Review

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A new horizon for neuroscience: terahertz biotechnology in brain research

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From the Contents

Abstract

Terahertz biotechnology has been increasingly applied in various biomedical fields and has especially shown great potential for application in brain sciences. In this article, we review the development of terahertz biotechnology and its applications in the field of neuropsychiatry. Available evidence indicates promising prospects for the use of terahertz spectroscopy and terahertz imaging techniques in the diagnosis of amyloid disease, cerebrovascular disease, glioma, psychiatric disease, traumatic brain injury, and myelin deficit. *In vitro* and animal experiments have also demonstrated the potential therapeutic value of terahertz technology in some neuropsychiatric diseases. Although the precise underlying mechanism of the interactions between terahertz electromagnetic waves and the biosystem is not yet fully understood, the research progress in this field shows great potential for biomedical noninvasive diagnostic and therapeutic applications. However, the biosafety of terahertz radiation requires further exploration regarding its two-sided efficacy in practical applications. This review demonstrates that terahertz biotechnology has the potential to be a promising method in the field of neuropsychiatry based on its unique advantages.

Key Words: biological effect; brain; neuron; neuropsychiatry; neuroscience; non-thermal effect; terahertz imaging; terahertz radiation; terahertz spectroscopy; terahertz technology

Introduction

Terahertz (THz) waves, also called T-rays, are electromagnetic waves with a frequency range of 0.1–10 THz (**Figure 1**). The THz band is falls between microwaves and infrared waves, and is known as a key transition region from macroelectronics to microscopic photonics (Ferguson and Zhang, 2002; Sirtori, 2002). THz technology has promising prospects due to the unique physical characteristics of THz waves. Firstly, the skeletal vibrations and dipole rotations of biomolecules and non-bonding weak interactions, such as hydrogen bonds and van der Waals' forces, can effectively resonate with THz electromagnetic waves, showing specific absorption peaks in the THz region (Niessen et al., 2019; Wang et al., 2020b; Banks et al., 2023). These so-called THz fingerprint characteristics within biomolecules enable the label-free detection of their structural and functional states via THz technology (Sun et al., 2021; Yan et al., 2022; Zhang et al., 2022a). Secondly, the energy of a single THz photon is only 10^{-7} to 10^{-8} times that of medical X-rays, greatly limiting the ionizing damage to the organism (Hintzsche et al., 2012; Liu et al., 2021b). The good penetrability and high spectral resolution make THz waves the ideal imaging method (Naftaly et al., 2019). Furthermore, there is abundant THz electromagnetic information in organisms, which can be detected and characterized to identify the biological status and may even have potential medical value (Liu, 2018). Therefore, THz biotechnology is considered as one of the potential interdisciplinary methods to detect, image, and diagnose some diseases owing to its unique physical characteristics with non-invasive and label-free advantages (Nikitkina et al., 2021; Valušis et al., 2021).

Studies have proposed the wide distribution of THz waves in the nervous system and their involvement in neural activities, such as signal transmission and communication. Liu (2018) conjectured that the generation, transmission, and coupling of vertebrate neural signals might be in the form of high-frequency electromagnetic fields from the THz to the infrared region, allowing high efficiency of the utilization of biological energy in the neural system. This conjecture has been supported by recent explorations (Peng et al., 2023a; Tan et al., 2023). Furthermore, the dimensions of most structural components in the brain, such as nerve cells, meninges, and capillary vessels, lie at the scale of the THz wavelength (Chernomyrdin et al., 2023). In addition, the width of the THz pulse is more transient than the process of most nerve cell activities (Chen et al., 2022; Couture et al., 2023). Therefore, the compatibility between nerve tissues and THz waves makes it greatly significant to explore the applications of THz technology in brain sciences.

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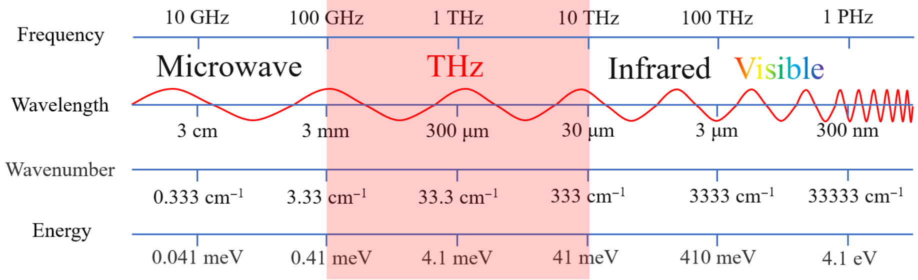

Figure 1 | The frequency, wavelength, wavenumber, and corresponding photon energy of THz waves in the electromagnetic spectrum.
THz waves are electromagnetic waves with a frequency of 0.1–10 THz, a wavelength of 0.03–3.0 mm, and a wavenumber of 3.33–333 cm^{-1}, corresponding to a photon energy of 0.41–41 meV. Created with Microsoft PowerPoint. GHz: Gigahertz; PHz: petahertz; THz: terahertz.

For a better understanding of the development of THz technology applied in brain sciences, we have reviewed the trends of published articles related to THz technology in five large databases, including Web of Science, IEEE Xplore, SPIE Digital Library, Scopus, and PubMed, over the past 20 years. The search term and retrieval type were "terahertz and X," where the "X" includes brain, neuroscience, cognitive, dementia, glioma, cerebrovascular, nerve, neurological, neuron, neurotransmitter, mental, psychiatric, psychological, mood, depression, anxiety, schizophrenia, and sleep. The results show a progressive increase in the number of published articles related to the application of THz technology in brain sciences over the last 20 years (**Figure 2**). The main neuropsychiatric diseases studied in the THz field are glioma, neural degeneration, traumatic brain injury (TBI), cerebrovascular disease, and mental disorders.

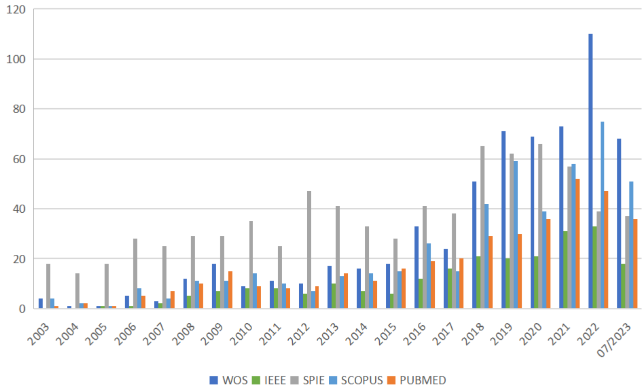

Figure 2 | The number of published articles related to the application of THz technology in brain sciences in the past 20 years (from January 2003 to July 2023).
The results of all five databases show an increasing trend in studies on THz technology applied to brain sciences. Created with Microsoft Excel. IEEE: The Institute of Electrical and Electronics Engineers; SPIE: International Society for Optical Engineering; THz: terahertz; WOS: Web of Science.

