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Effect of Mobile Phone Radiation on Neurobehaviour: Possible Mechanisms from Preclinical Studies

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Abstract

Excessive usage of gadgets Emitting Electromagnetic Radiation (EMR), especially smartphones, by people of all age groups, and so forth chronic exposure to the radiation, were indeed sounding the alarm about a multitude of health risks. The nervous system was significantly affected, altering the brain and behavior of people and animals. Many preclinical experimental studies have been performed to uncover the pathways that lead to injury, but the results have been contradictory. A strategic search was conducted to identify studies published between 2011 and 2020, using electronic databases such as PubMed and Science Direct. Based on predefined criteria, studies were identified for study and assessed individually. All of the included studies were assessed for the risk of bias, and no study was found to be free of bias. In preclinical research, heterogenicity was detected in the exposure settings (EMF-RF type, MW, pulsed, SAR value, and length of exposure) after a thorough assessment of the studies included. Exposure to mobile phone radiation can produce oxidative stress, which can lead to the activation of apoptotic and necrotic pathways if not reversed in time. The available scientific literature is insufficient to draw particular conclusions, but the possibility of harmful impacts cannot be ruled out, according to the authors. There is a great need to restrict extensive investigations and instead conduct a systematic and complete blinded study with significant reproducibility and long-term research. This review intended to explain the potential mechanisms and risks associated with mobile phone radiation exposure.

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1. Introduction

The spectacular surge in mobile phone use among young people raises worries about the potential negative effects of mobile phone radiation exposure on higher brain functioning at the cellular and molecular levels[1]. The Radio Frequencies (RF) for cell phones are system-dependent and range from 900 to 1800 MHz [Global System for Mobile Communications (GSM)] and 2200 MHz [Universal Mobile Telecommunications Systems (UMTS)][2]. The Federal Communications Commission (FCC) in the United States, as well as the International Commission on Non-Ionizing Radiation Protection (ICNIRP) in Europe and several other nations, have established safe RF electromagnetic energy levels ranging from 3 kHz to 300 GHz.[3]. The intensity and duration of RF exposure have a significant impact on the biological effects. Several research indicates researched the impact of RF radiation on various organ systems in humans and animals[4], such as the central nervous system[5,6], endocrine system[4,7], liver [8], kidney[9], male and female reproductive systems[10], blood cells, and immune function[11]. Although the biological effects of mobile phones are unknown, their electromagnetic radiation may interfere with cell function[12]. Because of the increased tissue damage, electromagnetic radiation exposure can be considered a stressor[13].

Brain damage is a risk because of the increased use of mobile phones over the ear for extended periods. The electromagnetic radiation and microwave radiation emitted by mobile phones can damage the brain proteome, Ca++ binding proteins, hippocampal pyramidal cells, and neuronal connections by generating reactive oxygen species, which affect cognitive and behavioural functions in experimental animals[14–16].

Notwithstanding the studies, no solid evidence exists that high-frequency electromagnetic fields are detrimental to memory function. On the contrary, the initial evidence showed that long-term exposure to GSM 918 MHz, Specific Absorption Rate (SAR) value of 0.25 W/kg) produces cognitive benefits in genetically modified Alzheimer's mice[17]. The lack of a recognized mechanism has spurred more disagreement, and more research is needed to understand the mechanics underlying the harmful effects of mobile phone radiation on neurobehavior. The potential pathways of neurobehavioral changes caused by mobile phone usage are discussed in this paper.

2. Methods

Our study used a broad search strategy to find peer-reviewed original studies published in electronic databases such as PubMed and Science Direct in 2011-2020. The MeSH and associated accessible terms "Cell

Table 1. Database search strategy

Database	Year	Search strategy	No of articles
Pub Med, EMBASE, Web of Science, Google Scholar, Science Direct.	2011 – 2020 Date of search October 2020	Mobile Phone Radiation OR Neurobehavioral Changes OR EMR Exposure OR GSM OR TDMA OR CDMA OR FDMA OR EDGE OR UMTS OR Memory OR Neurobehaviour OR 900 MHz mobile phone radiation OR behaviour OR electromagnetic radiation.	230

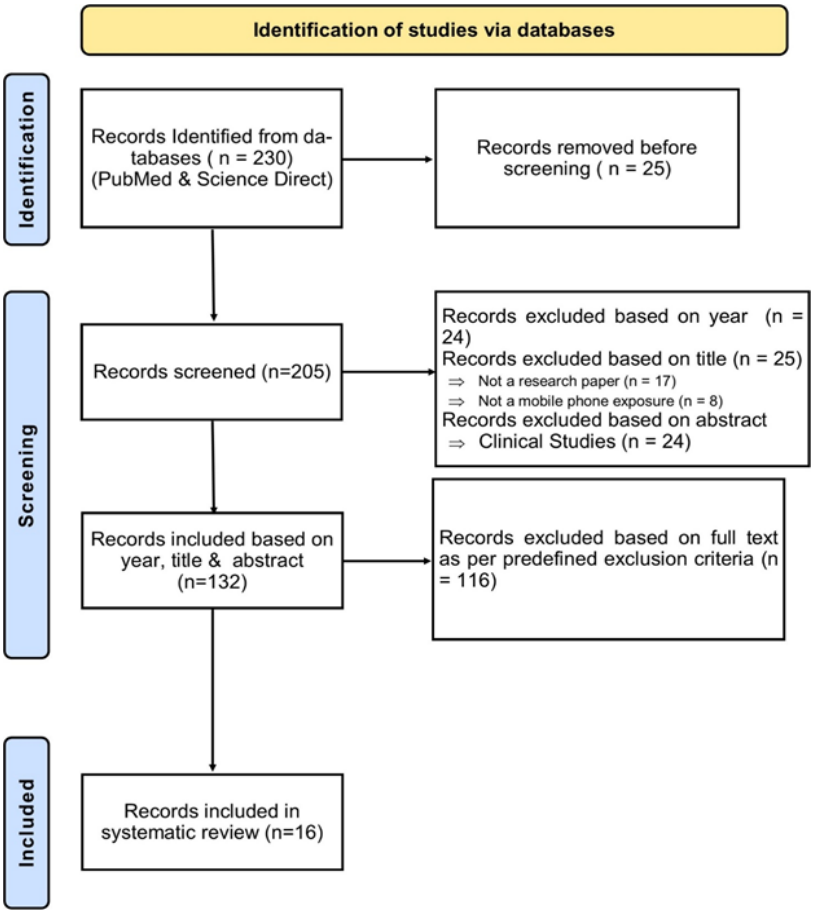


Figure 1. PRISMA flow diagram of study selection and inclusion.

