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www.bidgeyayinlari.com.tr - bidgeyayinlari@gmail.com
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CONTENTS

CHAPTER 0

NEUROTOXIC EFFECTS OF ENVIRONMENTAL POLLUTANTS

BEKİR GÜNERİ[1]

MEHMET CİHAN YAVAŞ[2]

[1]Mardin Artuklu University, Graduate Education Institute, Department of Biology, Master's Student
Orcid: 0009-0008-2561-5964.
[2]Assoc. of Prof. Mardin Artuklu University, Faculty of Medicine, Department of Biophysics.
Orcid: 0000-0002-2923-050X.

Abstract

Environmental pollutants are among the significant risk factors for the development of neurological and neuropsychiatric diseases and pose an increasing threat to global public health. This section examines the neurotoxic effects of heavy metals such as lead, mercury, arsenic, and cadmium; air pollutants such as particulate matter, ozone, and nitrogen dioxide; pesticides, endocrine-disrupting chemicals (bisphenol A and phthalates); polychlorinated biphenyls (PCBs), and other environmental toxic agents on the central nervous system in light of current literature. Key mechanisms involved in the neurotoxicity of environmental pollutants include oxidative stress, neuroinflammation, mitochondrial dysfunction, epigenetic changes, disruptions in ion channel and neurotransmitter systems, loss of blood-brain barrier integrity, and altered synaptic plasticity. Furthermore, the relationships between environmental exposures and neurodevelopmental disorders, neurodegenerative diseases, and cognitive function losses are evaluated. This chapter presents a holistic approach to current scientific evidence regarding the effects of environmental pollutants on the nervous system and includes assessments for future research areas.

Introduction

Industrialization, urbanization, and agricultural intensification, which accelerated from the second half of the twentieth century, have brought about an unprecedented transformation in environmental chemical load in anthropological history. Today, hundreds of thousands of chemical substances are used in the human environment, and the neurotoxic potential of the vast majority of these has not been adequately characterized (Landrigan et al., 2018). Environmental pollutants have extremely serious effects on human health. The burden of pollution-related diseases is increasing in both developing and developed countries; however, fully elucidating this relationship is difficult for various reasons. Due to inadequate waste management, poverty, and technological backwardness, measuring exposure levels in developing countries remains quite limited. Exposure to environmental pollutants such as industrial waste, pesticides, automobile exhaust, laboratory waste, and the incineration of terrestrial waste constitutes the main sources of neurotoxicity (Iqubal et al., 2020). Exposure to these sources is a major concern for the public, as particulate matter, nanoparticles, and toxic substances can easily cross the blood-brain barrier and have neurotoxic effects on astrocytes, microglia, and neurons (Shetty et al., 2023).

We assume that this chapter will contribute to a better understanding of the neurotoxic effects of environmental pollutants on brain health. The chapter discusses current scientific research results.

Heavy Metals and Their Effects on the Nervous System

Lead (Pb)

Lead is a dangerous heavy metal that can have serious negative effects on human health and the environment. Exposure to lead in workplaces or through various environmental sources can cause toxic effects by damaging cells. Lead exists in nature and the environment in three main forms: pure (metallic) lead, various lead compounds and salts, and carbon-containing organic lead compounds. Each of these forms can have different levels of harmful effects on living organisms (Aktepe et al., 2022). Human exposure to neurotoxic metals is a public health problem. Therefore, it has been reported that lead exposure in children leads to behavioral and cognitive disorders (Neal et al., 2013). Furthermore, increased lead levels in drinking water can increase lead accumulation in children who drink the water (Edwards et al., 2009). Lead can negatively impact hippocampus-mediated learning and memory processes because it targets the brain's learning and memory processes by inhibiting the N-methyl-D-aspartate receptor (NMDAR) (Morris et al. 1982; Morris et al., 1986). Lead is a toxic heavy metal that can accumulate in the body over time, particularly in bones. While it can affect many organs and systems, the nervous system is one of the most sensitive to the harmful effects of lead. To reduce the neurotoxic effects of lead, it is necessary to provide information and alternative protection programs to the most vulnerable groups in the population, namely children and pregnant women (Singh, et al., 2023).

Methylmercury (MeHg)

Methylmercury (MeHg) is an environmental toxic agent that causes long-term neurological and developmental damage in animals and humans. Although the molecular mechanisms mediating MeHg-induced neurotoxicity have not yet been elucidated, some studies suggest the presence of neurotoxicity caused by oxidative stress-induced toxic substances (Farina et al., 2011). Populations that feed on fish and shellfish are exposed to high MeHg levels (Clarkson et al., 2003).

Methylmercury targets sensory neurons in the peripheral nervous system, triggering cell death mechanisms such as apoptosis, necrosis, and necroptosis. Furthermore, macrophages stimulated by methylmercury release TNF-α, and this cytokine is said to contribute to the development of sensory impairments in Minamata disease by activating additional cell death pathways (Nakano et al., 2024). Mercury poisoning is a serious neurotoxic condition that affects the central nervous system (CNS) in various ways, leading to cognitive, sensory, and motor impairments (Gogia and Kumar, 2025). In an experimental study, zebrafish were reported to experience more severe behavioral disorders, including delayed neuromast development, due to methylmercury exposure during the first 30 days of their development (Oger et al., 2025).

Arsenic (As) and Cadmium (Cd)

Environmental heavy metal exposures such as arsenic and cadmium can enter the human body through contact and ingestion, leading to accumulation in the nervous system and potential cognitive impairment and neurodegenerative damage (Huang et al., 2025). Cadmium reaches nerve tissue by utilizing zinc and calcium transport systems, disrupting the intracellular balance of these ions. After accumulating in the nervous system, it negatively impacts mitochondrial function, reducing ATP production, increasing the formation of reactive oxygen species, and thus leading to oxidative stress. Furthermore, it disrupts the regulation of neurotransmitter release, impairing synaptic transmission, affecting the functions of neurotransmitter signaling proteins, damaging the integrity of the blood-brain barrier, and altering the normal regulation of glycogen metabolism (Arruebarrena et al., 2023). Oxidative stress and mitochondrial dysfunction are among the important mechanisms of neurodegenerative processes. Studies have shown that two different types of arsenic, sodium arsenite and dimethylarsinic acid (DMA), induce apoptosis in rat brain neuron cultures by stimulating the stress-activated p38 and JNK3 MAP kinase pathways. Arsenite, an inorganic form of arsenic, has been reported to exhibit higher neurotoxicity and more significantly reduce neuronal viability compared to DMA. Furthermore, arsenite has been shown to contribute to neuronal damage by selectively activating p38 and JNK3 kinases in cerebellar neurons (Balali-Mood et al., 2021).