Owing to the above specific physical features, THz techniques have attracted the attention of researchers in the fields of biomedicine and neurosciences (Chernomyrdin et al., 2021, 2023). Among these techniques, the most frequently used is THz time-domain spectroscopy (THz-TDS), which is widely applied to detect vibrations and weak interactions in biomolecules (Fan et al., 2019; Patil et al., 2022; Kitagishi et al., 2023). For example, studies have found that different amino acids, vitamins, nucleobases, and even mutant nucleosides have their own unique THz spectral signatures, including absorption coefficients and refractive indices, suggesting the potential use of THz spectroscopic techniques for distinguishing between different kinds of small biomolecules (Fischer et al., 2002; Yamamoto et al., 2005; Zhao et al., 2009; Tang et al., 2020, 2021b). On the other hand, THz spectroscopy has also been successfully applied to investigate the structural and conformational properties of larger biomacromolecules, such as DNA, peptides, proteins, and lipids (Sun et al., 2021; Wang et al., 2022b). Studies have demonstrated the feasibility of employing THz spectroscopy for the sensitive detection of DNA of pathogens, including viruses (Li et al., 2022d), bacteria (Yang et al., 2016), and parasites (Wang et al., 2020a). A recent study used THz-TDS to explore the hydration shell of monomeric and dimeric insulin, which provided models of peptide aggregates related to the pathological process of neurodegenerative disease at an early stage (Wang et al., 2019a). The unique dynamical fingerprint of chicken egg white lysozyme, dihydrofolate reductase, photoactive yellow protein, and RNA G-quadruplex that change with the functional state can be precisely measured using polarization varying anisotropic THz microscopy (Niessen et al., 2019). As the primary component of biomembranes, different kinds of phospholipid bilayers, including distearoyl phosphatidylethanolamine, dipalmitoyl phosphatidylcholine, sphingosine phosphorylcholine, and lecithin bilayer, have their own specific spectroscopic features in the THz region (Lin et al., 2023). The THz spectroscopic technique can also be used to explore weak interactions in molecules, which plays an important role in life systems, such as the formation of base pairs in DNA and RNA (King et al., 2011). Not only does THz spectroscopy help to obtain the vibrational absorption peaks of nucleosides generated by intra- and inter-molecular interactions, it can also help to detect the weak interaction position corresponding to each characteristic peak and its contribution rate (Wang et al., 2022a). The binding and interaction between ligands and receptors alters the resonance between THz waves and biomolecules, resulting in changes of the THz spectrum that can be detected as biomarkers (Woods et al., 2016; Li et al., 2022c). Taking calmodulin-peptide as an example, there are different THz vibrations when calmodulin combines with different ligands (Varvdekar et al., 2022).

The THz imaging technique is another frontier of biomedical engineering, which can provide information about the spatial distribution and chemical components of samples; it is regarded as a secure, effective, and convenient technique for biomedical applications (Zhang, 2002; Yang et al., 2021). In contrast to X-ray, computed tomography, and positron emission tomography, the THz photon has a much lower energy and, therefore, does not result in ionizing damage, which ensures its safe application (Kamburoğlu et al., 2019). When compared to magnetic resonance imaging, THz imaging, with much less noise, has no strict requirements for magnetic field intensity and a confined space (Bajwa et al., 2017). Different tissues can be distinguished by virtue of the different THz absorptivity, reflectance, and refractive indices (Bajwa et al., 2017; Bychanok et al., 2020; Valušis et al., 2021). Darmo et al. (2004) demonstrated clear delineation of the cerebral cortex, callosum, hippocampus, lateral ventricles, and basal ganglion of rats by a reflection imaging system with a THz quantum cascade laser. Furthermore, owing to their different reflectance spectra, white matter and gray matter were distinguishable by THz imaging (Oh et al., 2011). Although

THz waves are strongly absorbed by polar liquids, such as water (Ge et al., 2021), which has been always considered as a great shortcoming (Wang et al., 2020c), it offers spatially resolved maps of water content in tissues (Nikitkina et al., 2021). For example, both physiological and pathological organic tissues can be distinguished via the THz imaging system due to their different water contents (Sy et al., 2010; Lee et al., 2018). In addition, a significant difference was observed between the response of normal skin and basal cell carcinoma to THz radiation, which is attributed to the increased interstitial water within diseased tissues and the change in vibrational modes of water molecules with other functional groups (Woodward et al., 2003). In addition, the relaxation of water molecules and longitudinal vibration modes among molecules in an organism share a similar time-scale with THz pulse width, which allows transient spectral analysis by THz technology (Cao et al., 2020). In recent years, metamaterials, including metal nanoparticles, graphene, and hybrid materials, as detection intensifiers, have been introduced into THz techniques to enhance the interaction between THz waves and the analyte, resulting in a strong change in the spectral response (Ou et al., 2020; Tohari, 2020; Roh et al., 2022; Wang et al., 2023a). A high-contrast THz imaging platform for real bio-samples without a dehydration process based on the nano-slot array metamaterial structure proposed in a recent study enabled a clearer depiction of the anatomical structure of the mouse brain (Lee et al., 2020). THz near-field imaging is another newly developed method to improve the resolution (Wang et al., 2021a, 2023b). The THz scattering-type scanning near-field optical microscope and near-field THz-TDS scanning system were developed to realize the imaging of single proteins and single cells, respectively (Li et al., 2020b; Yang et al., 2021). These techniques were also employed to successfully identify the corpus callosum region from the cerebrum region in mouse brain tissue slices with a lateral spatial resolution of the order of micrometers (Geng et al., 2019).

Consequently, the applications of THz technology for the detection of biomacromolecules, cells, tissues, organisms, and bio-imaging at all levels have become a biomedical research hotspot. The THz techniques have been used to detect human superficial tissues, such as the skin, tooth, breast, and cornea; however, the applications in deeper tissues or organs are still limited because of the high water content (Nikitkina et al., 2021). The human brain is enclosed in a bony skull and is full of cerebrospinal fluid, which hampers the penetration of THz waves into living human brain tissues. Therefore, most studies on the application of THz technology in the central nervous system have been focused on animal brains and excised human brains. These studies have provided new perspectives for exploring the pathogenesis, diagnosis, and treatment of some complex neuropsychiatric diseases, including neurodegenerative diseases, brain tumors, cerebral trauma, demyelinating lesions, and some mental disorders.

This review is divided into four sections. Section 1 provides an overview of THz imaging and spectroscopic techniques used for detection; section 2 covers the applications of THz technology in neuropsychiatric diseases, including neural degeneration, cerebrovascular disease, glioma, TBI, and some mental disorders, from different perspectives; section 3 addresses the potential effects of THz radiation on the nervous system; and section 4 briefly summarizes the limitations and prospects of THz technology in neuroscience. The entire article pertains to the application of THz technology at the molecular, cellular, and tissue (organ) levels. The schematic roadmap of this review is presented in **Figure 3**.