Phone Radiation," "Neurobehavioral Effects," "EMR Exposure," in combination or individually, have been used in database searches. The search strategies are presented in Table 1. Full-text articles were selected for review according to the inclusion criteria. References from the resulting research articles and reviews were used to identify relevant publications. Preferred reporting items for systematic reviews and Meta-analyses (PRISMA) were used to demonstrate the quality of the review according to its checklist and represented the study design in a 4-phase flow chart (Figure 1).

2.1 Inclusion Criteria

2.1.1 Studies have used laboratory rodents as experimental animals to evaluate mobile phone radiation-induced neurobehavioral changes.

2.1.2 Animals with no restrictions on the strain, gender, age, life stage of experimental animals, mobile phone radiation exposure, and outcome assessment.

2.1.3 Only mobile phone exposure was considered without restrictions on the frequency of operation, SAR, signal modulation used, and duration.

2.1.4 Full-text articles from the year 2011 to 2020 only were considered.

2.2 Exclusion Criteria

2.2.1 Studies involving humans and *invitro* Studies

2.2.2 Studies on organ systems other than the brain and behaviour.

2.2.3 Studies that do not use a mobile phone as an exposure system or use a simulated mobile phone exposure system.

2.2.4 Studies with no pertinent information on the frequency of operation, SAR, signal modulation used, and duration.

Investigators assessed the titles and abstracts and obtained copies of articles describing the neurobehavioral changes against mobile phone radiation using inclusion and exclusion criteria. Disagreements between investigators were resolved by consensus after discussion, and the same was done to extract the data.

The risk of bias for each included study was established using SYRCLE's risk of bias tool for preclinical studies[18], and plots were generated using the Risk-of-bias visualization (robvis) tool[19]. Data of the included studies were extracted by the authors, including devices used, signal modulation system, Frequency (MHz), SAR (W/Kg), Duration, Mode, Animals, Age (Days),Sex, Number of Animals, Time of Outcome Measurement (Days), Outcome Measures, and Results.

3. Results

3.1 Description of Studies

We identified 230 articles from the databases Pub Med and Science Direct. The initial screening of titles and abstracts excluded 25 studies after deduplication[20]. A total of 210 studies were selected for full-text screening. Based on predefined criteria, 194 studies were excluded, leaving 16 studies for systematic review. The number of valid publications per year is shown in Figure 2.

3.2 Assessment of Risk of Bias

The risk of bias analysis showed that out of 16 studies, seven studies reported sequence generation; baseline characteristics were similar at the start of the experiment in all studies. Only two studies reported allocation concealment; none of the studies reported random housing, blinding, random outcome assessment, outcome assessor blinding, incomplete outcome data, and selective outcome reporting. Overall, no study was free from the risk of bias (Figure 3).

3.3 Study Characteristics

The study characteristics of the 16 included preclinical studies are reported in Table 2. Of the 16 studies, 19% (*n*=3) of the studies used normal control and exposure control groups, and 25% (*n*=4) used sham control and exposure control. 56 % (*n*=9) of the studies used normal control, sham control and exposure control groups to determine the effects of mobile phone radiation. A total of 81.25% (*n*=13) studies used GSM, 6.25% (*n*=1) used Code-Division Multiple Access (CDMA), 6.25% (*n*=1) of studies used UMTS, and 6.25% (*n*=1) of studies used GSM + Frequency-division multiple access (FDMA) + Time-Division Multiple Access (TDMA) as a system of

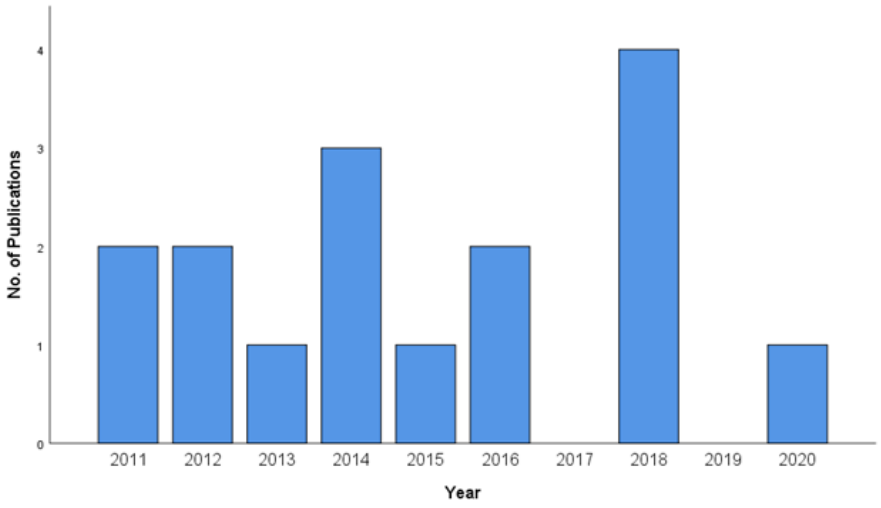


Figure 2. Number of publications per year.

