et al. reported that 2.856 GHz and 9.375 GHz microwave exposure at a power density of $10 \text{ mW}/\text{cm}^2$ impaired spatial learning and memory (Wang et al., 2023). Zhu et al. discovered that contact with microwave radiation at frequencies of 1.5 and 4.3 GHz, with a power density of $10 \text{ mW}/\text{cm}^2$, resulted in impaired

Table 5

Structural changes in neural circuits following EMFs exposure.

Reference	Subject	EMF frequency	Power density	SAR	Exposure time	Techniques used to study	Results and discussion
(Persson et al., 1992)	male and female Fischer 344 and Sprague-Dawley rats	915 MHz that are continuous wave (CW) and modulated at various low frequencies (8–215 Hz)			2 h	Extravasation of the dye and leakage of endogenous albumin and fibrinogen	Radio-frequency radiation enhances the permeability of the blood-brain barrier, particularly in pulsed radiation.
(Preston et al., 1979)	Adult male Sprague-Dawley	2450 MHz CW	0.1–30 mW/cm ²		30 min	The brain uptake index (BUI) was determined by comparing the absorption of mannitol to that of the extremely permeable reference substance, [3 H] water.	Microwave radiation did not alter the permeability of the blood-brain barrier.
(Tsurita et al., 2000)	Male Sprague ±Dawley	1439 MHz		2 W/kg in the brain 0.25 W/kg in whole body	1 h/day for 5 consecutive days For 2 or 4 weeks	Evans blue injection method and by immunostaining of serum albumin	Microwave radiation did not cause any detectable alterations in the permeability of the blood-brain barrier.
(Oztaş et al., 2004)	Wistar albino male rats	50 Hz, 5 mT			7 days after streptozotocin injection, for 8 h/day, for 21 consecutive days		Diabetes increases BBB vulnerability to EMFs.
(Kuribayashi et al., 2005)	immature and young F344 rats	1439 MHz		2, and 6 W/kg	The head of the rat was exposed 90 min/day for 1 or 2 weeks	Evans blue injection method	Head exposure to EMF did not have any harmful effects on the permeability of the BBB in young and developing rats.
(Masuda et al., 2007)	rat	1439 MHz		0.6, 2.4, 4.8 W/kg	The head of the rat was exposed for 10 min	closed cranial window method.	Head exposure to RF-EMF did not have any significant impact on the permeability of the BBB.
(Eberhardt et al., 2008)	male and female Fischer 344 rats	915 MHz		0.12 mW/kg, 12 mW/kg and 120 mW/kg	2 h	albumin extravasation	915 MHz EMF enhanced the permeability of BBB and the absorption of albumin in neurons after 14 days, but not after 28 days.
(Nittby et al., 2008)	male and female Fischer 344 rats	900 MHz		0.12 mW/kg, 1.2 mW/kg, 12 mW/kg and 120 mW/kg.	2 h	albumin extravasation	The permeability of BBB exhibited a rapid and sustained increase.
(Masuda et al., 2015)	in juvenile and young adult rats	1457 MHz RF		2 W/kg	50 min	intravital fluorescence microscopy	There were no alterations in the permeability of the BBB in rats at any developmental phase.
(Xiong et al., 2013)	male Sprague-Dawley rats	50 Hz, 0.5 mT			4 h/day for 14 days and 28 days	Golgi Staining	ELF-EMF exposure decreased spine density in stellate and pyramidal neurons. The density change was cell-type specific.
(Zhao et al., 2015)	female ICR mice	50 Hz, 1 mT			12 h/day for 7–10 day	Golgi staining Novel object recognition test	Exposure to ELF-EMF led to a time-dependent impairment in memory and a reduction in the number of dendritic spines in the hippocampus.
(Narayanan et al., 2015)	male Wistar rats	900 MHz	146.60 µW/cm ²	1.15 W/kg	1 h/day for 28 day	Golgi-Cox staining Morris water maze test	RF-EMR exposure affected dendritic arborization patterns in rats, and decreased rogressive learning abilities
(Zhi et al., 2018)	Male Wistar rats		30 mW/cm ²		6 min, 3 times a week, up to 6 weeks	Golgi Staining Morris Water Maze Transmission Electron Microscopy (TEM) Observation Total RNA Isolation and Real-	The microwave radiation caused a reduction and potential elimination of dendritic spines in the hippocampus via the SNK-SPAR pathway,

