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Terahertz wave applications and development in the field of neuroscience

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Abstract: Terahertz waves possess characteristics such as low photon energy and the ability to interact with biomolecules, inducing low-frequency intramolecular vibrations, which demonstrate great potential in the field of life sciences. Research indicates that terahertz radiation affects the nervous system, including the structure of neuronal membranes, gene expression, and cytokine levels. However, the interaction mechanisms between terahertz electromagnetic waves and complex biological systems are not yet fully understood, and further research is needed in the future. Terahertz sources with appropriate frequency, power, and operating modes are crucial for in-depth research on terahertz technology in the field of neuroscience. This paper categorically introduces the latest advancements in various terahertz sources based on principles of photonics and electronics, and explores the biological effects, mechanisms of terahertz radiation on the biological nervous system, as well as its applications in the biomedical field. These research findings will provide new insights and methods for the application of terahertz waves in biomedical fields.

Keywords: terahertz source; neuroscience; biological effects; terahertz detection technology.

1. Introduction

Terahertz waves are a type of electromagnetic wave with a frequency range of 0.1-10 THz, and their wavelengths range from 30 micrometers to 3 millimeters. Terahertz waves are located between microwaves and the infrared spectrum, serving as an important transitional field between electronics and photonics. In recent years, with the advancement of ultrafast optoelectronic technology and semiconductor technology, the development of terahertz technology has been rapidly promoted and has been widely applied in fields such as aerospace, communication, security detection, and biomedicine. Due to the close correlation between the frequency range of terahertz waves and weak interaction forces such as hydrogen bonds and van der Waals forces, terahertz waves can interact with the vibrations and rotations of biomolecules such as proteins, DNA, RNA, lipids, and polysaccharides. Therefore, terahertz spectral characteristics can be used to accurately identify and classify various biomaterials, analyze the structure of biomolecules, and understand their molecular mechanisms by studying the spatial conformation of molecules. Moreover, the single-photon energy of terahertz waves is approximately 0.3 millielectron volts, which is only one to one hundred thousandth of that of medical X-rays, and it almost does not cause ionizing damage to biological tissues. In recent years, significant progress has been made in understanding how terahertz radiation affects the function of the nervous system, including its impact on membrane dynamics, ion channels, and protein conformation. However, terahertz waves also have certain limitations, including strong absorption by water and the inability to penetrate deep into neural tissues; terahertz bioeffects being highly dependent on frequency and dose; the complexity of biological reaction patterns being difficult to identify; and insufficient terahertz radiation sources, among others[1].

The text starts from the perspective of terahertz radiation sources, introducing the radiation types, frequency ranges, bandwidth, and other parameters of various mainstream terahertz sources, explaining general application scenarios and methods, which provides some help for researchers in selecting light sources. Subsequently, it reviews the effects and mechanisms of terahertz waves on

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the nervous system at the molecular, cellular, synaptic and neural circuit, and organism levels. Finally, it introduces the applications of terahertz detection technology in the biomedical field.

2. Terahertz radiation source

Terahertz waves lie between microwaves and infrared, spanning the two major technical systems of electronics and photonics. They are divided into two major categories based on the core physical mechanism of energy radiation: photonic terahertz sources and electronic terahertz sources.