Detection Technology of Terahertz Applied in Neuropsychiatric Diseases

Applications of THz technology at the molecular level

Almost all psychiatric diseases, including dementia, delirium, schizophrenia, major depressive disorder, bipolar disorder, anxiety disorder, obsessive-compulsive disorder, and sleep disorder, are accompanied by changes in the concentration of neurotransmitters. Common neurotransmitters related to the biochemical mechanisms of psychiatric diseases include acetylcholine, dopamine, serotonin, norepinephrine, glutamic acid, γ-aminobutyric acid, and melatonin, which have significant effects on cognitive function, mood, behavior, sleep, and psychotic symptoms (Snyder and Ferris, 2000; Beecher and Wixey, 2023; García-Díaz et al., 2023; Romero et al., 2023; Su et al., 2023). Therefore, studying the interaction between neurotransmitters and THz electromagnetic waves is important for understanding the nervous system. Recent studies used the broadband air-plasma THz-TDS and combined it with density functional theoretical calculations to investigate the resonant absorption properties of a series of neurotransmitters, including dopamine (Cheng et al., 2019; Zhu et al., 2019, 2020; Guo et al., 2020; Shen et al., 2021; **Figure 4**), norepinephrine, γ-aminobutyric acid, melatonin, and glutathione. The results show that these molecules have characteristic THz absorption features, and the different absorption peaks correspond to the specific vibrational

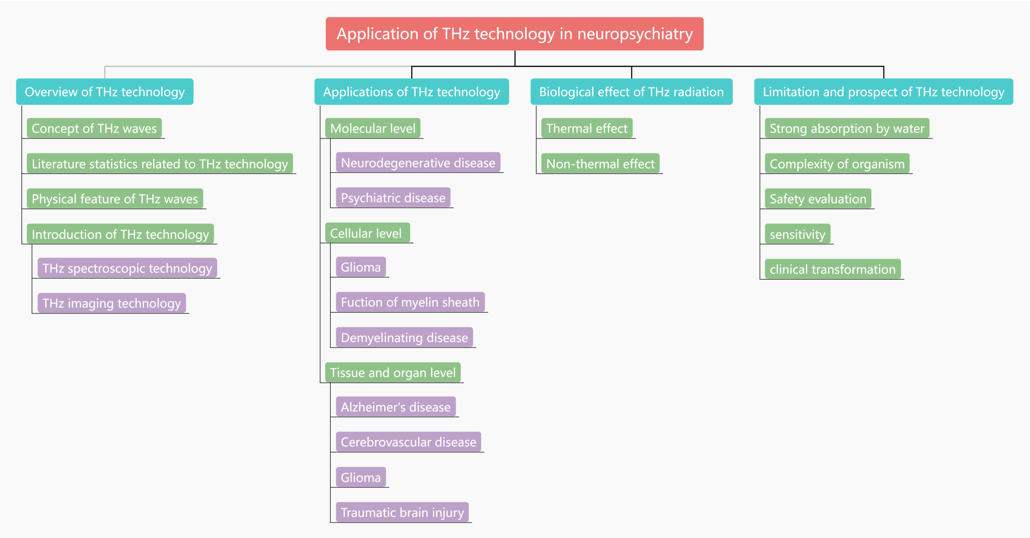

Figure 3 | The schematic roadmap of this review.
This review is divided into four sections. Section 1 provides an overview of THz technology; section 2 covers the applications of THz technology in neuropsychiatric diseases at the molecular, cellular, and tissue (organ) levels; section 3 addresses the biological effects of THz radiation on the nervous system; and section 4 briefly summarizes the limitations and prospects of THz technology in neuroscience. Created with Microsoft PowerPoint. THz: Terahertz.

modes that are related to the structures and conformations (Cheng et al., 2019; Zhu et al., 2019, 2020; Guo et al., 2020; Shen et al., 2021). Hydrogen bonds are found to play a critical role in the diversity of conformational changes in the neurotransmitters and the interactions between ligands and receptors (Zhu et al., 2020). The results suggested that the THz fingerprints have great potential applications for label-free biomedical detection. Another study by Peng et al. (2016) suggested that the components and proportions of different neurotransmitters and neurotrophies can be precisely identified and quantified based on the THz absorption spectra combined with the least square method, with an accuracy of approximately 95%. Puc et al. (2018) used THz spectroscopy and imaging to analyze melatonin and its pharmaceutical product Circadin. The results indicated that THz spectroscopic imaging can be an indispensable tool for spatial recognition of different substances.

Metabolic disorders (such as diabetes, hyperlipidemia, and obesity) and inflammatory reactions due to psychiatric diseases themselves and the application of atypical antipsychotics are vexing issues for both patients and psychiatrists (Pu et al., 2021). Patients with metabolic syndrome and chronic inflammation require long-term and frequent monitoring of blood glucose, lipid, and inflammatory markers; however, the currently available testing devices are usually invasive. THz technology may provide a new and noninvasive detection method for these patients. For example, Zhang (2009) reported the unique THz spectrum of cholesterol crystals in unstable atherosclerotic plaques. Some achievements have been made in blood glucose monitoring through THz techniques (Torii et al., 2017; Kim et al., 2021), laying the basis for the development of new monitoring devices. Cherkasova et al. (2016) showed the potential of THz attenuating total reflection for measurement of blood glucose levels. The THz signals reflected from the palms of six volunteers indicated qualitative trends between the variability of attenuating total reflection and the concentration of blood glucose (Cherkasova et al., 2016). Chen et al. (2018a) conducted quantitative research related to blood glucose tests by THz-TDS; they observed a linear correlation between the blood glucose level and THz spectra. The potential mechanism may involve the bonding of water molecules and glucose molecules, which alters the spectra shape. Recently, many studies have developed a series of advanced THz metasensors for the sensitive detection of glucose and inflammatory markers, which may facilitate in early diagnosis and real-time monitoring of metabolism and inflammation progress (Wang et al., 2021b, 2023c; Sun et al., 2022). They designed a broadband THz micro-photon sensor based on a pixelated frequency-agility metasurface and demonstrated its application ability to enhance and distinguish wideband absorption fingerprint spectroscopy detection. The target multiple enhanced absorption spectra of glucose molecules can be read with high sensitivity in a wide band region. This pioneering study is a tangible step towards the generalization and integrated miniaturization of wideband THz functional components (Sun et al., 2022; **Figure 5A**). They also developed an on-chip ultra-sensitive THz plasmonic metasensor based on a split-ring resonator combining functionalized gold nanoparticles conjugated with the specific antibody. The system sensitivity slope was up to 674 GHz/RIU, allowing for the detection of ultra-low concentrations of C-reactive protein and serum amyloid A down to 1 pM. The study opens up new avenues for the non-destructive and rapid quantitative detection of extremely dilute concentrations (Wang et al., 2023c; **Figure 5B**).