Air Pollutants and Neuroinflation

Particulate Matter

Among air pollutants, fine and ultrafine particles (PM2.5 and PM0.1) pose a particular risk for neurological damage. These particles can reach the CNS via multiple pathways depending on their diameter and surface chemistry. This has been shown to have toxic effects on the brain and to be linked to neurological diseases (Qin, et al., 2024). Epidemiological studies on respirable fine particulate matter (PM2.5), one of the best-known indicators of pollution, have shown a strong association with cerebrovascular damage (stroke) and neurological damage in the brain (changes in cognitive function, dementia, psychiatric disorders, etc.), in addition to lung and cardiovascular disease (li et al., 2022). PM2.5 exposure exacerbates the accumulation of β-amyloid, hyperphosphorylated tau, and α-synuclein in Alzheimer's and Parkinson's diseases; these particles intensify neuroinflammation and axonal damage in multiple sclerosis; and in epilepsy, they have been reported to promote neuronal hyperexcitability and recurrent seizures (Robio et al., 2025).

Ozone and Nitrogen Dioxide

Ozone (O_3), a potent oxidant, enters the body through the respiratory tract, producing reactive oxygen species (ROS) and triggering inflammatory processes. Studies show that prolonged O_3 exposure increases oxidative stress, triggering the formation of reactive oxygen species and potentially disrupting the integrity of the blood-brain barrier. This process can affect astrocyte and microglia activation, strengthening neuroinflammatory responses and increasing the production of pro-inflammatory mediators and neurotoxic factors. The resulting neuroinflammation and neuronal damage are reported to be associated with the development and progression of various neurodegenerative diseases, particularly Alzheimer's and Parkinson's disease (Rodriguez et al., 2024). Ozone (O_3) is a significant component of photochemical smog and, due to its strong oxidizing properties, is an air pollutant that causes various adverse effects on the respiratory and central nervous systems (Martínez-Lazcano et al., 2023).

Nitrogen dioxide (NO_2) is a significant component of air pollution, particularly traffic-related pollution. Epidemiological studies have shown that NO_2 exposure is associated with decreased cognitive performance, cortical atrophy, neuroinflammation, and an increased risk of dementia. The effects of NO_2 are largely thought to occur through oxidative stress and inflammatory mechanisms (Cho et al., 2023; Kong et al., 2024). Experimental and mechanistic studies demonstrate that NO_2 causes cellular oxidative/nitrosative stress by increasing the formation of reactive oxygen and reactive nitrogen species, which in turn triggers neuroinflammation, mitochondrial dysfunction, and neuronal damage (Goldstein and Samuni, 2024).

Pesticides: Synaptic Disruption and Neurodegeneration

Organophosphates

Organophosphate (OP) compounds have been among the widely used pesticides for many years and are being intensively researched due to their chronic health effects. Epidemiological and experimental studies show that OP exposure may increase the risk of developing neurodegenerative and neurodevelopmental diseases such as Alzheimer's, Parkinson's, amyotrophic lateral sclerosis (ALS), attention deficit hyperactivity disorder (ADHD), and autism. It is reported that common mechanisms such as cholinergic dysfunction, oxidative stress, neuroinflammation, and epigenetic changes underlie this relationship, and that certain genetic variations, particularly paraoxonase, may affect individual susceptibility (Mostafalou & Abdollahi, 2018). Organophosphates (OPs) represent a broad group of phosphorus-containing organic compounds and are widely used worldwide. These compounds have provided significant benefits in agricultural and industrial production processes as well as in the control of vector-borne diseases. However, exposure to organophosphates with high, moderate, mild, or low levels of toxicity; It can lead to various adverse health effects, primarily affecting the nervous system, such as nausea, vomiting, muscle fasciculations, tremors, and convulsions. Recent studies have shown that organophosphate pesticide exposure may be a potential risk factor in the development of neurological diseases such as dementia, neurodevelopmental disorders, and Parkinson's disease (Chen et al., 2024).

Organochlorine Pesticides

Organochlorine pesticides such as endosulfan, dieldrin, and lindane (γ-hexachlorocyclohexane) can accumulate in the food chain due to their environmental persistence and reach humans mostly through diet (Briz et al., 2011). Some studies report that organochlorine pesticide exposure increases the risk of Parkinson's disease (Xu et al., 2024). There are scientific studies that detail the relationship between DDT, dieldrin, and other persistent organochlorine pesticides and Parkinson's and other neurodegenerative diseases (Richardson et al., 2014).

Endocrine Disrupting Chemicals and Neurodevelopmental Effects

Bisphenol A (BPA)

Bisphenol A (BPA) is a synthetic compound classified as an endocrine disrupting chemical (EDC) and commonly used in the production of polycarbonate plastics and epoxy resins. Found particularly in food storage containers and baby bottles, BPA can bind to estrogen receptors, causing various adverse effects on the neuroendocrine system. Studies show that BPA exposure increases oxidative stress, neuroinflammation, and excitotoxicity; alters gene and protein expression; disrupts blood-brain barrier integrity; and triggers neuronal damage. Furthermore, disruption of intracellular Ca^{2+} homeostasis, increased reactive oxygen species, apoptosis, microglial DNA damage, astrogliosis, and decreased myelination highlight BPA's neurotoxic potential (Costa et al., 2024). Numerous studies have shown that even BPA exposure levels below current regulatory limits can cause neurotoxic effects and negatively impact learning, memory, and synaptic plasticity processes (Figueirôa et al., 2025).

Phthalates and Other Plasticizers

Phthalates are important additives used to increase the flexibility and durability of plastics and are commonly found in many everyday consumer products such as plastic products, pesticides, dyes, and cosmetics. More detailed studies are needed regarding the neurotoxicological effects of phthalates for public health safety (Gaur et al., 2024). Current epidemiological studies show that prenatal phthalate exposure may negatively affect neurodevelopmental processes in children. Exposure to phthalates is reported to be associated with impairments in cognitive, linguistic, behavioral, and psychomotor development, as well as decreased learning performance and intelligence levels (Yesildemir et al., 2023).