(continued on next page)

Table 5 (continued)

Reference	Subject	EMF frequency	Power density	SAR	Exposure time	Techniques used to study	Results and discussion
(Ning et al., 2007)	rat cultured hippocampal neurons	1800 MHz		2.4 and 0.8 W/kg	15 min/day from 6 days in vitro (DIV6) to DIV14.	Time RT-PCR Western Blot Immunofluorescence introducing farnesylated enhanced green fluorescent protein (F-GFP) and GFP-actin into hippocampus neurons.	leading to cognitive deficits. Microwave exposure with 2.4 W/kg reduced dendritic filopodia and mature spine density in neurons, while dendritic arborization remained unchanged.
(Shahin et al., 2015)	Swiss strain male mice	2.45 GHz (CW)	0.0248 mW/cm ²	0.0146 W/Kg	2 h/day For 15, 30 and 60 day	Golgi Staining	Extended exposure to microwave radiation results in an reduction in the dendritic spines.
(Wang et al., 2017)	female C57/LB mice	1.8 GHz		3.3 W/kg	30 min	Golgi Staining	Exposure to RF-EMR resulted in an increase in the density and length of dendritic spines.
(Rui et al., 2022)	Sprague-Dawley rats	5.8 GHz	74.25 W/m ²	1.15 W/kg in Whole-body 2.33 W/Kg in Brain	2 or 4 h/day for 15 day	Hematein-Eosin Stain Immunofluorescence stain Western Blot	There were no significant changes seen in the density of dendritic spines, the ultrastructure of synapse, and the levels of PSD95, Synaptophysin, p-CREB, and CREB.

spatial learning and memory, as well as destruction to the hippocampus tissue (Zhu et al., 2021). Tan et al. conducted an experiment where rats were subjected to microwaves with frequencies of 2.856 GHz or 1.5 GHz. The microwaves had a power density of 10 mW/cm² and a SAR of 3.3 and 3.7 W/kg. The exposure duration was 6 minutes. Both of microwaves induced acute inhibition of EEG, structural damage to the hippocampus, alterations in CREB-related signaling proteins and an impairment in spatial memory. This may be associated with p-AKT, p-CaMK II, p-CREB and p-ERK1/2 (Tan et al., 2021). According to Sharma et al., exposure to 900 MHz with power density of 7.737 μ W/m² and SAR of 0.231 W/kg for 1, 2 and 4 h/day for 90 days caused DNA damage, oxidative stress and an impairment of working memory according to a time-dependent process (Sharma and Shukla, 2020). Using the MWM test, the light dark box test (LDT), and the object recognition task (ORT), Varghese et al. investigated the effects of chronic exposure (4 h/day for 45 days) to 2.45 GHz with power density 7.88 W/m².

Rats exhibited an increased frequency of rearing in the light box during the LDT test when subjected to 2.45 GHz radiation. Furthermore, they exhibited a longer duration in reaching the target platform during both the training and testing stages of the MWM test, suggesting a decline in spatial memory. Nevertheless, there were no notable disparities in the duration of exploration between unfamiliar and recognized objects in ORT, nor in the proportion of time spent in the light box during LDT (Varghese et al., 2018). The majority of studies in this field indicate that RF-EMF reduce memory and learning; however, some studies do not confirm this phenomenon. For example, Rui et al. examined the outcomes of 5.8 GHz microwave exposure on spatial memory using MWM, ORT and Fear Conditioning Test. In none of the memory tests, EMW caused memory loss (Rui et al., 2022). Additionally, Keles et al. stated that 900 MHz microwave exposure (1 h per day for 25 days) does not affect learning, memory, or locomotor behavior in early and mid-adolescence (Keleş et al., 2018). Only in the study conducted by Arendash et al. was it demonstrated that exposure to 918 MHz EMW at a SAR of 0.25 W/kg for 1 h/day for 7 months enhanced memory in normal mice and Alzheimer's transgenic mice (Arendash et al., 2010). It should be pointed out that the results regarding the consequences of ELF-EMF exposure on cognitive functions differ slightly and there are more contradictions between them. Foroozandeh et al. mentioned that exposure to ELF-EMF 50 Hz, 8 mT, 4 h after and 60 min before the learning session in a passive avoidance task resulted in deficits in learning and