2.1. Photonics terahertz source

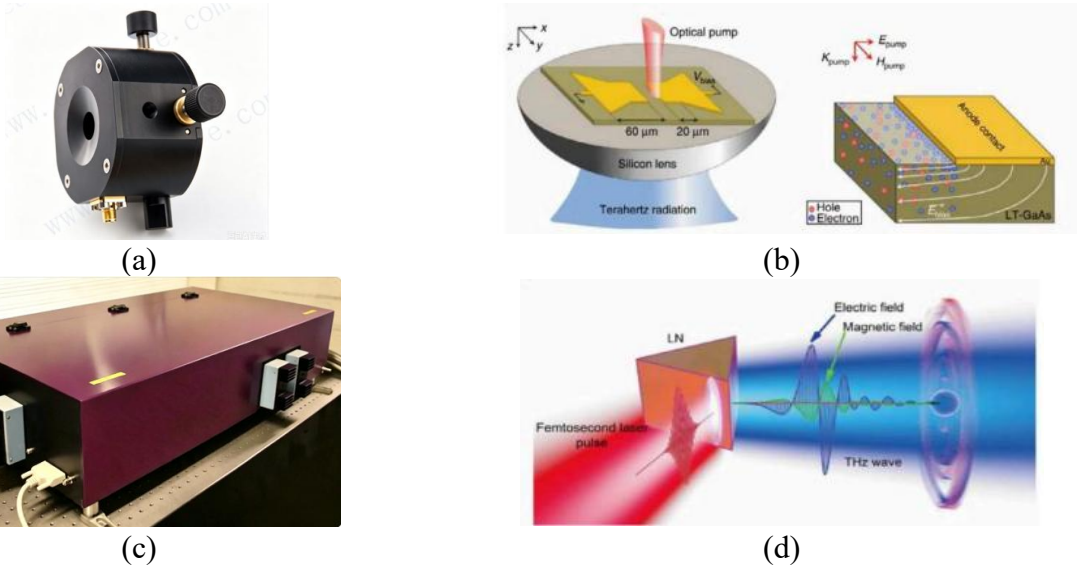
Due to the invention of femtosecond lasers, the technology for generating broadband terahertz pulses based on optical methods has made significant progress. Techniques such as transient photocurrent emission based on photoconductive crystals, optical rectification emission from nonlinear crystals, laser-induced plasma generation of terahertz radiation, and ferromagnetic/nonferromagnetic spin current emission have been widely used across various industries due to their advantages of simple operation, easy control of cost and size, and high emission energy. Below, we mainly introduce three mainstream commercial and laboratory general terahertz sources: photoconductive antenna sources, nonlinear crystal optical rectification sources, and laser-induced plasma sources.

The first type is the photoconductive antenna terahertz source (PCA) (Fig.1a). Its working principle involves femtosecond laser irradiation of the semiconductor electrode gap, where photon energy higher than the material bandgap excites a large number of electron-hole charge carriers. An external direct current bias field drives the photo-generated charge carriers to accelerate and recombine in a directional manner, forming subpicosecond-scale time-varying transient currents, which emit terahertz pulses based on the Maxwell equation radiation mechanism. It is typically composed of a semiconductor material substrate and two metal electrode antenna parts, with a hemispherical silicon lens on the back of the substrate (Fig.1b) for controlling the terahertz wave. Its spectrum is usually a broadband pulse in the 0.1–3 THz range; the instantaneous peak power of the pulse is in the milliwatt range, and the energy of a single pulse can be further enhanced through an array structure. However, limited by pulse duty cycle and carrier saturation effects, the time-averaged output power is only in the micro watt range. Its system structure is simple, with moderate cost, and is a standard configuration for most commercial desktop terahertz time-domain spectrometers. It is suitable for bio molecular detection, metasurface sensing, non-destructive material characterization, and low-cost laboratory terahertz time-domain detection, making it the most widely used terahertz source in biochemical and optoelectronic laboratories.

Nonlinear optical rectification terahertz sources are also one of the effective methods for generating terahertz waves. The principle involves the incidence of two or single ultrafast laser beams on a nonlinear crystal, generating terahertz radiation through the self-difference frequency generation/double-beam difference frequency generation effect (Fig.1c). The intensity of the terahertz radiation depends on the intensity of the laser pulse and the characteristics of the nonlinear medium. Common terahertz wave generation crystals include lithium niobate ($LiNbO_3$), zinc telluride (ZnTe), gallium phosphide (GaP), and gallium arsenide (GaAs). Traditional unstructured crystals can output broadband pulses in the 0.1-4 THz range and narrowband continuous tunability from 0.1 to 10 THz, with single pulses covering the entire molecular fingerprint range, enabling synchronous amplitude and phase acquisition, characterized by ultra-wide bandwidth and good coherence. However, constrained by phase matching and crystal damage thresholds, the average output power is low, typically in the nW~μW range. By using nonlinear metasurfaces such as open-loop resonators (SRR) and full dielectric structures, the pulse peak electric field or single-pulse energy can be enhanced by tens of times, optimizing instantaneous peak performance, but this does not significantly improve the average output power. Nonlinear optical rectification terahertz sources are mainstream solutions in the fields of ultrafast optics and strong-field terahertz, standard equipment for ultrafast platforms in research institutions, and widely used in molecular dynamics and metamaterial mechanism research.

In the field of neuroscience, they can be used for unmarked quantitative molecular detection, as well as for screening characteristic resonance bands to conduct mechanistic comparative experiments on ion channels and synaptic plasticity. However, this light source has low photovoltaic conversion efficiency, weak output power, and relies on large-scale femtosecond laser systems, making it suitable only for in vitro thin-layer sample detection and unable to support long-term deep-brain tissue neural modulation experiments in vivo, presenting significant shortcomings in animal and clinical translation research (Fig.1d).