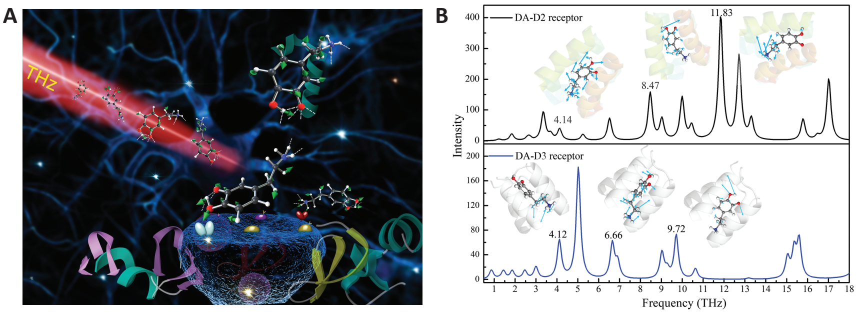

Figure 4 | THz signatures and vibrations of DA.
(A) Schematic illustration of interaction between THz waves and DA. (B) Simulated spectra in the THz region of the DA-D2 and DA-D3 receptors. Reprinted with permission from Zhu et al. (2020) Copyright © 2020 Royal Society of Chemistry. DA: Dopamine; THz: terahertz.

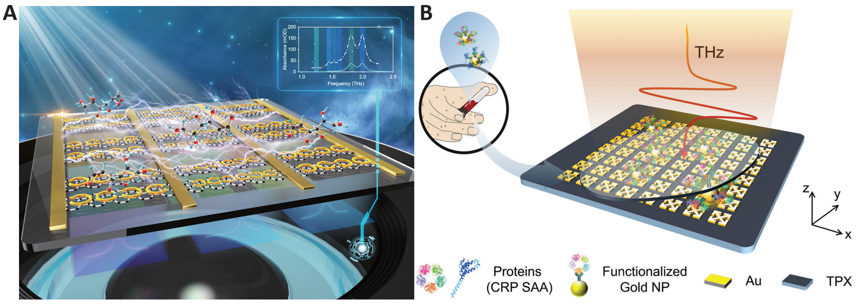

Figure 5 | THz metasensors for the sensitive detection of biomolecules and circulating biomarkers.
(A) A pixelated frequency-agile metasurface for THz molecular fingerprint sensing. (B) Schematic illustration of the THz plasmonic metasensor for distinguishing extremely dilute concentrations of solutions, including functionalized AuNPs immobilized antibody and the target analyte inflammatory markers on the low-loss l polymethylpentene substrate. Reprinted with permission from (A) Sun et al. (2022), Copyright © 2022 Royal Society of Chemistry, conveyed through Copyright Clearance Center, Inc.; and (B) Wang et al. (2023c), Copyright © 2023 John Wiley & Sons- Books, conveyed through Copyright Clearance Center, Inc. CRP: C-reactive protein; NP: nanoparticle; SAA: serum amyloid A; THz: terahertz; TPX: low-loss polymethylpentene.

Amyloidosis in the nervous system is a characteristic feature of neurodegenerative diseases, in which the core pathological mechanism involves protein misfolding and its excessive accumulation (Kaku and Berk, 2019). Common neurodegenerative diseases include Alzheimer's disease (AD), Parkinson's disease, dementia with Lewy body, frontotemporal dementia, and Huntington's disease; however, THz waves are readily absorbed by the cerebrospinal fluid due to its high moisture content, which is a big challenge for the application of THz technology to detect amyloidosis around neurons. In recent years, the combination of elaborately fabricated THz metamaterials, such as nanoconfined droplets, has shown great potential as biosensors to resolve this problem (Zhou et al., 2021). Yang et al. (2019) explored the influence of copper ions on the water dynamics at the nerve cell membrane interface using the abovementioned techniques; copper ion can bind to specific moieties in the lipid headgroups of the neuronal membrane and have a great impact on the outcome of neurodegenerative diseases. They integrated THz metamaterial sensor and nanoconfined droplets to improve the sensitivity of detection of amyloid-beta (Aβ) aggregates in liquids to a 1 nM limit, providing a valuable toolkit for bioanalytical applications in AD and other neurodegenerative diseases (Tang et al., 2021a). Due to the structural and conformational changes, amyloid proteins exhibit some spectral characteristics in the THz bands. The absorption spectra may provide information on the low frequency of vibrational modes, hydrogen bonds, and other weak interactions of the denatured amyloid proteins (Liu et al., 2010; Kawasaki et al., 2019). In a recent study, Heo et al. (2020) measured near-field THz conductance to identify the fibrillization state of Aβ protein. They found frequency-dependent conductance according to the different fibrillization states, including monomer, oligomer, and fibrillar forms of Aβ protein. The dementia quotient index was found to decline from the fibrillar form to monomer state (**Figure 6**). Patients with neurodegenerative disease are more sensitive to the effects of anesthetic agents (Li et al., 2022b). In contrast with the traditional view, new evidence points to the critical effects of anesthetics on intra-neuronal microtubules, which may play an important role in post-operative cognitive dysfunction (Craddock et al., 2015). The mechanism is related to the alteration of collective THz dipole oscillations in tubulins induced by their combination with anesthetics (Craddock et al., 2017).

Applications of THz technology at the cellular level

In a recent review of THz technology in intraoperative neurodiagnostics by Chernomyrdin et al. (2023), the dimensions of the nerve cell and their adjacent cellular structures were found to be comparable to THz wavelengths (**Figure 7**), making the nerve cell an equivalent miniature dielectric resonator to amplify intracellular THz signals. For example, Guo et al. (2021) found that THz waves were amplified if the dielectric constant of a nerve cell was higher than that of the external medium. Furthermore, as the dielectric constant of the external medium increased, the resonance became closer to the cytomembrane, and the focusing of THz waves induced by nerve cells grew stronger, which was referred to as the weak resonance effect (Guo et al., 2021). The resonance showed a positive relationship with cell size and THz frequency, and could simultaneously enhance the transmission of THz signals in nerve fibers (Guo et al., 2021). Thus, the weak resonance effect provides a new perspective to explore the interaction between THz waves and nerve cells, helping to explain the transmission mechanisms of THz waves in the central nervous system.

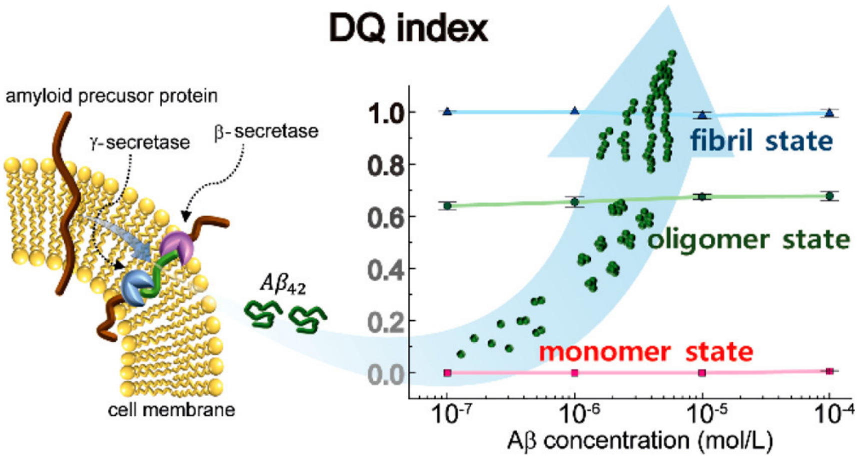

Figure 6 | Identifying fibrillization state of Aβ protein via near-field THz conductance measurement.
The dementia quotient index increased progressively from the monomer state to fibril state. Reprinted with permission from Heo et al. (2020) Copyright © 2020 American Chemical Society, conveyed through Copyright Clearance Center, Inc. Aβ: Amyloid-beta; DQ: dementia quotient; THz: terahertz.