Polychlorinated Biphenyls (PCBs) and Neurotoxicity

PCBs are a group of persistent organic pollutants, numerous and diverse in type, that are similar in their chemical structure to one another as a result of human activities. Scientific studies indicate that prenatal and adult exposure to PCBs can lead to the development of features associated with attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASD), and may pose risks to human health through neurotoxicity (Pessah et al., 2019). Another study reports that prenatal PCB exposure may have negative effects on childhood neurodevelopment (Ribas-Fito et al., 2001). Current findings demonstrate that PCB exposure is associated with neurodevelopmental and neurobehavioral changes, particularly during the fetal and early postnatal periods (Faroon et al., 2000).

Effects on Blood-Brain Barrier Integrity

The blood-brain barrier (BBB) plays a crucial role in the function of the brain and central nervous system. Besides its vital functions, this barrier limits the entry of pathogens and toxic substances into the brain. In recent years, it has been shown that environmental toxic agents such as polycyclic aromatic hydrocarbons (PAHs), dioxins, heavy metals, perfluoroalkyl substances (PFASs), and various air pollutants can alter blood-brain barrier (BBB) permeability; this suggests that BBB function could be used as a potential biomarker in assessing neurotoxicity (Kelly et al., 2023). Another study reports findings that inhalation of diesel exhaust can impair blood-brain barrier function and that continued exposure may increase the risk of neurovascular disease (Heidari Nejad et al., 2015).

Epigenetic Mechanisms and Hereditary Neurotoxicity

Oxidative stress resulting from exposure to environmental toxins is considered a significant biological link between epigenetic mechanisms and neurotoxic effects. Reactive oxygen species, triggered by mitochondrial dysfunction, NADPH oxidase activation, and disruptions in redox balance, can affect epigenetic processes such as DNA methylation, histone modifications, and non-coding RNAs, leading to permanent changes in gene expression. It is thought that these changes can cause neurodevelopmental and neurodegenerative consequences not only in exposed individuals but also in subsequent generations; however, the development of multiple omics approaches and reliable biomarkers is needed to confirm these relationships (Gonzalez Acevedo et al., 2026). Current studies show that manganese exposure can lead to an increase in α-synuclein expression. At the cellular level, α-synuclein can interact with histone proteins and play a role in the epigenetic regulation of apoptotic processes. Furthermore, it is reported that manganese can trigger genome-wide DNA hypomethylation by causing DNA methyltransferase enzymes to be retained in the cytoplasm. In addition, it is thought that genetic differences between individuals may affect susceptibility to the neurotoxic effects of manganese and the risk of developing Parkinson's disease (Tarale et al., 2016).

Discussion and the Future

Current scientific evidence indicates that environmental pollutants affect the nervous system not through a single mechanism, but through multiple biological processes such as oxidative stress, neuroinflammation, mitochondrial dysfunction, epigenetic changes, and blood-brain barrier disruption. However, the fact that individuals are often simultaneously exposed to more than one pollutant in real life necessitates a more detailed investigation of combination toxicity. In the future, it is thought that multiple omics approaches, biomarker development studies, human-derived neural organoid models, and long-term epidemiological studies will make significant contributions to a better understanding of environmental neurotoxicity.

Conclusion

Environmental pollutants are considered significant neurotoxic agents that can affect neurodevelopmental and neurodegenerative processes. Heavy metals, air pollutants, pesticides, endocrine-disrupting chemicals, and other environmental toxins can lead to structural and functional changes in the central nervous system. Therefore, reducing environmental exposures, protecting vulnerable populations, and supporting research into environmental neurotoxicity should be considered a major public health priority in reducing the burden of neurological diseases.

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CHAPTER 0

STRUCTURAL And MICROSTRUCTURAL MAGNETIC RESONANCE IMAGING FINDINGS In SUBFIELD OF THE HİPPOCAMPUS In PARKINSON'S DISEASE

1. Cemile AVCI AKAN[1]

Introduction

Neurological disorders are among the leading causes of morbidity and disability worldwide and contribute significantly to the global health burden ("Global, regional, and national burden of neurological disorders during 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015," 2017). Parkinson's disease (PD) is one of the most common neurodegenerative diseases after Alzheimer's disease and affects millions of people worldwide (Bloem, Okun, & Klein, 2021). Although the disease is primarily characterized by motor symptoms, non-motor symptoms such as cognitive impairments, sleep disturbances, and mood changes also significantly contribute to the clinical picture (Aarsland et al., 2021).

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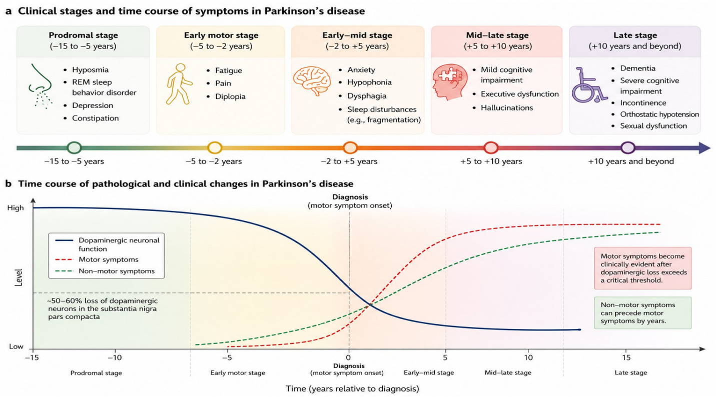
[1] Öğr.Gör., Ondokuz Mayıs Üniversitesi, Alaçam MYO, Büro Hizmetleri ve Sekreterlik Bölümü, Orcid: 000-0002-8436-438X

Although the diagnosis of Parkinson’s disease is largely based on clinical findings resulting from functional loss in the dopaminergic system, the pathophysiology of the disease is not limited to dopamine deficiency alone. Changes in various neurotransmitter networks—including serotonergic, cholinergic, and noradrenergic systems—in Parkinson’s disease contribute to the emergence of a wide range of motor and non-motor symptoms. Certain non-motor symptoms, such as olfactory dysfunction (hyposmia), rapid eye movement (REM) sleep behavior disorder, depression, and constipation, may appear years before classic motor symptoms and are considered important indicators of the disease’s prodromal phase (Schapira & Tolosa, 2010). However, some non-motor symptoms may emerge in the later stages of the disease (Figure 1). Furthermore, it has been reported that cognitive changes—particularly those affecting executive function and working memory—may begin early in individuals at risk of developing Parkinson’s disease and may become more pronounced over time (Chahine et al., 2016).