The third method involves using laser-induced plasma to generate terahertz radiation. High-energy ultrafast lasers focus on ionized gas, liquid, or solid targets to form a plasma, where free electrons oscillate at high speeds under optical pressure and transverse bias electric fields, radiating ultra-wideband terahertz. Through dual-color composite pumping, asymmetric transient current can be constructed, further enhancing the peak electric field. Air plasma terahertz sources can achieve ultra-wideband spectral output from 0.1–25 THz, and dual-color laser schemes can boost the peak electric field to kV or even MV/cm levels, producing subpicosecond ultrafast coherent pulses. This light source allows for independent control of the spectrum, polarization, and beam by adjusting the pumping phase and filament structure, offering flexible waveform and frequency trimming capabilities. However, due to the limitation of laser repetition frequency, the long-term steady-state average output power is extremely low. Currently, this method is a general and mature solution in the fields of strong-field terahertz, long-distance remote sensing, and atmospheric spectroscopy. In the field of neuroscience, it is currently limited to in vitro basic research on isolated molecules, cells, and brain tissue slices, and cannot meet the requirements for long-term, uniform neural intervention experiments in living animals[2].



(a) (b)

(c) (d)

Fig. 1 (a)Terahertz photoconductive antenna, (b)PCA technology schematic diagram, (c) LN optical rectification schematic, (d) Terahertz source based on the mixing effect on nonlinear crystals [3].

Table 1. Common photonic terahertz source parameters

Source Type	Typical Operating Frequency Range	Waveform	Spectral Bandwidth	Key Characteristics
Photoconductive Antenna (PCA)	0.1–3 THz (commercial mainstream); up to 0.1–5 THz with optimized structures	Single-cycle / sub-cycle pulses (pulsed THz)	Broadband continuous spectrum	Mature technology, high signal-to-noise ratio, compact optical setup; moderate output power; radiation decays rapidly above 3 THz; can serve as both emitter and detector
Nonlinear Crystal Optical Rectification (typical: $LiNbO_3$ with tilted-pulse-front pumping)	0.1–5 THz; extendable to ~7 THz with special configurations	Single-cycle pulses (pulsed THz)	Ultra-broadband	Large nonlinear coefficient, high peak-field intensity; requires precise phase-matching optics; bulk LN setup is relatively large
Laser-Induced Air Plasma	0.1–10 THz; theoretically covers an even wider range	Single-cycle pulses (pulsed THz)	Ultra-broad continuous spectrum, no crystal absorption cutoff	No optical damage threshold limitation, extremely wide spectrum; low conversion efficiency, large beam divergence, poor stability; requires high-energy ultrafast laser

2.2. Electronics terahertz source

With the development of terahertz science and technology, research on generating terahertz based on electronic methods has also made significant progress, divided into vacuum electronic terahertz radiation sources represented by devices such as backward wave oscillators (BWO), traveling wave tubes, and extended interaction devices, and solid-state semiconductor terahertz sources represented by Gunn diode, avalanche transit time diodes, and tunnel transit time diodes. These radiation sources have high average output power at lower terahertz frequencies and have broad application prospects in fields such as non-invasive medical diagnosis, high-resolution imaging, and non-destructive material testing.

Vacuum electronic devices generally refer to devices where free electrons interact with electromagnetic fields in a vacuum environment within high-frequency structures, converting the kinetic energy of electrons into electromagnetic energy. Vacuum electronic devices are the optimal solution for high-power and miniaturization in terahertz low-frequency band radiation sources[3].

A backward wave tube is a type of small vacuum electronic continuous terahertz oscillation device that relies on an electron beam generating reverse electromagnetic waves with a high-frequency structure to achieve radiation output. During its development, the output frequency of backward wave tubes at the same stage was the highest among other miniaturized vacuum electronic devices. Currently, mainstream commercial backward wave tubes have frequencies ranging from 0.16 to 0.37 THz, with laboratory peak frequencies reaching up to 1 THz. In the 0.1–0.4 THz range, average power can reach 5–20 mW, but power drops sharply to the μW level for frequencies above 0.5 THz. It has excellent monochromaticity and a narrow line width, making it suitable for high-precision molecular quantitative detection. It is commonly used in laboratory steady-state spectroscopy detection, biological trace molecular quantitative spectroscopy, and other applications (Fig.2a) [4].