memory (Foroozandeh et al., 2013; Foroozandeh et al., 2011). Based on the findings of Jadidi et al. exposure to a 50 Hz, 8 mT for 20 minutes immediately following training decreased retention in MWM (Jadidi et al., 2007). In another study, 45 min exposure to 50 Hz radiation between 7.5 μ T and 7.5 mT caused memory impairment (Sienkiewicz et al., 1998). In contrast, Kazemi et al. demonstrated that 4 h/day for 4-week exposure to 12 Hz, 0.7 μ T radiation improved visual memory (Kazemi et al., 2022). Additionally, Gao et al. found that rats with cerebral ischemia who were exposed to 50 Hz, 1 mT, for 2 h/day for 28 days were able to recover cognitive and memory function (Gao et al., 2021). An exposure to 20 Hz, 10 mT, for 2 h/day for 10 days improved learning and memory in STZ-induced dementia according to (Li et al., 2019). In most studies, the results indicate that short-term ELF-EMF exposure reduces memory and learning, whereas long-term exposure improves memory. Obviously, the available evidence does not allow us to confirm this issue, and further research is required. The exposure to ELF-EMF, however, has also been found to have no effect on cognitive function in some studies. As an illustration, Burman et al. demonstrated that exposure to 5–100 Hz for 6 weeks didn't induce a measurable effect on memory (Burman et al., 2018). In another study, exposure to a 50 Hz EMF once and for a short while at either 7.5 mT, 75 mT or 0.75 mT does not provide any evidence to indicate that the working memory of mice was impacted (Sienkiewicz et al., 2001). In summary, the findings of the studies are inconsistent, highlighting the need for more research to elucidate the underlying causes of these contradictions and to ascertain the overall impact of EMW on cognition.

13.2. Anxiety

Anxiety is a complex reaction that encompasses both mental and physiological aspects, capable of impacting the overall welfare of both humans and animals. It is frequently extended to human worries and is a flexible reaction to unfamiliar surroundings (Steimer, 2002). So far, scientists have employed diverse behavioral paradigms to examine EMR effects on anxiety-like behavior in animal models. Varghese et al. examined anxiety behavior after exposure to EMR at a frequency of 2.45 GHz with a power density of 7.88 W/m² for a duration of 45 days. Rat anxiety was seen in the Elevated Plus Maze and LDT tests (Varghese et al., 2018). Also, Othman et al. demonstrated that exposure to 2.45 GHz WiFi signal over a period of 20 consecutive days induced an

anxiety like behavior (Othman et al., 2017). Kumar et al. looked at how microwave waves, both modulated and non-modulated, affected the behaviors of mice that resembled depression and anxiety. After a month of exposure, they discovered that behaviors like depression and anxiety were brought on by non-modulated continuous sinusoidal waves at 2.45 GHz with a power density of 0.033 mW/cm^2 (Kumar et al., 2016). It was determined by Zhang et al. that exposure to 1.8 GHz RF-EMF at SAR of 2.7 W/kg for 28 days increased anxiety levels, and that a reduction in GABA and aspartic acid levels may have been responsible for this increase (Zhang et al., 2017). In addition, rats that were subjected to a 900 MHz RF-EMF from a functioning GSM mobile phone with a power density of 146.60 W/cm^2 for a duration of 28 days exhibited behavior resembling anxiety during the elevated plus maze test (Narayanan et al., 2013). In contrast, Keles et al. demonstrated that 25 days of one-hour daily exposure to 900 MHz does not cause anxiety-like behaviour in animals (Keleş et al., 2018). In addition, Arendash et al. discovered that being exposed to 918 MHz at a SAR of 0.25 W/kg does not have any impact on anxiety levels (Arendash et al., 2010).