Figure 1. Clinical stages of Parkinson’s disease and the temporal progression of symptoms



(a) The stages of Parkinson’s disease and its main clinical symptoms.

(b) The temporal relationship between dopaminergic neuron loss and motor and non-motor symptoms.

Source: Adapted from (Schapira & Tolosa, 2010).

In Parkinson's disease, cognitive impairment can manifest across a broad clinical spectrum, ranging from subjective cognitive decline (SCD) to mild cognitive impairment (PD-MCI) and Parkinson's disease dementia (PDD) (Aarsland et al., 2021). PD-MCI is considered an intermediate stage in which activities of daily living are largely preserved, but impaired performance is observed in one or more cognitive domains. As the disease progresses, some individuals may develop dementia, which can lead to significant functional impairment in daily living activities. In Parkinson’s disease, executive functions, attention, visuospatial skills, and memory processes are particularly affected. Findings from recent years indicate that cognitive changes may emerge not only in advanced stages but also in the early stages of the disease and even during the prodromal phase (Chahine et al., 2016). This has sparked increased interest in researching the neurobiological mechanisms underlying cognitive decline in Parkinson’s disease and the associated brain structures.

The hippocampus, which plays a central role in learning and memory processes, stands out as one of the key structures associated with cognitive decline in Parkinson’s disease. Neuropathological and imaging studies suggest that structural and functional changes in the hippocampus may be associated with a decline in memory performance in particular (La et al., 2019; Pereira et al., 2013; Xu et al., 2020). It has been reported that volume loss and microstructural changes observed in subregions of the hippocampus are associated with the severity of cognitive decline.

Although the underlying neurobiological mechanisms of cognitive impairments seen in Parkinson’s disease have not yet been fully elucidated, the hippocampus—which plays a critical role in learning and memory processes—is thought to play a significant role in this process (Aarsland et al., 2021). Neuropathological studies have shown that the hippocampus may be affected by α-synuclein accumulation and neurodegenerative changes in Parkinson’s disease (Dickson, 2018; Fereshtehnejad, Zeighami, Dagher, & Postuma, 2017). Additionally, structural magnetic resonance imaging studies have revealed that hippocampal volume loss and changes at the subregional level may be associated with declines in cognitive performance (Foo et al., 2017; Pereira et al., 2013; Xu et al., 2020). These findings have made the hippocampus a key focus of research in understanding the cognitive impairments observed in Parkinson's disease.

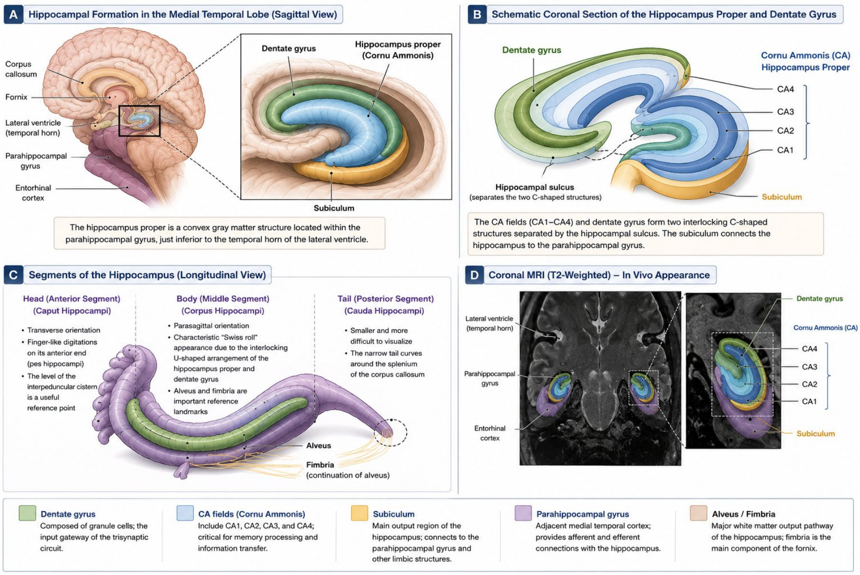
The Anatomical and Functional Organization of the Hippocampus

The Anatomy of the Hippocampus

The hippocampal formation is a complex structure located in the medial temporal lobe and consisting of the dentate gyrus, the hippocampus proper (Cornu Ammonis), and the subiculum (Wisse et al., 2017; Yushkevich et al., 2015). The hippocampus proper is a convex gray matter structure located within the parahippocampal gyrus and situated at the base of the temporal horn of the lateral ventricle. The main components of the hippocampus are the CA1, CA2, CA3, and CA4 subregions of the Cornu Ammonis and the dentate gyrus. These structures appear as two C-shaped convolutions separated and interconnected by the hippocampal sulcus. The subiculum forms a transitional region between the hippocampus and the parahippocampal gyrus, providing important connections. The basic anatomical components and subregions of the hippocampal formation are shown in Figure 2.

Anatomically, the hippocampus is divided into three sections: the head, body, and tail. The head of the hippocampus (caput hippocampi), which forms the anterior segment, is also referred to as the pes hippocampi due to the finger-like projections on its surface. The body of the hippocampus (corpus hippocampi), which constitutes the middle segment, exhibits a characteristic appearance due to its intertwined, convoluted structure formed together with the dentate gyrus. The cauda hippocampi, which forms the posterior segment, has a narrower structure and terminates around the splenium. The alveus and the fimbria, which continues from it, located on the surface of the hippocampus, are the primary white matter structures forming the hippocampal output pathways (Wisse et al., 2017).

Figure 2. The anatomical organization of the hippocampus and its major subfield



The hippocampus proper is a convex gray matter structure located within the parahippocampal gyrus, just inferior to the temporal horn of the lateral ventricle.

The CA fields (CA1–CA4) and dentate gyrus form two interlocking C-shaped structures separated by the hippocampal sulcus. The subiculum connects the hippocampus to the parahippocampal gyrus.

Head (Anterior Segment) (Caput Hippocampi)

- Transverse orientation
- Finger-like digitations on its anterior end (pes hippocampi)
- The level of the interpeduncular cistern is a useful reference point

Body (Middle Segment) (Corpus Hippocampi)

- Parasagittal orientation
- Characteristic "Swiss roll" appearance due to the interlocking U-shaped arrangement of the hippocampus proper and dentate gyrus
- Alveus and fimbria are important reference landmarks

Tail (Posterior Segment) (Cauda Hippocampi)

- Smaller and more difficult to visualize
- The narrow tail curves around the splenium of the corpus callosum

🟩 Dentate gyrus: Composed of granule cells; the input gateway of the trisynaptic circuit.