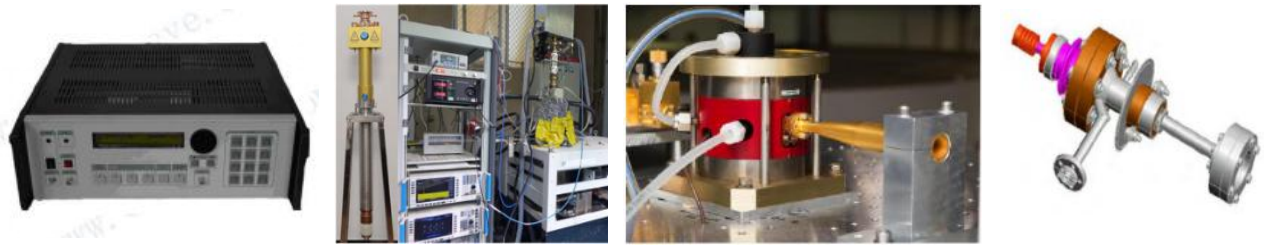
A traveling wave tube is a vacuum electronic device capable of linearly amplifying terahertz signals, being the most widely used and relatively more in-depth researched linear injection device in miniaturized vacuum electronics. Its principle involves continuous energy exchange between a vacuum electron beam and a co-propagating high-frequency electromagnetic wave within a high-frequency structure, converting electron kinetic energy into electromagnetic energy to achieve signal power enhancement. In the G-band, continuous wave power can reach 15–30W, with pulse peak power reaching up to 50–200W. It can achieve 3–10GHz broadband amplification with a gain of 26–40dB per tube; new harmonic traveling waves can be multiplied to extend to 0.34THz, outputting milliwatt-level amplified signals. Terahertz traveling wave tubes are currently primarily used as core devices for high-power broadband amplification, applied in terahertz synthetic aperture radar, inter-satellite long-distance high-speed communication, airborne electronic countermeasures, industrial non-destructive testing, and plasma diagnostics, among other scenarios (Fig.2b).

Extended interaction devices are linear vacuum electronic devices that combine the high gain of klystrons and the broadband advantages of traveling wave tubes, divided into two types: Extended Interaction Oscillators (EIO) and Extended Interaction Klystrons (EIK). Within the 90–270 GHz (W/G band) range, extended interaction devices have mature fabrication processes, stable prototype performance, and can achieve pulse peak power in the kilowatt level and continuous wave power in the hundreds of watts. Devices above the 270 GHz frequency band remain difficult to practicalize due to micro-fabrication limitations. Additionally, the EIK can achieve a gain of over 40 dB and a 3 dB bandwidth of 200 MHz–1 GHz. Currently, EIO and EIK are primarily used in high-power, narrow-band terahertz/mm-wave scenarios such as DNP nuclear magnetic instruments, plasma diagnostics, W/G band high-resolution imaging radar, spaceborne terahertz communication, meteorological detection, and industrial non-destructive testing (Fig.2c) [5].

The gyrotron is a device for gyromagnetic electron beams based on the principle of stimulated radiation of gyromagnetic electrons (Fig.2d). Compared to traditional microwave devices, it has advantages such as: overcoming the size confinement effect, eliminating the need for micron-level fine slow-wave structures; strong electron beam current carrying capacity, capable of outputting ultra-

high power levels of kilowatts to megawatts; the ability to operate on harmonics, significantly reducing the required magnetic field strength, and lower equipment development difficulty. The output terahertz wave frequency range covers 0.1–1.3 THz, with extremely high output power, typically continuous wave power reaching kilowatts, and pulsed power from kilowatts to megawatts. It can operate on the second harmonic, significantly reducing the magnetic field strength requirement. However, it has limitations such as the system requiring superconducting/pulsed strong magnets and high-voltage power supplies, and the overall bulky size. Currently, the gyrotron is primarily used for nuclear fusion plasma heating and diagnostics, DNP-enhanced nuclear magnetic resonance, high-temperature sintering of special ceramics, while supporting research and defense scenarios such as high-resolution radar, electronic countermeasures, and strong-field terahertz fundamental physics[6].

In the ongoing development of various miniaturized devices within traditional structures, many new structures and even new principles of miniaturized vacuum electronic devices suitable for advancing into the terahertz range have emerged, such as magnetrons and oblique injection tubes. As these are still in the laboratory research stage and have not been widely commercialized, this paper does not describe them in detail.



(a) **(b)** **(c)** **(d)**

Fig. 2 (a)Tunable backward-wave oscillator terahertz source, (b)Helix-TWT and Test Platform, (c) EIK operating at 187 GHz for dynamic nuclear polarization systems, (d)IAP-developed 1.3 THz cyclotron.