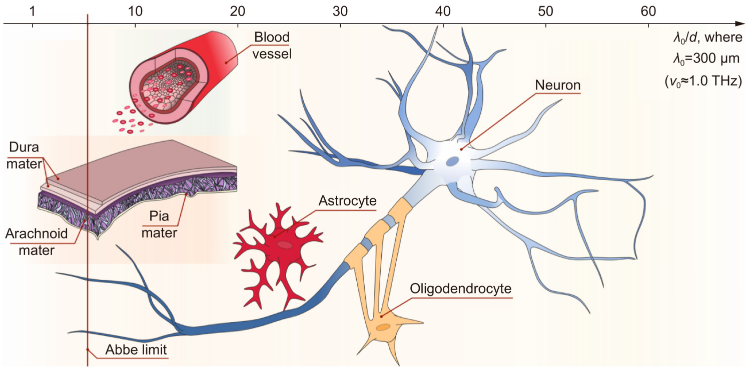

Figure 7 | Structural features of brain tissues at the THz wavelength scale.
The horizontal axis depicts the ratio between the typical size of the structural elements and the typical free-space wavelength λ_0 = 300 μm (ν_0 ≈ 1.0 THz), while the vertical solid red line shows the λ/2-Abbe diffraction limit. Reprinted with permission from Chernomyrdin et al. (2023), under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/lisceses/by/4.0/). THz: Terahertz.

The transient physiological processes of several nerve cell activities, such as the release of neurotransmitters in synapses, ion flow across membrane, dynamic changes in the membrane potential, and the conduction of electrochemical signals (Karpova et al., 2023; Krishnamoorthi et al., 2023), can be detected by THz waves in the femtosecond width of the THz pulse (Kampfrath et al., 2013; Chen et al., 2022; Couture et al., 2023). Furthermore, THz waves have a relatively high signal-to-noise ratio to ensure the stability (Mine et al., 2022). The transient and stability features endow THz waves with some advantages that affect the activities of nerve cells. Vernier et al. (2015) reported that sub-ns (≤ 500 ps) THz electric pulses induced action potentials in neurons of the rat hippocampus, which caused calcium transients in neuroblastoma-glioma hybrid cells, which resulted in increased membrane permeability within 1 ns.

Ionic contrast THz near-field microscopy can be used as a functional imaging tool for neurons and nerve fibers (Masson et al., 2006). When associated with full three-dimensional simulation of the axon-aperture near-field system, the axon geometry can be precisely measured, enabling direct visualization of neuronal swelling induced by temperature changes or neurotoxin poisoning. Variations in the axonal ion concentration as small as 10 μM and a water volume of 20 fL have been successfully detected by virtue of this technique (Masson et al., 2006).

The THz technology has been used to explore tumors for approximately 20 years. It was firstly adopted to perform diagnostic studies on cancers in superficial tissues, such as basal cell carcinoma (Woodward et al., 2003). Currently, THz technology has been utilized in the detection many kinds of tumors, including glioma (Globus et al., 2019; Li et al., 2020a, 2022a; Shi et al., 2021, 2022; Wang, 2021; Yoshida et al., 2021; Ke et al., 2022; Chakraborty et al., 2023; Cheon et al., 2023; Sun et al., 2023; Zhan et al., 2023). Wang et al. (2019b) offered a mode based on cell-free thickness to detect the dielectric characteristics of living cells. The THz dielectric characteristics of glioma cells were found to be different from glial-like cells, which were closely correlated to the quantity, intracellular fluid, and structure of cells (Wang et al., 2019b). The detection of biomarkers in glioma cells is another focus in THz applications. Peng et al. (2018) used THz-TDS to detect L-2-hydroxyglutaric acid disodium salt in real human brain glioma cells. Zhang et al. (2021b) developed a metamaterial-based biosensor, consisting of cut wires and split ring resonators, to realize polarization-independent electromagnetic-induced transparency at THz frequencies. The results showed that the mutant and wild-type glioma cells can be directly distinguished by observing the variations in the electromagnetic-induced transparency resonance frequency and magnitude, and that the dependence on cell concentration is quite different between these two types of glioma cells. These findings demonstrate the potential application of THz technology in the molecular classification of gliomas (**Figure 8**).

From the physiological perspective, the myelin sheath created by oligodendrocytes plays a key role in the function of the central nervous system. It is conjectured that the physical field of vertebrate neural signals should be the high frequency electromagnetic field from THz to infrared (Liu, 2018), which was demonstrated by recent studies (Liu et al., 2019; Zhang et al., 2022c). Zhang et al. (2022c) demonstrated the spatially resolved (in sub-nm) dielectric spectrum of the phospholipid bilayer of the myelin sheath in the abovementioned wide spectroscopic range. Liu et al. (2019) reported that myelin can serve as an infrared dielectric waveguide because its refraction index is approximately 2-fold higher than the outer medium or inner axon at that abovementioned spectroscopic range. They also suggested that the sheath can confine the infrared field energy within itself and allow the propagation of an infrared signal at the mm scale without dramatic energy loss. The energy of signal propagation is supplied and amplified when crossing the Ranvier node. Two recent studies proposed that nicotinamide adenine dinucleotide reduction in the tricarboxylic acid cycle releases dozens of THz nicotinamide adenine dinucleotide-photons, which are then coherently and resonantly harvested by the myelin sheath to form myelin polariton to enhance the energy utilization efficiency of neurons (Song and Shu, 2020; Peng et al., 2023a). As a hybrid state of photons and myelin, myelin polariton carries myelin information, transmitted through the Ranvier node, which is then exchanged between parallel neurons (Song and Shu, 2020; Peng et al., 2023a). These results demonstrate the positive role of the myelin sheath in increasing the conduction velocity and reducing the energy consumption from a quantum perspective (Song and Shu, 2020; Xiang et al., 2021). Other subcellular membrane structures, including the endoplasmic reticulum, Golgi apparatus, and mitochondrial cristae, may share similar energy-efficient mechanisms to the myelin sheath (Peng et al., 2023a).