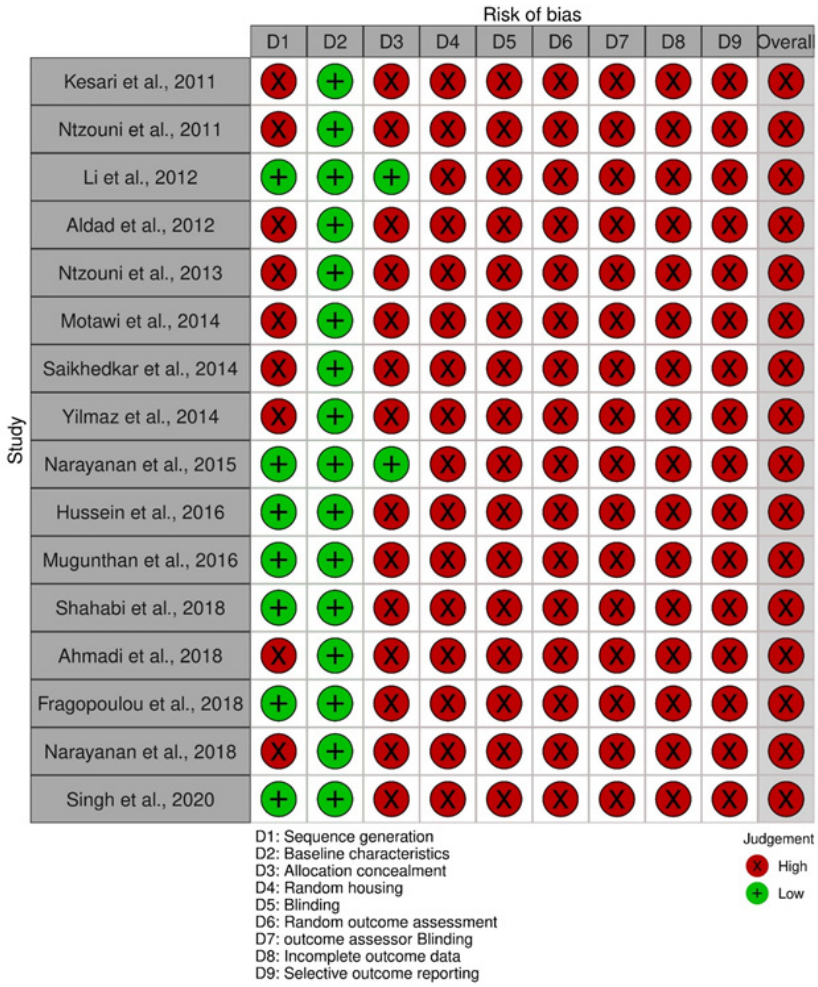


Figure 3. Traffic light plot of risk of bias.

radiation exposure. One study reported a sample size calculation[21].

Moreover, the frequency range used was 900–2100 MHz and SAR from 0.029 W/Kg to 1.69 W/Kg. The duration of exposure ranged from 5 min/day to 1440 min/day in the included studies. parameters assessed to evaluate the effects of mobile phone usage reported in the studies were listed in Table 2.

4. Possible Mechanisms of Electromagnetic Radiation from Mobile Phone

Radiation is a form of energy transmitted through space, either in waveform or in particles. Radiation with oscillating electric and magnetic fields travelling at the speed of light through space is called Electromagnetic Radiation (EMR)[22]. Apart from natural sources such as earth, sun, and ionosphere emitting EMR, many artificial sources such as radar, communication equipment, mobile phone base stations, substations, high voltage lines, radio, television transmitters, and electrical equipment emits a broad spectrum of EMRs (Figure 4). Radiofrequency – electromagnetic radiation (RF-EMR) causes considerable health hazards. However, it is one of the forms of non-ionising radiation which has no sufficient energy to ionise atoms or molecules. Technological advancement and utilisation of technical devices are running parallel in this century, influencing an individual's lifestyle. Among the technical devices, communication devices, mainly

Table 2. Study characteristics

References	Device Used	Signal Modulation System	Frequency (MHz)	SAR (W/Kg)	Duration	Mode	Animals	Age (Days)	Sex	Number of Animals	Time of Outcome Measurement (Days)	Outcome Measure	Result
37	mobile phone	GSM+ FDMA+ TDMA	900	0.9	2 h per day for 45 days	missed call/ 1min	Wistar rats	35	Male	12	45	Oxidative parameters	Significant oxidative damage was observed.
27	mobile phone	GSM	1800	0.22	90 min/ day for 30 days	Calling	C57BL/6 mice	45	Male	24	30	Short term memory using object recognition test	No significant effect during acute exposure and significant change during chronic-I exposure and reversibility of the effect during chronic II exposure was found
28	mobile phone	GSM	900	0.52 to 1.08	120 min/ day for 30 days	Calling	Wistar rats	56	Both	60	30	Learning and memory assessed by Morris water maze, Histopathology of the hippocampus CA1 region	Significant impairment in spatial learning and reference memory morphological changes in Hippocampal neurons in CA1 region

29	mobile phone	GSM	800–1900	1.6	24 h per day for 17 days	Calling	CD-1 mice	112	Both	169	20	Memory was assessed using an object recognition test, anxiety was tested using light-dark box and step-down assay	Hyperactivity, decreased anxiety and memory.
21	mobile phone	GSM	1800	0.11	90 min daily for 66 and 148 days	Calling	C57Bl/6J mice	42	Male	48	66	Spatial and non-spatial memory test using object recognition test and object location test	Transient memory deficits were observed.
44	mobile phone	GSM	900	1.13	120 min/ day for 60 days	Calling	Wistar rats	21 and 70	Male	36	60	Conjugated Dienes Protein Carbonyls Total Antioxidant Capacity Total Oxidant Status Tumour Necrosis Factor-Alpha Caspase-3 Protein DNA Fragmentation Histo pathological Examination	Significantly increased the levels of oxidative stress biomarkers. Apoptosis caused some histo pathological changes in brain tissue with an excellent possibility for neuronal damage.
31	mobile phone	GSM	900	0.9	4 hours per day for 15 days	Calling	Wistar rats	30	Male	27	15	Morris water maze test for memory and open field test and elevated plus maze test for anxiety and locomotor behaviour, antioxidant parameters and histological study	Reduced spatial memory and learning in animals but not significant, significant change in the antioxidant's status in brain and liver, observed significant neuronal damage in histology.
54	mobile phone	GSM	1900-2100	0.003 - 0.288	35 min per day for 28 days	Calling	Wistar rats	84	Male	30	30	Immuno histopathology	Significant effect on apoptotic and anti-apoptotic proteins in the brain tissue