Table 2. Common terahertz source parameters in electronics

Device Type	Typical Operating Frequency Range	Waveform	Tuning Bandwidth / Spectral Characteristics	Key Characteristics
Backward Wave Oscillator (BWO)	0.1–0.8 THz (100–800 GHz); commercially mature in 0.17–0.7 THz	Continuous wave (CW)	Continuous voltage tuning of tens to ~100 GHz per tube; narrow linewidth; single-mode oscillation	Electrically frequency-tunable, compact structure; output power drops rapidly above 0.6 THz; mW-level output; requires permanent magnet for electron beam focusing
Traveling Wave Tube (TWT)	0.1–0.5 THz; fabrication becomes extremely difficult at higher frequencies	Continuous wave (CW, amplified output)	Broadband amplification characteristic; wider relative bandwidth than resonant devices; cannot self-oscillate and must be driven by an external signal source	Broadband amplification and high gain; not an oscillator and cannot generate radiation independently; few mature commercial products at terahertz frequencies
Extended Interaction Oscillator (EIO)	0.1–0.4 THz (100–400 GHz); mainstream commercial products in 0.14–0.3 THz	Continuous wave (CW)	Narrow tuning range (a few GHz to ~20 GHz); extremely narrow linewidth and high frequency stability; quasi-single-frequency output	Excellent power stability and low phase noise; mW to hundreds-of-mW output; simple structure with water cooling only

Terahertz quantum cascade laser (THz-QCL) is an optically pumped solid-state semiconductor terahertz radiation source, commonly operating in the frequency range of 1–5.5 THz. Its output waveform is primarily narrow-linewidth continuous wave, but quasi-continuous pulse output can also be achieved. The device requires cryogenic cooling for operation, with continuous output power reaching 1–100 mW, and peak power up to the watt level in pulse mode. It features excellent spectral coherence and high coherence, making it widely used in material spectral analysis, high-precision terahertz imaging, and long-distance terahertz detection.

Solid-state frequency multiplication terahertz sources are based on the non-linear frequency multiplication technology of Schottky diodes, generating continuous terahertz radiation through multi-stage up-conversion of low-frequency microwave signals. The entire system is composed entirely of solid-state semiconductor devices, requiring no vacuum packaging, and features room-temperature operation, tunable frequency, excellent spectral quality, and structural miniaturization. It is widely used in bio-spectroscopic measurements and cellular irradiation research in the 0.1–1 THz frequency band; however, due to the conversion efficiency limitations of semiconductor devices, the output power in the high-frequency terahertz range is relatively low. Currently, most sources on the market are widely applied.

Current terahertz radiation sources in the two major categories of electronics and photonics face multiple common technical bottlenecks: both exhibit extremely low energy conversion efficiency, with room-temperature output power generally limited to the micro-watt to milli-watt range, and high-frequency power attenuation is prominent. A single set of equipment cannot achieve continuous tuning across the 0.1–10 THz full frequency range, leaving obvious tuning gaps; high-power, high-stability models require high-voltage power supply or cryogenic cooling, resulting in bulky system size and poor integration, making miniaturization for in vivo experiments difficult. Additionally, the beam uniformity of both types of light sources is poor, and intrinsic noise interference is significant. Furthermore, terahertz waves are easily absorbed by water, leading to extremely shallow penetration depth, which can cause dose errors and temperature rise interference during quantitative experiments on nerve cells and brain tissues. Moreover, the equipment is expensive, and industry standards are lacking, making it difficult to compare experimental data across different platforms, thereby hindering the standardized research on terahertz neurobiological mechanisms and biosafety systems.

3. The effects and mechanisms of terahertz radiation on the nervous system

In the field of biomedicine, the significant impact of terahertz radiation on the nervous system has attracted focused attention. Its effects on the biological nervous system can be categorized into thermal and non-thermal effects based on physical properties. Research indicates that the biological effects of THz radiation not only depend on its frequency, power intensity, exposure duration, and exposure method but are also closely related to the biological species of the organism and the external environment. Therefore, the biological effects of terahertz radiation are highly complex and diverse, and there are still no definitive conclusions on some issues (Fig.3).

Terahertz radiation has very low photon energy, approximately 0.3 meV. Biological media, including water, have a strong ability to absorb terahertz radiation. After absorbing the radiation energy, it is converted into thermal energy, leading to an increase in the temperature of biological tissues and thus producing a thermal effect. In biological tissues, excessive thermal effects can lead to protein structure damage, cell death, tissue coagulation, activation of intracellular stress responses, and dysfunction of organelles. These are factors to consider when using terahertz waves safely.