From the pathological perspective, a myelin deficit in the brain leads to paralysis, sensory-motor dysfunction, cognitive impairment, psychiatric disorder, and even death. Darmo et al. (2004) considered that the white matter has a relatively lower signal intensity in THz images due to the mass content of myelin, which consists of lipids. Ohno and Ikenaka (2019) reported that the absorbance and reflectivity of THz waves in the white matter

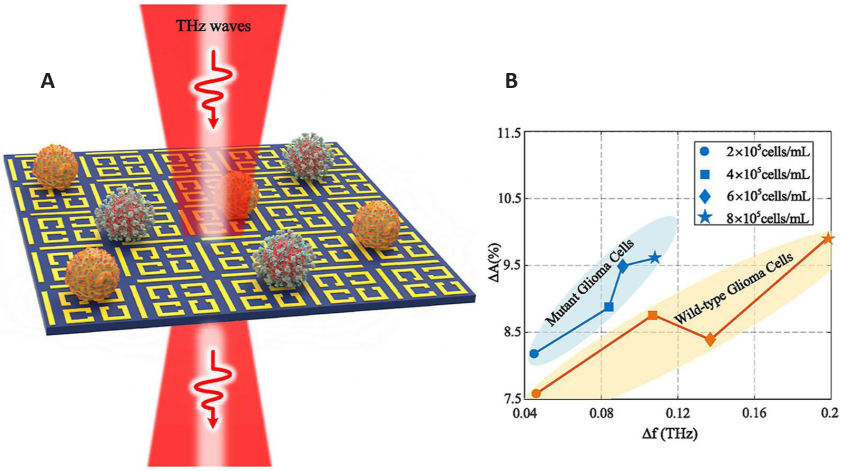

Figure 8 | Highly sensitive detection of malignant glioma cells using a metamaterial-inspired THz biosensor based on electromagnetically-induced transparency.
(A) Schematic illustration of the polarization-independent THz metamaterial biosensor based on electromagnetically-induced transparency. (B) The resonate frequency shifts and the peak magnitude variations for mutant and wild-type glioma cells as the concentration changes. Reprinted with permission from Zhang et al. (2021b) Copyright © 2021 Biosensors & Bioelectronics published by Elsevier Ltd., conveyed through Copyright Clearance Center, Inc. THz: Terahertz.

were lower than in the gray matter for the same reason. A recent study conducted by Zou et al. (2017) used principal component analysis of the time-domain THz signal to explore myelin deficits in mice and rhesus monkeys. The amplitudes of spectra in myelin-deficit mouse brains were lower than those of normal brains, while the amplitudes of these regions in rhesus monkey brains with a myelin deficit were higher than those of normal brains. These studies indicate the potential use of THz techniques for the detection of myelin deficits in the brain; however, the complexities and challenges of these methods should be acknowledged and addressed by further investigations.

Applications of THz technology at tissue and organ levels

Due to the nonionizing and noninvasive nature of THz waves, as well as the resolution of the THz spectrum, the application of THz spectroscopy and imaging in the study of tissues and organs has attracted extensive attention (Fitzgerald et al., 2003; Chernomyrdin et al., 2023). Using snap-frozen human brain tissue samples from AD patients, Png et al. (2009) found reduced THz absorption in the cingulate gyrus and inferior frontal gyrus and increased absorption in the superior frontal gyrus. They also studied the refractive index of these AD tissues by THz-TDS, which was found to be significantly higher than that of normal brain tissues, indicating more amyloid plaques in AD patients (Png et al., 2009).

Early detection of atherosclerotic plaques is of paramount importance as it is the fundamental pathological change in cerebrovascular disease. As a potential detection method, the THz technique has been utilized in dermatology. Similar to the skin, blood vessels also consist of three layers, namely the intima, media, and adventitia. Although the intima is too thin to meet the THz spatial resolution, the media and adventitia can still be distinguished by THz spectroscopic techniques. Furthermore, the intima-media thickness can be determined if the intima and media are considered as a single entity (Nezu et al., 2016; Sun et al., 2018). Accumulation of lipids in the atherosclerotic plaque between the intima and media will increase the intima-media thickness, rendering it amenable to detection by THz-TDS (Zhang, 2009). In addition, it will provide more information about the atherosclerotic plaque if the cholesterol spectrum can be detected. A previous study showed a lower frequency of atherosclerotic plaques than normal vascular tissues due to the less water content in plaques. For the same reason, smaller peaks occurred in the absorption spectrogram of atherosclerotic plaques compared to normal vascular tissues (Zhang, 2009).

Cerebral ischemia is one of the most common neuropsychiatric diseases and one of the primary causes of stroke. Sustained ischemia leads to irreversible neuronal damage; therefore, early diagnosis and treatment of cerebral ischemia is a contemporary research hotspot (Leiva-Salinas et al., 2011). Due to the different optical characteristics of interstitial water, cell arrangement, and cell density, THz techniques provide a new method to detect cerebral ischemic tissues. Li (2014) used transmission-type THz-TDS to detect fresh brain of rats at four time points (3, 6, 12, and 24 hours). The absorption coefficient curves of cerebral ischemic tissues at all these four time points were significantly different from those of normal brain tissues, and the peak-valley difference of cerebral ischemic tissues was obviously decreased at frequencies of 1.4–1.9 THz. These findings were attributed to the reduced cell density and increased water content in the cerebral ischemic area. In this study, cerebral ischemic tissues were detected after 3 hours via THz-TDS, which was in accordance with the results of the hematoxylin and eosin staining. Zhang et al. (2016b) conducted a similar study comprising six time points (0, 1, 3, 6, 12, and 24 hours). They reported that, with the prolongation of ischemic time, the absorption of THz waves in cerebral ischemic tissues increased initially and then decreased after reaching the peak at 6 hours. In another study by Wang et al. (2020e), with the extension of ischemic time, the relative difference in the absorption coefficient between bilateral cerebral hemispheres of rat fresh tissues increased initially and then decreased, while that of paraffin-embedded tissues gradually decreased. These findings suggest that THz-TDS can detect cerebral ischemia at the earliest of 2 hours. The following potential underlying mechanisms may implicated in the detection of cerebral ischemia by THz technology: (1) brain edema caused by cerebral ischemic injury leads to the increased absorption of THz waves; (2) the decreased density of neurons after ischemic injury affects the peak-valley difference; (3) increased deoxyhemoglobin and intermediate products, such as excitatory amino acids and lactic acid, due to cerebral anoxia result in a variability in the absorption characteristics (Zhang et al., 2016b; Wang et al., 2020e).