30	mobile phone	GSM	900	1.15	1 h/day for 28 days	Missed calls	Wistar rats	28	Male	72	28	Spatial learning using Morris water maze and histopathology	Chronic and repeated RF-EMR exposure from a mobile phone altered spatial cognition to an extent in rats, as demonstrated by their deficits in progressive learning, consolidation and retrieval of spatial information in a spatial cognition testing paradigm. It also induced dendritic remodelling and decreased viable cell number in the CA3 region of the hippocampus.
40	mobile phone	GSM	1800	0.6	120 min/ day for 60 days	Calling	Wistar rats	120	Male	40	90	Oxidative study and histology	Significantly lead to oxidative stress and apoptosis to brain tissue
58	mobile phone	GSM	900 to 1800	1.6	48 minutes/ day	Calling	mice	neonates	both	72	30-180	Histo morphology	Caused reduction in the density of neurons in the hippocampus region of CA1, CA2 and DGDB; increased neuron density in CA3 and DGVB region. Similarly, significantly lower nuclear diameter in the hippocampus region of CA1, CA2, CA3, and DGDB & DGVB of 2G exposed neurons.

																	Significantly enhanced the level of ACTH and cortisol hormones over time, structural changes in brain
55	mobile phone	CDMA	900	1.01	6 Hr/day for one month	Calling	Wistar rats	42	Male	32	90	ACTH and cortisol assessment, Histology					
32	mobile phone	GSM	900	0.69	30 min/ day for 28 days	missed call/ 35 sec at an interval of 15 sec	Wistar rats	84	Male	280	28	Inhibitory avoidance (IA) memory performance as well as the involvement of endogenous opioids and nitric oxide (NO) and histology					Impairment of memory
59	mobile phone	GSM	1800	0.366	2hr	Calling	C57BL/6 mice	42	Male	16	1	Hippocampal lipidome and transcriptome					alters the levels of several lipids and also the expression of a multitude of genes in the mouse hippocampus
33	mobile phone	GSM	900	1.15	1hr/day for 28 months	Calling	Wistar rats	28	Male	36	28	Light-dark chamber test, caspase-3 activity in the amygdala, hippocampus, and prefrontal cortex.					Hyperactivity-like behaviour was observed, and brain caspase-3 activity did not change.
34	mobile phone	UMTS	1915	0.36	2hr/day for 16 weeks	Calling	Wistar rats	42	Male	12	112	Fear memory, hippocampal oxidative stress, level of circulatory PICs, and stress hormones were assessed					Oxidative stress, inflammatory response, and HPA axis deregulation were induced.

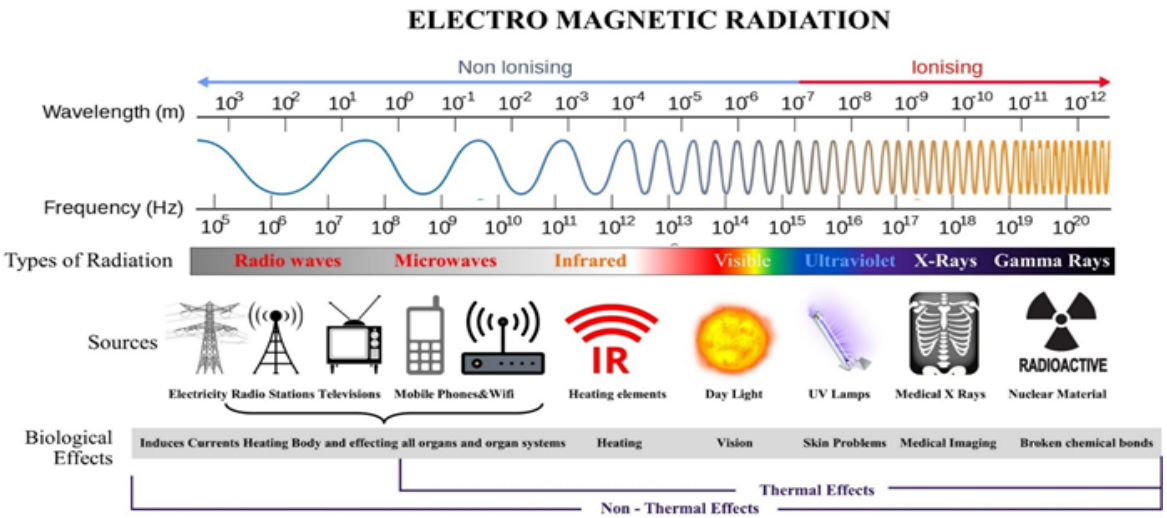


Figure 4. Electromagnetic radiation and its effects.

mobile phones, are widely used for longer durations by all age groups, especially children. The advancement in technology makes life easier and causes serious health issues due to uncontrollable exposure. Majorly stress and associated problems such as headache, tiredness, impairment of behavioural and cognitive functions resulted from the exposure to radiations emitted from mobile phones were reported by several clinical and non-clinical studies[13,23,24].

The electromagnetic waves, based on the conductivity of the exposed object and frequency of the source, are either reflected, refracted, transmitted, or absorbed when conceded from one to another medium. Absorbed EMF energy can be converted to another form of energy[23]. The EMF released from mobile phones can impact the cellular metabolic process and wield several biological effects of thermal or non-thermal mechanisms[25]. Thermal effects are primarily understood than non-thermal effects, and the results of the research were controversial. Non-thermal impacts on biological systems are unfathomable within the parameters set by the physics and chemical reaction laws in biological systems.