Compared to the thermal effect, the non-thermal effect is much more diverse and complex (see Figure 8), and it is the primary way terahertz radiation affects living organisms, making it a key focus of current research. This paper will explore these effects separately at the molecular level, cellular level, synaptic and neural circuit level, as well as the tissue and animal behavior level[7].

At the molecular level, terahertz photons can match energy levels with hydrogen bonds, peptide bonds, and molecular van der Waals weak interactions, relying on non-thermal resonance perturbations to disrupt the protein hydration layer and alter spatial folding conformations, thereby targeting the regulation of neuro-related biomolecules such as amyloid proteins, neurotransmitter receptors, and nucleic acids, without breaking covalent chemical bonds. Png et al. first utilized terahertz time-domain spectroscopy in 2009 to distinguish Alzheimer's brain tissue from normal brain tissue, confirming that Aβ protein aggregation increases the tissue's characteristic absorption and refractive index, establishing a pathological protein detection method at the molecular fingerprint level. Subsequently, Zhu et al. discovered in 2022 through molecular dynamics simulations that 44.5 THz

radiation can shorten the hydrogen bond lifetime of the dopamine-DRD2 receptor, promoting ligand dissociation and regulating dopamine signaling. Peng et al. further validated in 2023 that 34.88 THz resonance can disrupt the β-sheet structure of Aβ protein, significantly inhibiting protein oligomerization, providing a basis for molecular intervention in Alzheimer's disease.

At the cellular level, terahertz waves exhibit both thermal and non-thermal effects on neurons, with the effects highly dependent on frequency, power, and irradiation duration. They primarily alter membrane permeability, ion channels, and mitochondrial homeostasis, presenting bidirectional outcomes of protection and damage. Borovkova et al. (2017) pioneered gliocyte toxicity experiments, irradiating rat gliocytes with 0.12–0.18 THz at 3.2 mW/cm², where apoptosis cells reached 2.4 times the control group after 5 minutes, confirming low-dose, long-duration non-thermal damage. Cherkasova et al. (2020) conducted frequency control experiments, showing that 2.3 THz irradiation induces hydrophilic nanopores in neurons and enhances transmembrane transport capacity, whereas 2.0 THz under the same conditions showed no significant changes, clarifying that membrane regulation has frequency-specificity.

Additionally, different terahertz waves can bidirectionally regulate synaptic plasticity and neural network excitability by modulating ion channels, synaptic proteins, and neurotransmitter secretion. Tan et al. first explored the effects of low-frequency terahertz on synaptic proteins and transmitters in 2019; 0.16/0.17 THz irradiation altered the secretion of glutamate and glycine in hippocampal and cortical neurons, while high-power long-term irradiation downregulated PSD95 and inhibited synaptic transmission. Zhong et al. further supplemented the high-frequency resonance mechanism in 2025, showing that 34.5 THz can activate the ATP-cAMP signaling pathway, promote dendritic spine growth, enhance glutamatergic circuit firing, and long-term potentiation.

At the organizational and animal behavior levels, changes in molecules and cells caused by terahertz waves will be progressively transmitted to the overall function of brain tissue, which can be used for unmarked spectral imaging of brain tissue and may also cause abnormalities in animal emotions and cognitive behavior. Kirichuk et al. first conducted in vivo animal behavior experiments in 2009, where continuous irradiation of rats with 0.15 THz and 3 mW/cm² for 60 minutes could induce depression-related behaviors; Png et al. completed in vitro brain tissue spectral detection in the same year 2009, finding that the brain tissue of Alzheimer's mice had significantly higher absorption and refractive indices at 1.44, 1.8, and 2.14 THz bands compared to normal samples, enabling unmarked identification of amyloid plaques[8].