Klimek et al. conducted a recent study to investigate the potential of 50 Hz, 1 mT, and 7 mT EMW to influence the adaptation of the hypothalamic-pituitary-adrenal (HPA) system. They also examined whether this process is affected by EMF intensity (Klimek et al., 2023). They found that EMF exposure changes the functioning of the HPA axis. Intensity and number of exposures determine the direction and dynamics of this process. There was an adaptive stress response in response to EMFs of 1 mT, but sensitization was observed in response to EMFs of 7 mT. Compared to control animals, exposure to EMFs of 7 mT decreased anxiety-related behavior, while exposure to 1 mT did not change behavior in open field test (Klimek et al., 2023). Also, Kazemi et al. documented that animals subjected to 12 Hz, 0.7 T, and 4 h/day for 1 month had reduced serum cortisol levels and glucocorticoid receptor gene expression (Kazemi et al., 2022). Khajei et al. provided evidence that being exposed to a frequency of 100 Hz, a magnetic field strength of 10 mT, for one hour each day over the course of seven days resulted in a reduction in the overall distance traveled. Furthermore, it resulted in an increase in the duration of time spent on the peripheral zone of the open field test (Khajei et al., 2021). Mahdavi et al. conducted a study to investigate the impact of exposure to ELF-EMF with radiation frequencies of 1 and 5 Hz for varying durations of 1, 3, 7, 12, and 21 days on stress-related behaviors and stress hormones in rats (Mahdavi et al., 2014). Among mice exposed to 5 Hz, stress-related behaviors increased over time, whereas mice exposed to 1 Hz showed no change over time. Furthermore, Adrenocorticotrophic hormone (ACTH) concentrations in plasma increased in both frequencies, whereas corticosterone concentrations decreased overall. Nonetheless, Burman et al. found that exposure to ELF-EMF for 6 weeks does not cause anxiety in rats (Burman et al., 2018). Also, according to Kumari et al. reports, exposure to 7.5 kHz, 12 μT or 120 μT for 5 weeks did not affect anxiety levels (Kumari et al., 2017).

13.3. Mood disorders

Human beings are constantly surrounded by natural and man-made EMFs, which have the potential to impact our emotions and actions (Sher, 2000; Jumain et al., 2017; Ozdemir and Kargi, 2011). This is especially true for individuals with mood disorders, as these fields can negatively affect their overall well-being. In urban areas, where electromagnetic pollution is common, people often experience mood disorders and emotional problems (Sher, 2000; Bagheri Hosseinabadi et al., 2019).

Exposure to ELF-EMF can have harmful effects on brain activity, the nervous system, and cognitive behavior. Specifically, ELF-EMF affects the functioning of the hippocampus, which is a vital part of the brain responsible for cell growth, the creation of new neurons, and memory and learning abilities (Son et al., 2023; Wyszowska et al., 2023).

For instance, a study conducted by Preece et al. found that mothers

who lived within 100 m of high-voltage power lines had an increased risk of depression both before and after giving birth. Similarly, Verkasalo et al. discovered that individuals living within 100 m of a high-voltage power line had a 4.7-fold higher risk of severe depression. Various theories have been proposed to explain the behavioral effects of EMFs. However, the specific mechanisms through which these fields impact mood, behavior, and cognition are still not fully understood.

Recent research has indicated that ELF-EMF disrupts the functioning of the hippocampus, affecting cell growth, neurogenesis (the creation of new neurons), and impairing memory and learning processes.

Put simply, research has found a link between being exposed to LF-EMF and experiencing depression and anxiety in both animals and humans. Studies on rats and people living near power lines have shown higher rates of these mental health issues. Animal studies have also shown that prolonged exposure to EMF can affect the production of adrenal hormones, which may contribute to symptoms of depression. Overall, these findings suggest that both short-term and long-term exposure to EMF can lead to states similar to depression or disruptions in metabolism. According to Kazuyoshi et al. mice exposed to ELF-EMF at 3 mT for 200 hours had increased secretion of corticosterone, resulting in depressive and anxious behaviors. A study demonstrated that exposure to static magnetic fields significantly increases depression, anxiety, and sleep disorders among workers in a copper electrolysis unit (Jumain et al., 2017).

In simpler terms, research has found a link between being exposed to LF-EMF and experiencing feelings of depression and anxiety in both animals and humans. Studies on rats and people living near power lines have shown higher rates of these mental health issues. Animal studies have also shown that prolonged exposure to EMF can affect the production of hormones related to stress, which may contribute to symptoms of depression. Overall, these findings suggest that both short-term and long-term exposure to EMF can lead to similar states as depression or disruptions in metabolism. Researchers have also found that exposure to EMF among electric utility workers may lead to depression and suicidal behavior. Therefore, chronic exposure to EMF may be a significant risk factor for poor sleep quality, stress, anxiety, and depression (Klimek et al., 2023; Bagheri Hosseinabadi et al., 2019).