Glioma is associated with the highest morbidity and mortality rates among primary brain tumors due to difficulties in distinguishing the boundaries between normal and tumor tissues (Ohgaki and Kleihues, 2005; Chernomyrdin et al., 2023). Despite developments in microsurgical techniques and neuronavigation, only approximately 60% of gliomas were found to be totally removed, as shown by magnetic resonance imaging performed within 48 hours after the surgeries (Brown et al., 2016). Therefore, new improved imaging methods are urgently required for glioma. THz techniques may be potentially useful for the precise detection of glioma (Chernomyrdin et al., 2023). Li (2014) explored surgically-removed human glioma specimens and found that the THz absorption coefficient, refractive index, and the dielectric constant in gliomas were all higher than those in normal tissues, especially at frequencies of 0.3, 0.55, and 0.76 THz. Gavdush et al. (2019) found different absorption coefficients and refractive indices for different pathological grades of glioma through THz-pulsed spectroscopy (**Figure 9**). Their subsequent study analyzed the effective complex dielectric response of glioma tissues featuring different grades at THz frequencies to develop models to describe the interactions between THz waves and glioma tissues in the framework of classical electrodynamics; the models demonstrated that water is the main endogenous label of glioma in the THz range (Gavdush et al., 2021). A pilot study by Mu et al. (2022) demonstrated that isocitrate dehydrogenase mutant and wild-type glioma tissues can be effectively distinguished using attenuating total reflection THz-TDS. In addition, THz imaging showed a high sensitivity in recognizing the boundaries between normal tissues and glioma tissues in rat brains, which may potentially help in the accurate delineation of surgical regions (Ji et al., 2016). Wu et al. (2019) used a continuous-wave THz reflection imaging system to explore brain gliomas in mouse models, which could clearly distinguish the glioma tissues from normal brain tissues at the frequency of 2.52 THz. The THz images showed a good correlation with magnetic resonance imaging, visual, and hematoxylin and eosin-stained images (Wu et al., 2019). In addition, the glioma tissues in this study presented higher refractive indices and absorption coefficients than normal brain tissues in the range of 0.6–2.8 THz (Wu et al., 2019). Furthermore, their spectral differences increased with frequency amplification. Yamaguchi et al. (2016) found that the water constant in gliomas of rats increased by 5%, and the nuclear proportion per unit area increased by 15% in gliomas through THz-TDS, which is considered to be the cause of the higher refractive index. Another study on the *in situ* recognition of brain gliomas in mice suggested that the main

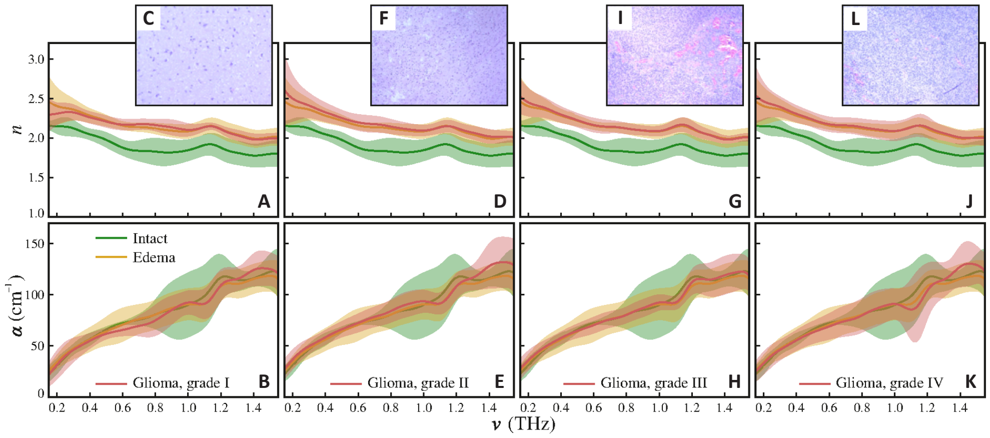

Figure 9 | **Different WHO grades of gelatin-embedded human brain gliomas *ex vivo*.**
(A–C) grade I; (D–F) grade II; (G–I) grade III; (J–L) grade IV. Reprinted with permission from Gavdush et al. (2019), under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/lisceses/by/4.0/). α: Amplitude absorption coefficient; *n*: refractive index; THz: terahertz; WHO: World Health Organization.

differences in the refractive index between glioma and normal brain tissues was concentrated around 0.4–0.6 THz, while the distinctions in the absorption coefficient primarily lay within the 0.4–0.9 THz range (Chen et al., 2018b). Based on the above studies, there are two noticeable broad trends in the use of THz technology for the detection of glioma. One is to conduct a pathological diagnosis by virtue of the high THz resolution, and the other is to develop specific and sensitive *in vivo* THz diagnostic techniques in surgeries.

TBI is one of the leading causes of morbidity, mortality, and disability worldwide. Due to the obvious post-TBI edema belt and the characteristic optical properties of the water content, water distribution, and cell density, THz technology may potentially help detect TBI at an early stage (Shi et al., 2018). A series of studies performed by the Key laboratory of Opto-Electronics Information Technology of Tianjin University used the THz transmission system to observe the spatial distribution of traumatic region inside rat brains. The rat TBI regions were found to have lower transmittance than normal areas, and the absorption coefficient varied with different degrees of severity (Zhao et al., 2018; **Figure 10**). Further studies explored the three-dimensional reconstruction of rat TBI based on THz imaging, which clearly demonstrated the three-dimensional distribution of TBI regions, thus showing the great potential of THz multi-depth slice imaging for the accurate diagnosis of TBI (Zhao et al., 2018; Wang et al., 2019c). Guo (2020) used THz-TDS to image brain tissue slice samples from TBI mice. The results suggested that the injured regions can be identified from the normal ones by TDS owing to the different THz refractive indices and absorption coefficients in these two regions. Wang et al. (2020d) reported a new method for the early diagnosis of blast-induced TBI through serum and cerebrospinal fluid based on THz-TDS. They demonstrated the spectral differences of serum and cerebrospinal fluid for different degrees of blast-induced TBI in rats at the early stage. Furthermore, the THz spectra of total protein in hypothalamus and hippocampus of blast-induced TBI rats were investigated at different time points after blast exposure, both of which indicated an increase in the differences from those in normal brains as the time extended.

Biological Effects and Safety of Terahertz Radiation on the Nervous System

The neuropsychiatric effects and safety aspects of THz radiation have evoked considerable concerns. Based on the physical characteristics of THz waves, the principle biological effects of THz radiation can be discussed with respect to thermal effects and non-thermal effects (Cherkasova et al., 2021). In 2000, the THz-BRIDGE project developed by the European Union marked the research surge of THz biological effects, bioventure, and potential genotoxicity (Gallerano et al., 2004). Subsequent studies have shown that the biological effects of THz radiation are related to the frequency, power intensity, exposure time, and irradiation mode. The biological effects also depend on the sample itself and the types. The response and sensitivity to THz waves differ depending on the biological target and the species. The results of bioeffects show complexity and diversity, some of which remain controversial (Hintzsche and Stopper, 2012; Zhao et al., 2014).