🟦 CA fields (Cornu Ammonis): Include CA1, CA2, CA3, and CA4; critical for memory processing and information transfer.

🟨 Subiculum: Main output region of the hippocampus; connects to the parahippocampal gyrus and other limbic structures.

🟪 Parahippocampal gyrus: Adjacent medial temporal cortex; provides afferent and efferent connections with the hippocampus.

🟫 Alveus / Fimbria: Major white matter output pathway of the hippocampus; fimbria is the main component of the fornix.

(a) The location of the hippocampal formation within the medial temporal lobe. (b) A schematic representation of the dentate gyrus, Cornu Ammonis (CA1–CA4), and subiculum. (c) The head, body, and tail regions of the hippocampus, along with the alveus and fimbria structures. (d) Anatomical localization of the subregions of the hippocampus in a coronal magnetic resonance image.

Source: Prepared by the author based on (Small, Schobel, Buxton, Witter, & Barnes, 2011; Wisse et al., 2017; Yushkevich et al., 2015).

Subfield of the Hippocampus

The hippocampus is an anatomically specialized structure comprising the subregions CA1, CA2, CA3, and CA4—collectively known as the Cornu Ammonis (CA)—as well as the dentate gyrus and subiculum (Wisse et al., 2017; Yushkevich et al., 2015). The CA1 region plays a role in transmitting a significant portion of hippocampal output to cortical areas and plays a critical role in memory processes. The CA2 region is a narrow area located between CA1 and CA3 and exhibits structural and functional characteristics distinct from other hippocampal subregions. The CA3 region is one of the primary targets of mossy fibers originating from the dentate gyrus and contributes to information processing in memory networks. The CA4 region, on the other hand, is located within the concavity of the dentate gyrus and is often referred to as the hilum. Furthermore, while the CA1 region is considered more susceptible to hypoxia and various neurodegenerative processes, the CA3 region is regarded as a relatively more resilient structure.

The dentate gyrus is one of the primary input regions of the hippocampal formation and serves as one of the first structures where information from the entorhinal cortex is processed (Chauhan, Jethwa, Rathawa, Chauhan, & Mehra, 2021). The dentate gyrus, which projects to the CA3 region via mossy fibers originating from granule cells, plays a significant role in the formation of new memories and pattern discrimination processes (Kesner & Rolls, 2015; Knierim, 2015).

The subiculum is a transitional region located between the hippocampus and the parahippocampal cortex and serves as one of the primary output centers of the hippocampal formation (Chauhan et al., 2021). A significant portion of hippocampal output is transmitted to neocortical and limbic structures via the subiculum, and this structure plays a key role in functions related to memory processes and spatial orientation (O’Mara, 2005).

These structural and functional differences among subregions of the hippocampus are critical for the regulation of memory and learning processes. Therefore, understanding the hippocampus's internal connections and information processing mechanisms contributes to the interpretation of cognitive changes observed in neurodegenerative diseases.

The Functional Organization of the Hippocampus

The classical view of the functional organization of the hippocampus is based on a trisinaptic circuit model in which information is transmitted from the entorhinal cortex to the dentate gyrus, then sequentially to the CA3 and CA1 regions, and finally relayed to cortical areas via the subiculum (Buzsáki & Moser, 2013; Farrell & Soltesz, 2025). This circuit forms the neurobiological basis for fundamental cognitive processes such as learning, memory consolidation, and spatial navigation. The flow of information between the dentate gyrus, CA3, and CA1 regions plays a critical role in the processing, storage, and retrieval of new information, while the subiculum ensures the transmission of hippocampal outputs to other brain regions. Although recent studies have shown that, in addition to the classical trisynaptic circuit, the CA2 region and other hippocampal connections also contribute to information processing, the trisynaptic circuit remains the primary model for explaining hippocampal functions (Farrell & Soltesz, 2025).

The dentate gyrus is considered one of the key components of the pattern separation process, which enables the differentiation of similar inputs and their conversion into distinct neural representations. In contrast, the CA3 region is thought to play a role in pattern completion mechanisms, which can reconstruct unique memory traces from partial or incomplete cues. These two complementary processes are of critical importance for the accurate encoding of new information and its subsequent effective retrieval (Schmidt, Marrone, & Markus, 2012).

The CA3 region is considered one of the hippocampus's primary information processing centers due to its dense network of recurrent connections. One of the region's most important functions is its contribution to the pattern completion mechanism, which enables the reconstruction of unique memory traces from incomplete or partial cues. Supported by mossy fiber inputs from the dentate gyrus, the CA3 network plays a critical role in the processes of storing and retrieving learned information. Due to these characteristics, the CA3 region is considered a key component of the hippocampal memory network (Kesner & Rolls, 2015).

The CA1 region is a key component of the hippocampal information processing network and plays a critical role in learning, episodic memory, and spatial navigation. In particular, the dorsal CA1 region has been reported to be associated with spatial memory and the processing of environmental information, while the ventral CA1 region contributes to social behaviors and emotional processes. CA1, which integrates information from the CA3 region and relays it to other hippocampal and cortical structures, holds a central position in memory formation and consolidation (Xie et al., 2023).

The subiculum is a transitional region located between the hippocampus, the entorhinal cortex, and other cortical areas, and is considered the primary output structure of the hippocampal formation. Anatomically, it consists of the molecular layer, the pyramidal cell layer, and the polymorphic layer. Receiving dense inputs from the CA1 region, the subiculum transmits this information to numerous cortical and subcortical structures, primarily the entorhinal, perirhinal, and prefrontal cortices. For this reason, the subiculum is thought to play a central role in the distribution and integration of hippocampal information. Furthermore, it has been reported that the dorsal subiculum is associated with spatial memory and navigation processes, while the ventral subiculum is associated with emotional and neuroendocrine functions (O'Mara, 2006).