One specific neurotransmitter, dopamine plays a role in regulating hormone secretion and has been found to be affected by EMF exposure. Studies have shown that EMF exposure can reduce dopamine production in the brain, leading to issues with arousal, learning, and memory. Another neurotransmitter, serotonin is involved in regulating mood, cognition, and sleep. EMF exposure has been found to increase serotonin levels in the brain, which can disrupt learning and memory abilities. The complex interactions between different neurotransmitters in the brain make it difficult to determine the exact effects of EMF on each one. Additionally, EMF exposure can activate the HPA axis, which is responsible for the body's stress response. The intensity of EMF exposure determines whether it has a positive effect on brain plasticity or a negative effect on stress response, potentially increasing the risk of stress-induced disorders (Jumain et al., 2017; Sher, 2000), Table 6.

14. The model description under electromagnetic field from computational neuroscience

Electromagnetic fields can have a significant impact on the electrical and chemical activities within the brain, resulting in changes to cognitive functions. Diffusive ions create an electromagnetic field that regulates membrane potential, while external energy disrupts the balance between magnetic and electric fields in cells. This energy flow is crucial for activating biophysical functions and maintaining synaptic connections in neurons (Ma, 2023). Computational models and memristors play a vital role in understanding how these fields affect neural dynamics. Memristors, which are capable of simulating synaptic connections, enable researchers to model the influence of electromagnetic fields on neural activity patterns, offering valuable insights into their effects on

Table 6

The effect of EMFs on cognition and mood.

Reference	Subject	EMF frequency	Power density	SAR	Exposure time	Techniques used	Results and discussion
(Wang et al., 2023)	Wistar rat	1.5-GHz	5, 30, 50 mW/cm ²		6 min	Morris water maze	1.5-GHz microwaves caused memory dysfunction in a dose-dependent manner.
(Wang et al., 2023)	Wistar rat	2.856 GHz and 9.375 GHz	10 mW/cm ²		6 min/day 5 day/week For 6 week	Morris water maze	There was a deterioration in the ability of spatial reference learning and memory.
(Qin et al., 2022)	Adult male mice	4.9 GHz (5 G)	50 W/m ²		1 h/day for 21 day	Y maze Open field test	The anxiety-related behaviour and memory capacity of mice were unchanged.
(Rui et al., 2022)	Sprague–Dawley rats	5.8 GHz	74.25 W/m ²	1.15 W/kg in Whole-body 2.33 W/Kg in Brain	2 or 4 h/day for 15 day	Morris water maze Novel object recognition Fear conditioning	5.8 GHz microwave did not significantly affect the learning and memory process.
(Hasan et al., 2022)	Swiss albino male mice	2400 MHz	738 µW/cm ²	2.7 W/kg	40 or 60 min/day for 60 days	Elevated plus-maze	The microwave irradiation resulted in elevation in anxiety-related behavior.
(Zhu et al., 2021)	Male Wistar rats	1.5 and 4.3 GHz	10 mW/cm ²		6 min	Morris water maze	Performance in spatial learning and memory was negatively impacted by the microwave irradiation.
(Tan et al., 2021)	Wistar rats	2.856 and 1.5 GHz	10 mW/cm ²		6 min	Morris water maze	The exposure to 2.856 GHz and 1.5 GHz resulted in a decrease in memory.
(Sharma and Shukla, 2020)	Male Wistar rats	900 MHz	7.737 µW/m ²	0.231 W/kg	1 h, 2 h, 4 h/day For 90 day	T-Maze	Working memory decreased in a time-dependent manner.
(Varghese et al., 2018)	Female Sprague Dawley rats	2.45 GHz	7.88 W/m ²		4 h/day for 45 day	Elevated plus maze Light dark box Object recognition Morris water maze	The rats subjected to 2.45 GHz radiation had a decrease in memory function and displayed anxious behavior.
(Keleş et al., 2018)	Male Sprague Dawley rats	900 MHz			1 h/day for 25 days	Passive avoidance test Radial arm maze test Y-maze	There was no noticeable alteration in learning and memory.
(Zhang et al., 2017)	Male C57BL/6 mice	1.8 GHz		2.7 W/kg in whole body 2.2 W/kg in brain	6 h/day for 28 days	Open Field Test Elevated Plus Maze MorrisWater Maze	RF exposure had no impact on spatial memory, but it elevated anxiety levels.
(Tan et al., 2021)	Male Wistar rats	2.856 and 1.5 GHz	5 and 10 mW/cm ²		6 min	Morris water maze	Both spatial learning and memory declined.
(Othman et al., 2017)	Male Wistar rats	2.45 GHz			2 h/day for 20 days	Elevated plus maze Morris water maze	The rats exhibited anxiety-like behavior, but their spatial learning and memory skills were not affected.
(Altun et al., 2017)	Male Wistar rats	900 MHz	1 ± 0.4 mW/cm ²	2 W/kg	1 h/day for 15 days	Passive avoidance	There was a decrease in memory.
(Kumar et al., 2016)	Male Swiss mice	2.45 GHz modulated with a 400 Hz sinusoidal wave form or a continuous sinusoidal wave	0.029 mW/cm ² and 0.033 mW/cm ²	0.019 W/Kg and 0.023 W/Kg	2 h/day for 30 days	Elevated plus maze Open field	Exposure to non-modulated microwave radiation, as opposed to modulated microwave radiation, resulted in anxiety-like behavior.
(Wang et al., 2015)	Male Wistar rats	2.856 GHz	50 mW/cm ²	15 W/kg in whole body 35 W/kg in brain	6 min	Morris water maze	The rats exhibited deficiencies in spatial learning and memory.
(Shahin et al., 2015)	Male Swiss mice	2.45 GHz	0.0248 mW/cm ²	0.0146 W/Kg	2 h /day for 15, 30 and 60 days	Morris water maze	Microwave radiation exposure resulted in learning and memory impairments according to a time-dependent pattern.