Non-thermal effects may be caused by the oscillatory force generated by a high energy electric field of an EMF, which causes every free ion on either side of the bi-lipid layer to cross and disrupts chemical structures of the cell such as ion channels and other biomolecules of the plasma membrane, impairing cellular functions[26]. Thermal effects occur by converting the absorbed radiation into heat which is stabilised and decreased by blood circulation. Even though the raised body temperature is insufficient to impair body functions, the generated heat can raise the free radical levels in the cells.

EMF energy absorbed by the body is dependent on several factors such as radiation parameters (wavelength, frequency, type of signal (pulsating, triangular, etc.,) polarisation, coupling energy, body grounding, resonant absorption), cellular parameters (cell shape, size, the composition of membranes, organelles, cell junctions, cell cycle stages) and duration of exposure. These parameters are uncontrollable, and it is challenging to distinguish thermal and non-thermal effects at a particular time that makes effect estimation uncertain[23]. Head during handheld use and other parts closest to phone during hands-free use is most commonly exposed to the radiation from mobile phones. EMR in the frequency range of 900 – 2200 MHz can penetrate the cranium and reach the deep brain, altering brain function and behaviour[21,27–34]. The process of mobile phone induced neuronal damage is presented in Figure 6.

4.1 Reactive Oxygen Species and Mobile Phone Radiation

Several studies have found that being exposed to EMF increases oxidative stress. The excessive production of

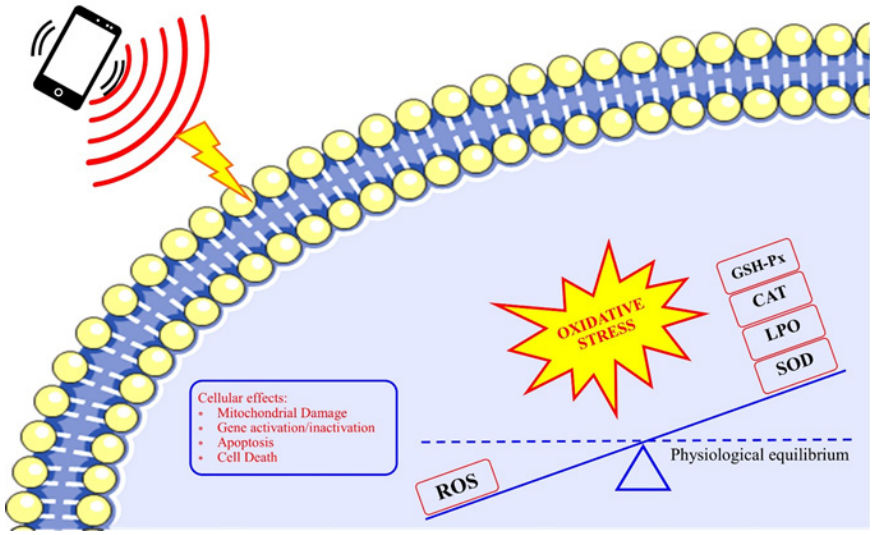


Figure 5. Oxidative stress due to mobile phone radiation.

ROS- Reactive Oxygen Species; GSH-Px- Glutathione peroxidase; CAT- Catalase; LPO-Lipid Peroxidase; SOD- Superoxide dismutase

reactive oxygen species (ROS) or free radicals over the antioxidant defence system is called oxidative stress (Figure 5). ROS are highly reactive small molecules with short half-life mainly derived from the electron-deficient oxygen molecule, an anion of superoxide (O_2^-)[35]. EMF exposure causes the non-enzymatic generation of ROS through thermal and non-thermal actions on the organism. Furthermore, EMF influences the transcription and translation of genes such as JUN, HSP 70, and MYC through the epidermal growth factor receptor EGFR-ras[13,36]. The brain is more susceptible to ROS and oxidative damage than other organs due to its high metabolic rate. It can be seen in the studies reporting a significant increase in ROS levels of serum[37] and hippocampus[34] when experimental animals were exposed to mobile phone radiation resulted in the impairment of neurobehavioral parameters in the exposed animals.

4.2 Antioxidant Mechanisms and Mobile Phone Radiation

Organisms have evolved antioxidant defence systems to control the formation of free radicals and protect themselves from their harmful effects. Antioxidants impact biological systems via a variety of mechanisms, including electron release, metal ion chelation, co-antioxidants, and gene expression maintenance. Assume that EMF exposure has harmed these antioxidant defence mechanisms. In that case, antioxidants may be insufficient, or free radical formation may increase when it overwhelms antioxidant defences[13]. In living organisms, antioxidative systems such as glutathione (GSH), glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD) are present to mitigate the damage caused by ROS and their derivatives[38].

GSH is a vital cellular and endogenous antioxidant that binds to free radicals in the neurons, reducing the hydrogen peroxide's entry and preventing sulfhydryl group oxidation in the protein structure in tissues. It functions as a radical scavenger by acting as a substrate for antioxidant enzymes such as glutathione peroxidase, glutathione reductase (GR), and glutathione-S-transferase (GST). GSH levels fall during the oxidative stress process, while glutathione disulfide levels rise. In this case, the effects of reductase and glutathione peroxidase scavenge the accumulation of hydrogen peroxide (H_2O_2).Another key enzyme that protects phagocytic cells from free radical damage is GPx. Decreased GPx activity results in the accumulation of hydrogen peroxide, cell damage, and the