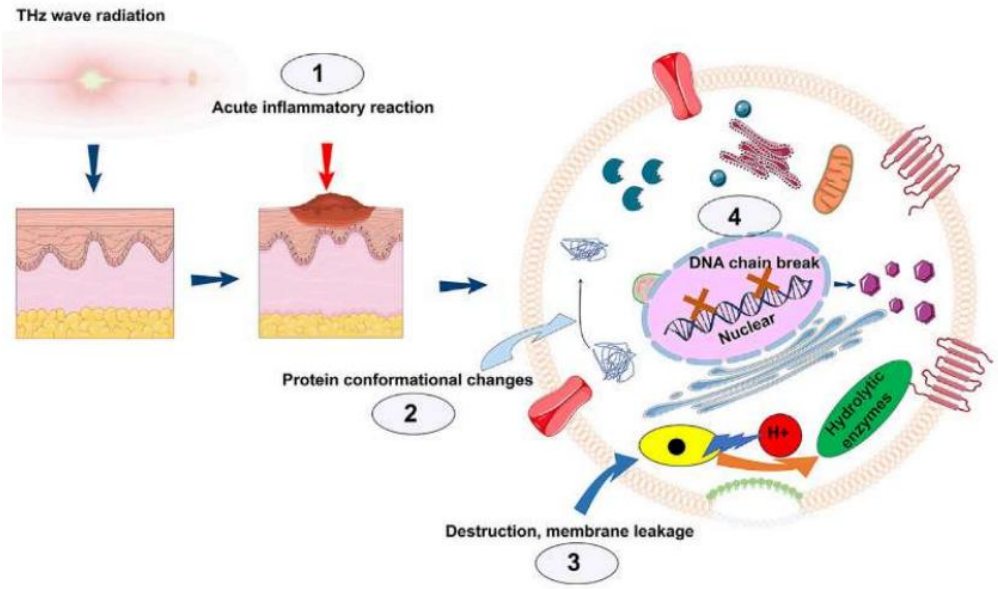


Fig. 3 (1) Terahertz wave induces acute inflammatory response in skin tissue, (2) Protein conformational changes, (3) Membrane damage or leakage, (4) Breakage of double-stranded DNA repair or replication.

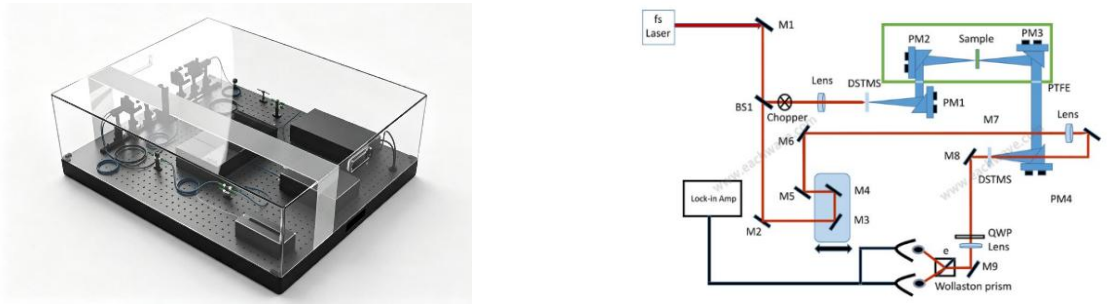
4. Terahertz detection technology in the application of the nervous system

Based on the unique physical properties and biological effects of terahertz waves, terahertz detection technology has enormous development potential in the biomedical field. At the current stage, the most widely used applications are terahertz time-domain spectroscopy and terahertz imaging technology.

Terahertz time-domain spectroscopy (THz-TDS) (Fig.4a) acquires the unique terahertz absorption and refractive index fingerprints of different biomolecules and brain tissues by detecting transmitted and reflected waves, enabling label-free, non-invasive qualitative and quantitative detection (Fig.4b). It is primarily used for the identification of neuropathological biomarkers, screening for brain tissue abnormalities, and quantitative analysis of neurotransmitters. In the detection of neurodegenerative diseases, Alzheimer's disease brain tissue, due to the extensive fibrous aggregation of Aβ amyloid protein, exhibits significantly higher refractive indices and absorption coefficients in the 0.1–10 THz band compared to healthy brain tissue. THz-TDS can directly differentiate Alzheimer's patients' brain tissue from normal samples. Additionally, the 34.88 THz characteristic spectrum can monitor the dynamic changes in the three aggregation forms of Aβ protein (monomers, oligomers, and fibers), quantify the inhibitory effects of fibrosis, and provide molecular detection methods for AD intervention research. In the context of brain injury and myelin disease, this technology can detect myelin-deficient brain tissue in rhesus monkeys, where the spectral signal amplitude of the diseased tissue at 0.5 THz and 1.0 THz is significantly lower than that of normal myelin samples, enabling early identification of demyelinating diseases. For traumatic brain injury, THz-TDS can capture spectral shifts caused by post-injury brain tissue edema and hemoglobin changes, allowing for lesion differentiation within 2 hours post-injury. Furthermore, THz-TDS can precisely quantify the concentrations of neurotransmitters such as glutamate and glycine in brain regions like the hippocampus and cortex. Spectral signals from neuronal samples treated with different irradiation parameters can distinguish changes in neurotransmitter levels, facilitating molecular validation of terahertz neuroregulation mechanisms. The entire detection process does not require fluorescent or staining markers and involves low photon energy, eliminating ionizing damage, making it suitable for batch pathological screening of ex vivo brain tissue samples. However, due to the strong water absorption properties of tissues, it is limited to thin ex vivo brain tissue samples[9].