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Table 6 (continued)

Reference	Subject	EMF frequency	Power density	SAR	Exposure time	Techniques used	Results and discussion
(Deshmukh et al., 2015)	Male Fischer–344 rats	900, 1800 and 2450 MHz		5.953×10^{-4} , 5.835×10^{-4} and 6.672×10^{-4} W/kg	2 h/day for 180 days	Elevated plus maze Morris water maze	Microwave exposure caused a decline in cognitive function.
(Maaroufi et al., 2014)	Male Wistar rats	900 MHz		0.05 W/kg minimum and 0.18 W/kg maximum	1 h/day for 21 days	Morris Water Maze 8-Arm radial maze Object exploration	Rats subjected to EMF displayed impairments in the object exploration test, while their performance in memory tests remained unaltered.
(Wang et al., 2013)	Male Wistar rats	2.856 GHz	5, 10 and 50 mW/cm ²		6 min	Morris water maze	Exposed rats demonstrated notable deficiencies in their ability to learn and remember spatial information.
(Hao et al., 2013)	Male Wistar rats	916 MHz	10 W/m ²		6 h/day for 10 weeks	8-Arm radial maze	Although rats' learning and memory were negatively impacted by EMF, they were able to adjust with time.
(Narayanan et al., 2013)	Male Wistar rats	900 MHz	146.60 μ W/cm ²	1.15 W/kg	1 h/day for 28 days	Elevated plus maze	Mobile phone radiation resulted in anxiety-like behavior.
(Ntzouni et al., 2011)	C57BL/6 mice	mobile phone radiation		0.22 W/kg	acute exposure or 90 min/day for 17 and 31 day	Object recognition	Prolonged exposure to mobile phone radiation leads to cognitive deficits in memory.
(Fragopoulou et al., 2010)	Balb/c male mice	900 MHz		0.41–0.98 W/kg	30 min or 9 h for 4 days	Morris water maze	Exposed animals showed deficits in learning and memory
(Arendash et al., 2010)	Normal and transgenic mice Alzheimer's disease	918 MHz		0.25 W/kg	2 h/day for 7 months	Radial arm water maze Y-maze	The exposure to EMF demonstrated positive effects on cognitive function in both normal mice and transgenic mice.
(Daniels et al., 2009)	Male and female Sprague-Dawley rat	840 MHz	60 μ W/m ²		3 h/day from day 2 to day 14 after birth	Morris water maze Open field	The spatial memory assessment did not reveal significant differences, but behaviors linked to stress were observed.
(Klimek et al., 2023)	Wistar rat	50 Hz, 1 or 7 mT			1 h/day for 3 week once every 3 weeks	Open-field	1 mT EMF triggered an adaptive stress response, whereas 7 mT EMF led to sensitization.
(Kazemi et al., 2022)	Macaque monkeys	12 Hz, 0.7 μ T			4 h/day for 4 week	Visual memory response task	Exposure to the 12-Hz frequency resulted in an enhancement in visual memory.
(Khajei et al., 2021)	Wistar rats	100 Hz, 10 mT			1 h/day for 7 days	Morris water maze Open field	The use of EMF in the kindling + EMF group resulted in the restoration of learning and memory. Also, EMF resulted in anxiety-like behavior.
(Gao et al., 2021)	Sprague-Dawley rats	50 Hz, 1 mT			2 h/day for 28 days	Morris water maze	ELF-EMF exposure improves memory restoration in rats with brain ischemia.
(Li et al., 2019)	Sprague-Dawley rats	20 Hz, 10 mT			2 h/d for 10 days	Morris water maze	ELF-EMF enhanced learning and memory in STZ-induced dementia.
(Karimi et al., 2019)	Male Wistar rats	50 Hz, 1 μ T, 100 μ T, 500 μ T, and 2000 μ T			2 h/day for 60 days	Morris water maze Elevated plus maze Passive avoidance learning	Exposure to ELF-EMF enhanced memory retention, but not memory acquisition. Also, it induced the formation of an anxious state.
(Akbarnejad et al., 2018)	Wistar rats	50 Hz, 10 mT			14 days	Morris water maze	ELF-EMF improved the A β injection-induced learning and memory impairments.
(Mahdavi et al., 2014)	Male Wistar rats	1 and 5 Hz, 0.1 mT			1, 3, 7, 14 and 21 days	Open field	5 Hz ELF-EMF increased stress-related behaviors.