Hippocampal Changes in Parkinson's Disease

α-Synuclein and Lewy Body Pathology in the Hippocampus

It is increasingly recognized that the cognitive impairments observed in Parkinson’s disease cannot be explained solely by changes in frontostriatal networks, and that the hippocampus also plays a significant role in this process. In particular, it has been reported that impairments in episodic memory performance may be associated with changes in hippocampal structures and related memory networks. Neuroimaging and neuropathological studies indicate that findings such as hippocampal atrophy, changes in connectivity, and Lewy body pathology in Parkinson’s patients are associated with declines in cognitive performance. Therefore, the hippocampus is considered a key target structure in investigating the underlying mechanisms of cognitive impairments in Parkinson’s disease (Das, Hwang, & Poston, 2019).

One of the key pathological features of hippocampal involvement in Parkinson’s disease is α-synuclein aggregation and the associated Lewy pathology. While α-synuclein is a protein that plays a role in synaptic function under normal conditions, in pathological processes it can misfold to form aggregates and constitutes the primary component of Lewy bodies and Lewy neurites. It has been demonstrated that these pathological accumulations in Parkinson’s disease are not limited to the substantia nigra but also extend to structures associated with cognitive functions, such as the limbic system and the hippocampus. It is thought that the accumulation of α-synuclein observed in the hippocampus may negatively affect synaptic transmission, neurotransmission, and neurogenesis processes, which in turn may contribute to the development of cognitive impairments and neuropsychiatric symptoms (Yang & Yu, 2017).

Neuropathological studies indicate that Lewy body pathology extends to the hippocampal formation and associated limbic structures in the later stages of the disease. In particular, the accumulation of α-synuclein in subregions of the hippocampus has been linked to impairments in episodic memory and other cognitive functions. These findings suggest that the hippocampus is not merely a structure secondarily affected in Parkinson’s disease but may play an active role in the emergence of cognitive symptoms.

Changes in Hippocampal Volume and Subfield in Parkinson's Disease

Recent volumetric studies have shown that hippocampal volume loss is more pronounced in mild cognitive impairment associated with Parkinson’s disease (PD-MCI). It is thought that structural changes occurring in memory networks associated with the hippocampus may negatively affect memory encoding and retrieval processes (Sahin et al., 2024). Furthermore, significant associations have been reported between the presence of cognitive impairment and reduced hippocampal volume in Parkinson’s patients, making hippocampal atrophy a potential imaging marker of cognitive decline (Hu et al., 2026).

It has been suggested that hippocampal changes are not limited to a loss of total volume, and that certain subregions may be more susceptible to neurodegenerative processes. Consequently, studies conducted in recent years have focused on the separate evaluation of hippocampal subregions in Parkinson’s disease and have shown that changes occurring in regions such as CA1, the dentate gyrus, and the subiculum may be associated with cognitive performance. These findings suggest that the hippocampus is not merely a structure affected secondarily in Parkinson’s disease but may play an active role in the development of cognitive symptoms.

The Impact on Subfield of the Hippocampus in Parkinson's Disease

The CA1 region is one of the key components of the hippocampal information processing network and plays a significant role in episodic memory, learning, and spatial navigation processes. CA1, which integrates information from the CA3 region and transmits it to the hippocampal output pathways, is considered a critical component of memory formation and retrieval processes. It has been reported that the cognitive impairments observed in Parkinson’s disease cannot be explained solely by changes in the frontostriatal networks, and that hippocampal subregions may also contribute significantly to these processes. In particular, it is noted that impairments in episodic memory performance are associated with changes in hippocampal structures, and that the CA1 region holds a central position within this network (Das et al., 2019; Pourzinal et al., 2021). Neuropathological and imaging findings indicate that subregions of the hippocampus may exhibit varying degrees of susceptibility to neurodegenerative processes; in this regard, the CA1 region is considered one of the key structures for assessing cognitive decline in Parkinson’s disease (Bouwman et al., 2025).

The dentate gyrus serves as the gateway to the hippocampal circuit and contributes to the differentiation of similar experiences through the mechanism of pattern separation. This function is critical for the accurate encoding of new information and the formation of episodic memory. Studies investigating the underlying mechanisms of cognitive impairments observed in Parkinson’s disease suggest that subregions of the hippocampus may be affected by neurodegenerative processes to varying degrees. Studies focusing specifically on atrophy of subregions of the hippocampus have reported that the dentate gyrus may also be affected by structural changes in Parkinson’s disease and that these changes may be associated with a decline in cognitive performance (Lenka et al., 2018). Additionally, MRI-based volumetric segmentation studies suggest that volumes of subregions of the hippocampus may serve as potential biomarkers for assessing cognitive status (Tarhan, Atalay, Buz Yaşar, & Özdilek, 2024).

The subiculum serves as the primary output center of the hippocampus and facilitates the transmission of hippocampal information to cortical and subcortical regions. Imaging studies conducted in Parkinson’s disease indicate that the subiculum is among the hippocampal subregions affected by neurodegenerative processes. In particular, it has been reported that volume loss in subicular structures is associated with cognitive decline and the development of dementia. Furthermore, longitudinal studies suggest that volume changes in the subiculum and presubiculum regions may be associated with a decline in cognitive performance. These findings suggest that the subiculum is a key structure in understanding the neurobiological basis of cognitive impairments observed in Parkinson’s disease (Low, Foo, Yong, Tan, & Kandiah, 2019; Xu et al., 2020).

Hippocampal structures and associated memory networks play a significant role in the development of cognitive impairments observed in Parkinson’s disease. In particular, structural changes occurring in hippocampal subregions involved in episodic memory, learning, and information retrieval have been reported to be associated with declines in cognitive performance. Recent neuroimaging studies have shown that hippocampal volume loss and changes at the subregional level may be associated with the development of mild cognitive impairment and dementia (Das et al., 2019; Pourzinal et al., 2021). Furthermore, longitudinal studies have shown that volume changes in subregions such as the subiculum, presubiculum, and dentate gyrus may serve as early indicators of cognitive decline (Xu et al., 2020). These findings suggest that hippocampal subregions are not merely passive targets of the neurodegenerative process in Parkinson’s disease but may also play an active role in the development of cognitive symptoms.

Conclusions and Future Prospects

Although Parkinson’s disease has long been regarded as a neurodegenerative disorder characterized primarily by motor symptoms, it is now recognized that cognitive impairments play a significant role in the clinical course of the disease. The hippocampus and associated memory networks have become a major focus of research in understanding the underlying mechanisms of these cognitive changes. While neuropathological studies have shown that α-synuclein accumulation and Lewy body pathology can occur in the hippocampus, neuroimaging studies have revealed that hippocampal volume loss and structural changes at the subregional level may be associated with declines in cognitive performance (Das et al., 2019; Yang & Yu, 2017).