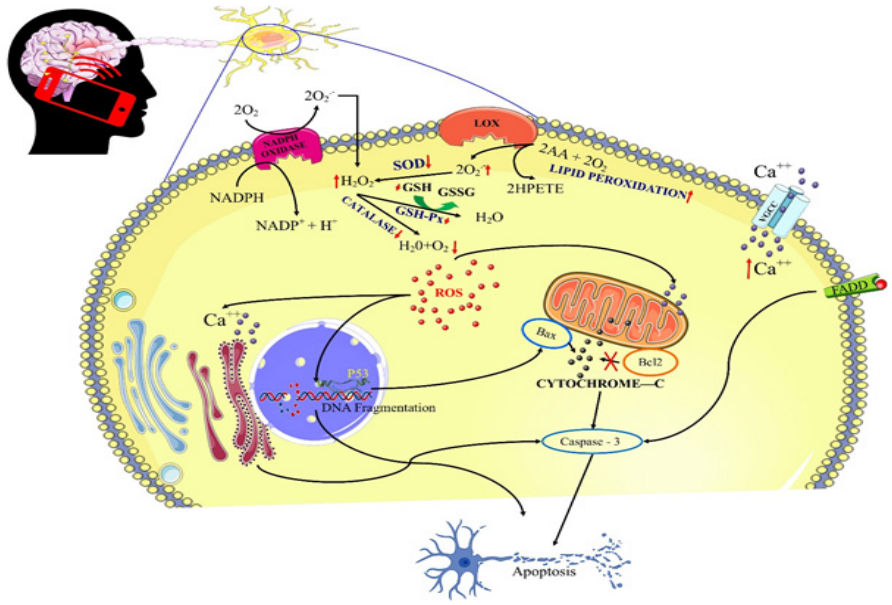


Figure 6. Possible mechanisms of neuronal damage induced by mobile phone radiation. O_2-Oxygen; O_2^-Superoxide; H_2O_2- Hydrogen Peroxide; H_2O-Water; AA-Arachidonic Acid; HPETE- 5-Hydroperoxyeicosatetraenoic Acid; VGCC-Voltage Gated Calcium Channel; FADD- Fas-associated protein with death domain; ROS- Reactive Oxygen Species; LOX-Lipoxygenase; GSH-Px- Glutathione peroxidase; SOD- Superoxide dismutase; Bax- BCL2 Associated X, Apoptosis Regulator; Bcl2- B-cell lymphoma 2 Apoptosis Regulator; NADPH- Nicotinamide adenine dinucleotide phosphate.

prevention of lipid peroxidation. The oxidative stress seen in neurological diseases has been linked to a degraded GSH system in the brain[39]. EMF from mobile phones is known to decrease GSH and GPx levels in the brain. It was in line with the results reported by Saikhedkar et al. (2014). They found that there was a significant decrease in the GSH levels in the brain when exposed the rats to mobile phone radiation (GSM; 900MHz; SAR-0.9 W/Kg) at a rate of 4 hours per day for 15 days[31]. Hussein et al. (2016) found a significant decrease in the levels of hippocampus and cerebellum GSH levels in rats exposed to mobile phone radiation (GSM; 1800MHz; SAR-0.6 W/Kg) at a rate of 2 hours per day for 3 months40. GPx was also assessed in exposed rats' brains and found a significant decrease in its levels compared to control[37,41].

SOD is an enzyme that catalyses the toxic superoxide (O_2) radical conversion to molecular oxygen (O_2) or hydrogen peroxide. As a byproduct of oxygen metabolism, superoxide is produced, causing various types of cell damage. SOD is found in the cytosol and mitochondria, where it deactivates existing superoxide radicals while also protecting cells from their harmful effects[42]. Many studies reported a significant decrease in SOD levels in the brain and in regions like cerebral cortex, hippocampus and cerebellum, leading to a rise in ROS levels[31,37,40].

Lipid peroxidation is a significant biological outcome of oxidative cellular damage and ageing. Lipid peroxidation is the process by which oxidants such as free radicals or nonradical species attack lipids with carbon-carbon double bonds, particularly polyunsaturated fatty acids (PUFAs), resulting in lipid peroxyl radicals and hydroperoxides. Cells may promote cell survival or induce cell death in response to membrane lipid peroxidation, depending on specific cellular metabolic circumstances and repair capacities[43]. EMF is the external factor leading to the generation of LPO and promotes neurodegeneration. The study reported the rise in LPO levels in the hippocampus in the animals exposed to mobile phone radiation[34].

One of the end products of polyunsaturated fatty acid peroxidation in cells is malondialdehyde (MDA). An increase in free radicals causes MDA overproduction. The malondialdehyde level is commonly used to assess oxidative stress and antioxidant status[43]. According to researchers, MDA levels were reduced but not significantly[41], which may be due to oxidation in some cellular structures in brain tissue at the beginning of the study, resulting in resistance against oxidative attacks at the end of the study, but found a significant increase in the exposed group when compared to control groups[31,40].

CAT is an enzyme that degrades hydrogen peroxide to water and oxygen. It is a crucial enzyme in the protection of the cell against oxidative damage caused by ROS. The decrease in its levels leads to an increase in the levels of free radicals and promotes neurodegeneration. was found to be significantly decreased[31,41], and increased levels[37], suggests an overproduction and consumption of enzymes related to increased production of H_2O_2 in vivo by SOD, and hence oxidative damage.

The Total Antioxidant Capacity (TAC) levels were significantly lower relative to their respective control values. Total Oxidant Status (TOS) levels of young rats were significantly decreased, those of adult rats exhibited significant increments[44], and total antioxidant capacity of the hippocampus was also decreased significantly in the exposed group as compared with the control group[34]. Overall, the oxidative stress markers were significantly changed when the animals were challenged to mobile phone radiation, which might be causative for neurobehaviour and neuronal damage.

As discussed above, free radicals have recently been discovered to play a vital role in cellular signalling, particularly in neurons. Free radicals alter the structural and functional integrity of cells through various mechanisms, including lipid peroxidation, sulfhydryl oxidation, proteolysis, and nuclear material shearing, resulting in severe cell injury and cell death via either necrosis or apoptosis. Furthermore, the free radicals produced can damage the respiratory components, increasing free radical production and thus amplifying the overall damaging effect. It can be related to the apoptotic activity in the neuronal cells induced by free radical generation in the brain using mobile phone radiation.