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Table 6 (continued)

Reference	Subject	EMF frequency	Power density	SAR	Exposure time	Techniques used	Results and discussion
(Foroozandeh et al., 2013)	Male and female mice	50 Hz, 8 mT			4 h immediately after the learning session	Passive avoidance task	Memory consolidation was severely impacted by ELF-EMF exposure.
(Foroozandeh et al., 2011)	Male and female mice	50 Hz, 8 mT			60 min immediately before the learning session	Passive avoidance task	Exposure to ELF-EMF had devastating effects on learning.
(Jadidi et al., 2007)	Male Wistar rats	50 Hz, 2 or 8 mT			20 min immediately after training or shortly before retention testing	Morris water maze	Acute exposure to ELF-EMF impaired consolidation of spatial memory.
(Sienkiewicz et al., 2001)	Male C57BL/6 J mice	50 Hz, 0.75 mT 7.5 mT and 75 mT			45 min	Novel object	Acute exposure to 50 Hz did not impact non-spatial working memory.
(McKay and Persinger, 2000)	Male Wistar rats	50 Hz, 200–500 nT			60 min	8 arm radial maze	Exposures to ELF-EMF immediately after the training session resulted in a decline in spatial memory.
(Sienkiewicz et al., 1998)	Male C57BL/6 J mice	50 Hz, 7.5 μT and 7.5 mT			45 min prior to testing sessions	8-arm radial maze	Exposure to ELF-EMF led to temporary memory reductions, which were influenced by the intensity of the magnetic field.
(Sienkiewicz et al., 1998)	Male C57BL/6 J mice	50 Hz, 0.75 mT			45 min prior to testing sessions	8-arm radial maze	Exposure to ELF-EMF led to temporary memory reductions.
(Lai et al., 1998)	Male Sprague–Dawley rats	60 Hz, 1 mT			1 h immediately before each training session and 1 h after the last training session	Morris water maze	Spatial memory was affected negatively by the ELF-EMF exposure.
(Lai, 1996)	Rat	60 Hz, 0.75 mT			45 min immediately before each training session	12-arm radial maze	The exposure to ELF-EMF resulted in spatial learning deficit.

cognition.