Analyses of hippocampal subregions conducted in recent years indicate that the entire hippocampus is not affected uniformly in Parkinson’s disease. In particular, early volume losses occurring in the CA1, subiculum, and presubiculum regions have been reported to be associated with cognitive decline and the development of dementia. Additionally, it is thought that structural changes in the dentate gyrus and other subregions may also contribute to the development of mild cognitive impairment. Assessing hippocampal subregions may provide more sensitive indicators of cognitive decline compared to total hippocampal volume measurements (Low et al., 2019; Xu et al., 2020).

In the future, it will be possible to examine hippocampal subregions in greater detail through the use of high-resolution magnetic resonance imaging techniques, automated segmentation algorithms, and AI-supported analysis approaches. These approaches may help identify the risk of progression from mild cognitive impairment to dementia in patients with Parkinson’s disease at an early stage. Additionally, the use of changes specific to hippocampal subregions as biomarkers offers significant opportunities for patient monitoring and the development of personalized treatment strategies.

In conclusion, the hippocampus and its subregions play a central role in understanding the neurobiological basis of cognitive impairments observed in Parkinson’s disease. In particular, structural changes occurring in the CA1, dentate gyrus, and subiculum regions have been shown to be associated with cognitive decline. Therefore, a detailed evaluation of hippocampal subregions is considered a promising approach for the early diagnosis of cognitive impairments in Parkinson’s disease and the development of future neuroimaging-based biomarker studies.

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CHAPTER 0

NEUROBIOLOGICAL EFFECTS OF ELECTROMAGNETIC FIELDS

MEHMET CİHAN YAVAŞ[1]

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[1] Assoc. of Prof. Mardin Artuklu University, Faculty of Medicine, Department of Biophysics, Mardin Türkiye.
Orcid: 0000-0002-2923-050X.

Abstract

Electromagnetic fields (EMFs) have become one of the most prevalent environmental exposures of the modern era due to the widespread use of wireless communication technologies, smart devices, and emerging 5G networks. Increasing human exposure to a broad spectrum of electromagnetic frequencies has raised scientific interest regarding their potential effects on the nervous system. This chapter reviews current evidence on the neurobiological effects of electromagnetic fields, focusing on experimental, clinical, and epidemiological studies published in recent years. Potential mechanisms include modulation of voltage-gated ion channels, alterations in calcium signaling, increased production of reactive oxygen species, oxidative stress, glutamatergic dysregulation through NMDA receptors, neuroinflammatory responses, and changes in blood–brain barrier permeability. In addition, the effects of electromagnetic field exposure on electroencephalographic activity, sleep architecture, circadian rhythms, and cognitive functions are discussed. Recent findings related to fifth-generation (5G) communication systems and millimeter-wave exposures are also evaluated. Although several studies have reported biological and neurophysiological alterations associated with electromagnetic field exposure, current evidence remains insufficient to establish definitive causal relationships for adverse neurological outcomes under internationally accepted exposure limits. Future research should focus on standardized exposure protocols, long-term prospective studies, advanced dosimetric approaches, and the identification of reliable biomarkers to better elucidate the potential neurobiological consequences of electromagnetic field exposure.

Keywords: electromagnetic field, neurotoxicity, mobile phone, exposure, EEG

Introduction

Electromagnetic Fields and Exposure

Exposure to electromagnetic fields (EMFs) has become an unavoidable component of modern life with the proliferation of mobile communication technologies. The effects of radiofrequency electromagnetic fields (RF-EMFs) on the central nervous system, in particular, have been extensively researched over the past two decades. Experimental studies on human volunteers have shown that RF exposure, similar to cell phone signals, can cause minor changes in electroencephalography (EEG) activity and sleep architecture; however, a clinically significant association between these changes and health outcomes has not yet been established. Furthermore, studies on cognitive performance, attention, and reaction time have failed to demonstrate consistent and reproducible negative effects. Nevertheless, experimental and epidemiological studies indicate that some uncertainties remain regarding the neurobiological effects of RF-EMFs. Systematic reviews evaluating the potential effects of long-term exposure, particularly in children and adolescents, highlight that current evidence generally has low to moderate certainty and that higher-quality prospective studies are needed to establish a causal relationship. Current scientific consensus is that there is no strong evidence to support proven harmful effects on the nervous system from RF-EMF levels below international exposure limits, but research into neurophysiological changes and long-term outcomes is needed (Van Rongen et al., 2009; Bodewein et al., 2022).

Fundamental Biophysical Mechanisms of Electromagnetic Fields

Ion Channels

With the advancement of technology today, humans are exposed to electromagnetic fields in both a very low and a wide frequency spectrum. Research indicates that electromagnetic fields can interact with biological systems and particularly affect fundamental cellular processes such as the activity of ion channels in the cell membrane, transmembrane potential, and the cell cycle. The increase in human exposure to millimeter waves and terahertz frequencies, whose applications have rapidly expanded in recent years, necessitates a broader understanding of the biological effects and safety limits of these frequencies (Romanenko et al., 2017). It has been suggested that low-intensity electromagnetic fields may be associated with neurodegenerative processes and may contribute to the pathogenesis of Alzheimer's disease, and researchers have reported that they increase amyloid beta and amyloid precursor protein levels in experimental animals with AD (Pall, 2022). However, in a cell culture study, they reported that exposure of neuroblastoma (IMR32) cells to 50 Hz electromagnetic fields increased the expression of the voltage-gated Ca2+ channel subunit α1 (Grassi et al., 2004). The opening and closing of neuronal ion channels generally occur via voltage- and ligand-dependent channels, and even very low-frequency electromagnetic fields at the microvolt level can alter the neuronal membrane potential, leading to certain physiological changes (Mathie et al., 2003).

Reactive Oxygen Species and Oxidative Stress Mechanisms

Exposure to radiofrequency radiation from cell phones affects the expression of many proteins. This may occur via MAPK (mitogen-activated protein kinase) cascades that regulate all cellular processes. It has been reported that the initial effect is mediated by NADH oxidase in the plasma membrane, which rapidly produces ROS (reactive oxygen species) (Friedman et al., 2007). A similar study experimentally investigated the effect of 872 MHz radiofrequency (RF) radiation on intracellular reactive oxygen species (ROS) production. It was reported that exposure to radiofrequency electromagnetic fields in human SH-SY5Y neuroblastoma cells increased ROS production (Luukkonen et al., 2009). Although there is evidence that static and very low-frequency electromagnetic fields increase oxidative stress, detailed studies are needed to elucidate the mechanism (Lai, 2019).