4.3 Apoptosis due to Mobile Phone Radiation

Apoptosis is a well-characterized active process of gene-directed cell destruction presenting distinctive morphological and biochemical features. Cell shrinking, membrane blebbing, chromatin condensation and nuclear fragmentation, followed by the formation of apoptotic bodies that are digested by neighboring cells or macrophages, are the main characteristics of apoptosis[35].

Current findings have shown that Reactive Oxygen Species (ROS) and the ensuing oxidative stress contribute to apoptosis. Changes in the cell's redox status to a more oxidizing environment occur before activating the final phase of caspase activation in several models of apoptosis. A class of enzymes known as 'caspases,' which are cysteine-dependent and sensitive to the cell's redox status, is also a major player in cell death by apoptosis.Caspases inactivate proteins that are essential for cell viability. These enzymes damage the cytoskeleton, shut down DNA replication and repair, interrupt splicing, degrade DNA, disturb the nuclear structure, cause biochemical changes on the cell surface for easy detection by phagocytes, and finally disintegrate the cell to vesicular bodies[45]. In cells undergoing apoptotic cell death in response to oxidative stress, Caspase-3 serves as a confluence point for both mitochondria-dependent and -independent pathways. It is evident from a plethora of studies that ROS increases the levels of caspase 3. Caspase 3 levels increased significantly when the experimental animals were subjected to mobile phone radiation, leading to neurodegeneration due to apoptosis[33,37,44]. TNF, a master regulator of the immune system, plays a crucial role in spreading inflammation through immune cell activation and recruitment. TNF-induced oxidative stress and inflammation both collaborate to promote neurodegeneration[46]. TNF-alpha can damage DNA by releasing reactive oxygen species. TNF-alpha has the same mutagenic effect as ionising radiation[47]. Motawi *et al.* (2014) found increased TNF-α levels in animals exposed to mobile phone radiation[44].

Protein kinase C (PKC) is a group of 11 phospholipid-dependent serine/threonine kinases involved in several pathways that control cell growth, death, and stress response. PKC is involved in regulating the balance between cell survival and death. Its loss of function is often linked to cancer, whereas its increased activity is linked

to neurodegeneration. By phosphorylating transporters, ion channels, and G protein-coupled receptors, PKC has long been involved in regulating neurotransmission and synaptic plasticity. PKC depletion has been linked to tumour development, while ROS-mediated alterations altered PKC activity. PKC has a unique structural feature that makes it vulnerable to oxidant tumour promoters like H_2O_2, and periodate-related tumour promoters activating it EMF may be linked to a decrease in PKC activity, which promotes carcinogenesis[37,48].

Creatine kinase (CK) is an enzyme that plays an essential function in the energy metabolism of neural tissue and may be one of the targets of reactive oxygen species. Creatine kinases are oxidatively sensitive and may be one of the brain's targets of reactive oxygen species. Creatine kinase isoenzymes are precisely positioned in the cell at ATP consumption sites to efficiently renew ATP in situ via phosphocreatine or at sites of ATP synthesis to build up a phosphocreatine pool. As a result, the creatine kinase/phosphocreatine system is essential for cellular energy buffering and energy transport, especially in cells with high and fluctuating energy requirements, such as neurons[49]. An increase in the levels of Creatinine kinase was observed in the animals exposed to mobile phone radiation. Increased CK levels indicate a decrease in CK activity. Changes in CK activity may be involved in a neurodegenerative pathway that leads to neuronal degeneration in the brain. Several studies have confirmed this concept, demonstrating that CK activity is drastically diminished in various neurodegenerative disorders. The decline in CK activity in the brain correlates closely with the markers of neurodegeneration[37].

p53 is a pro-apoptotic protein that is involved in neuronal death. p53 is also involved in oxidative stress-induced apoptosis. In cellular responses to low or high levels of oxidative stress, p53 plays critical yet context-dependent roles. In the presence of moderate levels of oxidative stress, p53 exhibits antioxidant activities that promote cellular survival; in high levels of oxidative stress, p53 exhibits prooxidative activities that cause cellular apoptosis. Both p53's roles can limit oxidative damage in cells, hence maintaining genetic stability. P53 carries out these tasks by directly controlling genes involved in oxidative stress responses or by influencing other pathways involved in oxidative stress responses[50].

Bcl-2 family proteins can be found in the mitochondrial and endoplasmic reticulum as soluble proteins in cytosolic fractions or bound to cytoskeletal elements. Bcl-2 mRNA and protein levels are relatively high in the developing nervous system and significantly lower in the postnatal brain. In the adult peripheral nervous system, Bcl-2 expression remains relatively high in sensory and sympathetic neurons. Several experimental approaches have been used to study the role of Bcl-2 in neuronal programmed cell death. The BCL-2 protein family primarily regulates cell death through direct binding interactions that regulate mitochondrial outer membrane permeabilization (MOMP), which leads to the irreversible release of inter-membranous space proteins, caspase activation, and apoptosis. The predominant interactions between anti-apoptotic and pro-apoptotic BCL-2 family proteins that regulate MOMP are determined by the affinities and relative abundance of BCL-2 family proteins[51–53]. As discussed above, the levels of P53, Bcl-2[54], mRNA expression of Bax/bcl2 [44], were increased in studies that exposed animals to mobile phone radiation, the loaded ROS and resultant biochemicals leads to DNA fragmentation and was found the same in the studies done on the exposure of animals to mobile phone radiation[40,44].