Memristors are electronic components that can store memory, making them well-suited for simulating neurons and synapses. When utilized as artificial synapses in neural models, they can modify the strength of neural connections, facilitating synchronized activity among neurons. This integration can lead to the creation of neural circuits that process information in a manner similar to the human brain, with promising applications in artificial intelligence, robotics, and information processing. Due to their unique characteristics, memristors are considered excellent candidates for functioning as synapses in brain-inspired computational architectures (Junsangsri and Lombardi, 2012). Additionally, due to their history-dependent resistance, effectively replicate neural dynamics and enable the creation of compact artificial synapses and neurons for efficient on-chip operations (Zhang et al., 2020). From a dynamical viewpoint, memristor-based regulation and coupling introduce nonlinear terms and energy balance, leading to synchronized neural firing in nonlinear circuits (Yang et al., 2024).

From a physical standpoint, each neuron in a multi-layer network is embedded in an overlapping field node, resulting in continuous ion exchange between intra- and extracellular environments. This induces coexisting magnetic and electric fields, making it challenging to study the network's collective behavior when neuron coupling is influenced by varying field ratios. Recent studies suggest that considering synaptic plasticity and memristive synapse function makes synchronization stability and transition more interesting in neuronal signal processing and communication (Sharma et al., 2019; Zayer et al., 2019).

For instance, when neurons or neural circuits are subjected to electromagnetic radiation, the coupling mechanisms or interconnected synapses are capable of harnessing energy in the following manner:

$$\begin{cases} \&H_c = 0.5C'(v_1-v_2) + c_1H_{ext}, \\ \&H_L = 0.5Li_L^2 + c_2H_{ext}. \end{cases}$$

In this context, L refers to the equivalent inductance of the coupling

synapse, while v_1 and v_2 represent the membrane potentials of the neurons, which also correspond to the output voltages from the terminals of the neural circuits. HC and HL refer to the energy stored in the coupling capacitor and the induction coil, respectively. H_{ext} denotes the energy flow from electromagnetic radiation, while c_1 and c_2 are coefficients related to energy absorption. These coefficients are linked to the intrinsic properties of the media and neurons (Ma et al., 2019). On the other hand, inductor coupling bridges magnetic field coupling by balancing the energy estimated as $H=0.5LiL^2$, where L is the inductance and i the current across the coupling induction coil (Lv et al., 2019).

Electromagnetic fields significantly influence neural networks and cognitive changes, highlighting the need for neuron models that incorporate auditory, visual, and perceptual effects. Traditional models often overlook electromagnetic variables, complicating the estimation of neuronal activities. Understanding synapse coupling as field coupling can enhance insights into neurodynamics, while noise plays a crucial role in mode transitions. Reliable neuron models must include biophysical effects to accurately estimate electrical activity modes, and field coupling in multiscale networks offers new perspectives for optimizing signal propagation and energy efficiency.

15. Conclusion

The studies discussed in this review determined that exposure to EMFs, depending on the pattern and amount of radiation, has very different effects on the remodeling of the neuronal system and changes in the cognitive processes resulting from these neuronal changes. These alterations include changes in neurogenesis, apoptotic pathways, gene expression, epigenetic mechanisms, neuronal transmissions, synaptic plasticity, also functional and structural changes in glial cells, ion channels, BBB and dendritic spine that affect cognitive and behavioral consequences. However, in many cases, ELF-EMF seems to act as a neuroprotective and cognitive-enhancing agent, while often, long-term

exposure to high-frequency EMFs causes changes in the nervous system that lead to cognitive impairments. Anyway, more detailed complementary studies with detailed methodologies should be designed to determine the exact mechanisms of EMFs on neuronal change and cognition.

CRedit authorship contribution statement

Hadi Aliakbarian: Writing – review & editing, Methodology, Conceptualization. **Mohammad Ismail Zibaii:** Writing – review & editing, Conceptualization. **Tayeb Ziveh:** Writing – original draft, Data curation. **Fazel Moshrefi:** Writing – original draft, Data curation. **Shima Abtin:** Writing – original draft, Data curation. **Abbas Haghighiparast:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Mostafa Rezaei-Tavirani:** Writing – review & editing, Methodology, Conceptualization. **Amirmohammad Farrokhi:** Writing – original draft, Data curation. **Zahra Aalidaei:** Writing – original draft, Data curation. **Fatemehsadat Seyedaghamiri:** Writing – original draft, Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

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