NMDA Receptor and Glutamatergic Hyperactivity

NMDA receptors, which are critical for brain development and the maintenance of normal nervous system functions, play a fundamental role in regulating neuronal communication. Environmental stimuli such as magnetic fields can alter the activity of these receptors, potentially influencing various neurophysiological processes (Nair et al., 2024). Exposure to a very low-frequency electromagnetic field (50-Hz, 1.0-mT ELF MF) was induced in cell cultures. It has been suggested that very low-frequency magnetic fields may affect glutamatergic Ca2+ channels and N-methyl-d-aspartate (NMDA) receptors in the human neuronal differentiation process, and that more detailed information is needed in this area (Özgün et al., 2019). It has been reported that daily exposure to 900 and 2100 MHz radiofrequency radiation for 2 hours altered the hippocampal NMDA-dependent signaling pathway and increased hippocampal activity in rats (Gökçek-Saraç et al., 2017).

Neuroinflammation and Microglia Activation

The inflammatory effect of electromagnetic fields (2.5 and 5 Hz, 1V, 3 min) on the human microglia cell line HCM3 and the human cortical neuron cell line HCN-2 was investigated. It has been reported that electromagnetic field applications may support recovery after traumatic brain injury by modulating neuronal and microglial functions. However, further studies are needed to determine suitable exposure conditions for clinical applications (Mendoza-Mari et al., 2025). In another study, it was stated that electromagnetic pulse exposure (600 kV/m, 1000 pulses, 2 weeks) in mice could lead to neuroinflammation and disruption of the blood-brain barrier as a result of activating the NLRP3 inflammasome/NF-kB signaling pathway (Lin et al., 2025).

Blood-Brain Barrier Permeability

The effects of a 900 MHz electromagnetic field (900 MHz, 1 mW/cm2 EMA, 14 and 28 days) on Mkp-1/ERK and the blood-brain barrier in rats were investigated. It has been reported that long-term exposure can impair the integrity of the blood-brain barrier (Tang et al., 2015). Due to variations in exposure conditions, free absorption rates, and methodological approaches, some studies show changes in blood-brain barrier permeability, while many others show the opposite. Therefore, rigorous exposure characterization, validated blood-brain barrier biomarkers, and more standardized studies are needed in this field (Simsek et al., 2026).

Effects of Electromagnetic Fields on EEG

A study conducted on healthy adults indicated that a 902 MHz electromagnetic field (antenna approximately 20 mm away from the head) did not directly alter the resting EEG, but could significantly change brain reactions in memory function processes (Krause et al., 2000). A study investigating the effects of intensive cell phone use on neural function reported that EEG analysis of 24 volunteer participants altered the resting EEG, reducing 1-4 Hz activity and increasing 8-12 Hz activity depending on the exposure time (Croft et al., 2002). A study investigating the effect of cell phone-induced electromagnetic fields (SAR, head 0.346 W/kg) on brain EEG delta waves found that short-term exposure did not cause significant changes in frequency and power spectral densities in the EEG delta value (Yavaş, 2020).

Sleep and Circadian Rhythms

RF and Sleep Stages

Increased exposure to electromagnetic fields (EMF), particularly from low-frequency electrical sources and radiofrequency telecommunication devices, has become a significant area of research regarding health. Studies have examined the effects of EMF on melatonin secretion, sleep architecture, and electroencephalographic (EEG) activity; however, findings regarding its effects on melatonin have been inconsistent due to variations in exposure conditions. While radiofrequency fields have generally not been shown to have a significant effect on sleep architecture, some research reports that exposure to pulsating radiofrequency can alter brain physiology and activity in specific EEG bands before or during sleep (Ohayon et al., 2019). Research into the biological effects of radiofrequency exposure related to cell phone use has focused particularly on potential effects on brain activity and function due to the high energy absorption in the head region. In this context, sleep studies have become a widely used method for evaluating the effects of radiofrequency fields from mobile phones on human health and have provided important information, particularly in revealing possible changes in sleep architecture (Loughran, 2007). It has also been noted that the Earth's natural electromagnetic field and electromagnetic pollution from wireless devices affect circadian rhythms (Martel et al., 2023). With the proliferation of mobile telecommunication devices, the non-thermal biological effects of high-frequency electromagnetic fields (EMF) are being increasingly investigated. While current epidemiological studies do not show a strong association between

EMF exposure and sleep disorders, sleep laboratory studies have reported effects such as mild changes in sleep regulation and increased alpha activity in sleep EEG. However, current data are insufficient to demonstrate that these effects lead to negative health outcomes, and further research is needed to better understand the EMF-sleep interaction (Mann and Röschke, 2004).

Neurobiology of 5G and Millimeter Wave Exposure

The proliferation of wireless communication devices in the modern era is creating increasing exposure in society. Scientific studies are ongoing in this field. While the use of fifth-generation (5G) mobile communication networks offers many positive contributions, such as data transfer speed, concerns are growing about potential risks to the electrical activity of the human body, especially the brain (Michelant et al., 2025). A study investigating the effects of 3.5 GHz 5th generation radio frequencies on the electrical activity of the brain and the autonomic nervous system in 34 healthy volunteers showed no significant changes (Jamal, 2023). In a study where a total of 59 young Sprague-Dawley rats (240–322 g) were exposed to 28 GHz frequency for 40 minutes, the experimental study showed that whole-body exposure to 28 GHz quasi-millimeter waves (qMMW) could affect the stress response by raising corticosterone levels, particularly in animals showing a significant increase in body temperature. It has also been suggested that exposure may alter norepinephrine levels, playing a role in thermoregulation and heat distribution processes, and that these findings may contribute to understanding the biological basis of international exposure limits (Matsumoto et al., 2025).

Conclusion

Electromagnetic fields may influence various neurobiological processes through mechanisms involving calcium signaling, oxidative stress, neuroinflammation, and neuronal excitability. While experimental studies have demonstrated measurable cellular and physiological responses, current human evidence does not conclusively support the existence of significant adverse neurological effects under established exposure limits. Nevertheless, the rapid expansion of wireless technologies, particularly 5G systems, highlights the need for continued multidisciplinary research to clarify long-term neurological outcomes and ensure evidence-based public health recommendations.

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