Terahertz imaging technology is another cutting-edge technology in the field of biomedical engineering. It is considered a safe, effective, and convenient biomedical application technique for obtaining information about the spatial distribution and chemical composition of imaged samples. Terahertz radar imaging visualizes the spatial distribution of brain lesions based on the differences in dielectric and absorption properties between normal and pathological brain tissues, primarily used for brain tumor, traumatic brain injury, and neuroanatomical layering imaging. In brain tumor diagnosis, human glioma tissues exhibit higher refractive indices and absorption coefficients than normal brain tissues in the 0.3–1.5 THz range, with more significant spectral differences at higher WHO grades. Terahertz 2D imaging can clearly delineate glioma boundaries, differentiate tumor regions, edema regions, and normal brain tissue, providing support for rapid intraoperative pathological discrimination. For ex vivo rat traumatic brain injury models, multiscale terahertz imaging can reconstruct three-dimensional images of damaged brain tissues, intuitively presenting hemorrhagic edema areas. The detection process is non-invasive, with imaging contrast superior to conventional optical photos, and can be cross-validated with MRI results for injury assessment. In neuro-microstructure observation, near-field terahertz imaging technology uses atomic force microscopy and terahertz radiation to capture variations in near-field surface field strength of samples. Its ultra-high resolution can resolve cortical, corpus callosum, hippocampus, and white/gray matter layering structures in the brain. Relying on the dielectric constant differences between myelin and axons, it enables submicrometer-scale observation of nerve fibers, capturing microscopic injuries such as axonal swelling and ion concentration changes. This technology is non-ionizing and suitable for visualizing ex vivo brain tissue samples, but cerebrospinal fluid, skull, and tissue moisture

significantly attenuate terahertz signals, making in vivo deep brain tissue imaging currently unfeasible. It is primarily used for ex vivo brain slice and animal brain tissue pathology visualization research[10].



(a) (b)

Fig. 4 (a) Terahertz Time-Domain Spectroscopy System, (b) System optical schematic.

5. Conclusion

Current research indicates that terahertz radiation can significantly modulate the nervous system at multiple levels, including altering the conformation of biomolecules at the molecular scale and the dynamics of neurotransmitters; regulating neuronal excitability and synaptic plasticity; improving the pathological extent of neurodegenerative diseases; and even influencing the psychological state and behavioral patterns of organisms. However, at the same time, the study of the biological effects of terahertz waves still faces significant limitations. First, the mechanisms of terahertz biological effects are highly complex and related to the frequency, power, duration of terahertz irradiation, the structure and type of the organism, and the external environment. The reproducibility and relevance of different experiments are poor, making it difficult to standardize terahertz parameters. Second, the current academic consensus suggests that terahertz can induce non-thermal biological effects by disrupting weak interactions such as hydrogen bonds and protein hydration networks, but most of these remain at the level of observational and simulation calculations, making it challenging to directly capture molecular conformational dynamics in living cells. Biological tissues are rich in water, and terahertz radiation can easily cause local heat accumulation. Existing experimental methods struggle to fully distinguish between the observed cellular and neural responses resulting from non-thermal resonance effects versus thermal effects caused by secondary temperature rises, hindering the elucidation of mechanisms. Additionally, limited by the extremely shallow penetration depth of terahertz in hydrated biological tissues (only hundreds of micrometers), most current experiments focus on biomolecules, cells, and ex vivo brain tissue slices; stable irradiation of deep brain regions in living animals remains difficult. Furthermore, due to the limitations of terahertz source performance, the high cost and complexity of experimental equipment, and other constraints, most current research focuses on short-term acute effects, with a lack of data on the neurosafety of long-term low-dose continuous exposure and chronic cumulative damage. This creates a significant gap between the regulation of neurological diseases and the clinical application of non-invasive diagnosis and treatment.

Research on the neurobiological effects of terahertz radiation is still in its preliminary stages, but it has already demonstrated significant development potential in multiple fields, including biomedicine. In the future, with advancements in nanofabrication technology, improvements in terahertz source performance, and progress in brain-computer interface technology, it is expected to achieve a deeper understanding of the biological effects of terahertz waves and their mechanisms. This holds great significance for the theoretical development of neuroscience as well as clinical applications.

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