4.4 Histological Damage due to Mobile Phone Radiation

EMR emitted by mobile phone resulting in the eliciting thermal and non-thermal effects on the brain. It generates ROS and overproduces ROS by altering the endogenous antioxidant mechanism in the brain, resulting in the activation of neuronal and neuro-parenchymal damage. This leads to a change in the histoarchitecture of the brain, which is reflected in histological and immunohistological studies—neuronal damage results in changes of behaviour. The alteration in behaviour and histoarchitecture can be correlated with the studies (Table 3). It is known that the brain is responsible for controlling and coordinating many bodily functions. The cerebral cortex contains physical structures responsible for cognition, speech, comprehension, imagination, and visual information processing. It was discovered that rats exposed to mobile phone radiation (900 MHz, SAR-0.99W/Kg) for 4 hours per day for 15 days had resulted in cerebrocortical neurodegeneration which lead to alteration in behaviour and memory, [31]. In the brains of younger rats, chronic exposure to mobile phone radiation resulted in prominent vacuoles, increased eosinophilic plaques, and dark neurons. This indicates a change in neuronal integrity, neurodegeneration, and

Table 3. Impact of mobile phone radiation on neurobehaviour

	Behaviour	Test	Result
[27]	Short-term memory Non-Spatial Memory	Object recognition test	Acute exposure did not affect mice memory, Chronic-I exposure had an impact on the recognition memory.
[28]	Learning & Memory Spatial Memory	MWM	Mobile phone radiation can significantly impair spatial learning and reference memory.
[29]	Learning & Memory Anxiety Fear	Light and Dark Box Object recognition test Step Down assay	Mice exposed in-utero were hyperactive and had impaired memory as determined using the object recognition, light/dark box and step-down assays.
[21]	Spatial Memory Non-Spatial Memory	Object recognition test	Impairment in both memories
[31]	Fear Learning and memory (spatial)	Open field test MWM & Classic maze Elevated plus-maze	General anxiety, Reduction in spatial memory and learning in animals, Reduced anxiety in test rats in Elevated plus-maze.
[30]	Spatial Memory	MWM	Poor spatial memory retention.
[32]	Learning & Memory	Inhibitory avoidance apparatus	Four weeks of GSM radiation impaired IA memory performance, mainly in the memory consolidation phase in rats.
[33]	Place preference behaviour	Light and Dark Box	Altered place preference and hyperactivity-like behaviour
[34]	Contextual fear memory	Contextual fear conditioning test	Alteration in contextual fear memory was not significant enough.

neurodegeneration, which impairs behaviour in the exposed animals[44,55]. Structures beneath the cerebral cortex control movement, consciousness, senses, and other functions. The hippocampus is one of the main structures in the cerebrum's limbic system, connected to the temporal region of the cerebral cortex by several association neurons that connect to all other areas of the brain[56]. The hippocampus comprises the dentate gyrus (DG), CA3, and CA1 regions, all of which play essential roles in forming and reconstructing relational memory representations, which underpin flexible cognition and social behaviour[57]. Several studies have found that neuronal damage in the hippocampal region causes behavioural changes. Morphological changes in the CA1 region, such as mitochondrial degeneration, fewer synapses, and shorter postsynaptic densities[28], neurodegeneration in the DG (dentate gyrus), CA1, and CA3 regions[31], reduced neuron density and nuclear diameter in hippocampus neurons[58], impaired learning and memory behaviour. With vascular congestion, degenerative changes were observed in the hippocampus pyramidal cells, dark cells, and cerebellar Purkinje cells[40].

Moreover, In exposed animals, viable cell count in the dorsal hippocampal CA3 region and dendritic arborisation pattern of both apical and basal dendritic trees were found to be affected in the impairment of cognition[30]. Morphological evaluation of TUNEL

(terminal deoxynucleotidyl transferase dUTP nick end labelling) stained brain sections from mobile phone radiation exposed group revealed several TUNEL positive cells (apoptotic cells) in the amygdala compared to other groups[33]. The damage in the amygdala leads to fearful behaviour and increased anxiety, which is in lieu with the reports[29,33,34]. The studies did not address the levels of neurotransmitters related to the observed changes in the neurobehaviour. Assessment of levels of neurotransmitters could provide a possible explanation for the behavioural changes observed.

Upon examining the included studies, heterogenicity was observed in the exposure conditions (EMF-RF type, MW, pulsed, SAR value, and duration of exposure) and experimental protocols in preclinical studies. It was recognised that technological innovation is a continuous process. As a result, scientists had to investigate advanced systems and study their effects and consequences on animals, which could translate to humans. The observed difference is the ongoing development of mobile phone technology and the study of its effects on various species and age groups. However, alterations in neurobehavior and associated pathologies were found in most studies. We contend that simply increasing the number of studies without addressing the limitations of previous works will not lead to fruitful conclusions and may not contribute to this field. As a result, there is a need to conduct innovative research with sound design and appropriate methodologies that overcome the shortcomings of previous research.

In a nutshell, the findings of the included studies indicate that exposure to mobile phone radiation can cause oxidative stress, which, if not reversed in time, can lead to the activation of apoptotic and necrotic pathways and changes in the brain histomorphology. All of these are manifestations of behavioural changes. These changes are more visible in children and adolescents than in adults.

5. Summary and Conclusion

In conclusion, definitive research on health risks is needed, maintaining the universality of electromagnetic fields and their constant linearity in increasing use without awareness of their harmful effects. The available published evidence was not significant enough to draw specific conclusions, but the possibility of negative consequences cannot be ruled out. Although an established interaction mechanism was lacking, this does not affect the reliability of some studies that have used an appropriate method to reflect the adverse effects of radiation emitted by cell phones. Several credible mechanisms, such as oxidative stress, explain what is observed. There is a great need to limit extensive investigations and instead initiate a systematic and comprehensive blinded study with adequate replication and long-term investigation with follow-up to overcome all the limitations and demerits of previous studies. A standardized methodology with adequate exposure assessment is needed, which is crucial for identifying dose relationships and establishing biological interaction mechanisms. It is more important to validate research findings on achieving endpoints than on similarity and difference studies. In this vast expansion of cell phone technology, it is difficult to protect from radiation. The only way is to keep distance and reduce the use of radiation-emitting devices by adults. It is indispensable to monitor their use by children.

6. Conflict of Interest

None

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