Thermal effects

Partial THz energy transmitted to organic tissues with a high water content was shown to be largely absorbed by water molecules, and then transformed into thermal energy, which directly heats up the objects (Kristensen et al., 2010). Mathematical models have shown that even a tiny duration of THz exposure can significantly increase the tissue temperature (Spathmann et al., 2015). Studies have indicated that the thermal effects generated by high-energy THz radiation might be the primary reason for biological damage. The thermal effects of THz radiation usually involve tissue coagulation, damage to structural proteins, induction of apoptosis, activation of stress reaction, and organelle dysfunction (Yu and Zhang, 2020). For example, it leads to changes in neuronal structure and function (Zhang et al., 2021a). However, acute inflammatory reactions induced by hyperthermia can help trigger the reparative process, and a proper thermal effect may also stimulate the growth and metabolism of cells (Yu and Zhang, 2020). A similar positive effect was also observed in neurons. In a recent study, short duration cumulative THz radiation (0.1–2 THz, maximum radiated power 100 μW, 3 min/d, 3 days) was found to promote the growth of neuronal cytosomes and protrusions (Shaoqing et al., 2023; **Figure 11**). The results suggested that the frequency and power of THz waves are the main determinants of field strength and temperature in neurons. The damage threshold for short THz exposure (0.1–1 THz) was shown to be 7.16 W/cm^2 (Danielle et al., 2010).

Non-thermal effects

The non-thermal effects of THz radiation have attracted widespread attention since being first proposed in the 1970s (Fröhlich, 1975). THz radiation can generate fierce oscillation, resulting in some biological effects, but without an obvious increase in the temperature (Xie, 2019). Studies have suggested that THz waves promote the unwinding of DNA duplexes in a non-thermal manner, due to the resonance of THz waves with the vibration of DNA bases, triggering disruption of the hydrogen bonds (Wu et al., 2020; Zhang et al., 2022a). Previous studies

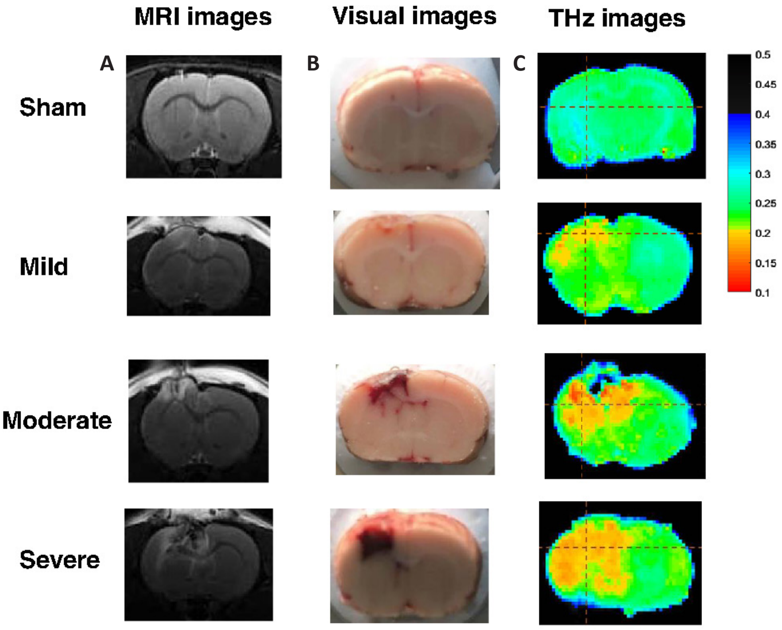

Figure 10 | High-sensitivity THz imaging techniques applied to TBI rats.
(A–C) MRI (A), visual (B), and THz (C) images of fresh brain tissues without and with different degrees of TBI. Reprinted with permission from Zhao et al. (2018), Copyright © 2018 SPIE, conveyed through Copyright Clearance Center, Inc. MRI: Magnetic resonance imaging; TBI: traumatic brain injury; THz: terahertz.

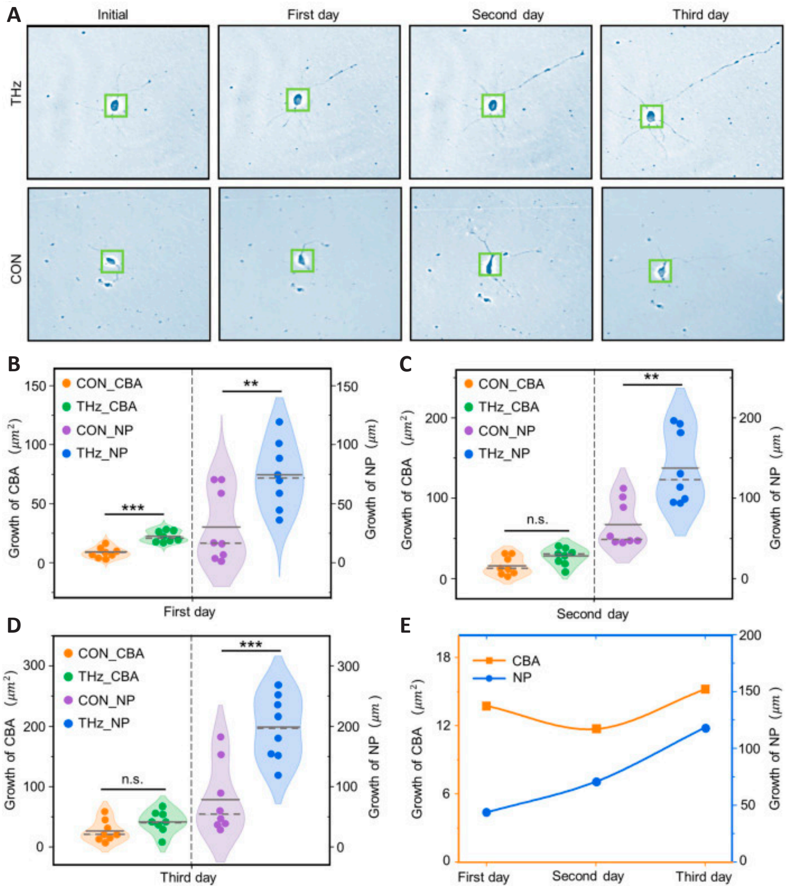

Figure 11 | THz radiation promotes the dynamic growth and development of cortical neurons.
(A) THz radiation promotes the dynamic growth and development of cortical neurons. (B–D) Cumulative THz radiation for 3 days promotes the growth of NP and CBA. (E) Relationship between THz radiation days and the growth of NP and CBA. Reprinted with permission from Ma et al. (2023), under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/lisceses/by/4.0/). CBA: Cell body area; CON: control; NP: neuronal protrusion; THz: terahertz.

have demonstrated that interactions between THz radiation and hydrogen bonds in organisms can generate low-frequency vibration within the molecules, resulting in conformational changes in proteins, thus affecting their catalytic activity (Fischer et al., 2002; Cherkasova et al., 2009; Lundholm et al., 2015). In addition, according to several theoretical models, non-thermal effects may be produced via nonlinear resonance mechanisms (Maniadis et al., 2011).

Neuronal membranes are highly active and sensitive to electromagnetic waves (Hu et al., 2022a). Despite the relatively low photon energy of THz waves, the resonance absorption by neuronal membranes can alter the electrical activity via non-thermal effects, providing information about their functional status. Several studies have explored the permeability of ion channels in neuronal membranes, which plays a key role in membrane permeability, nerve excitability, and signal transmission. They demonstrated that the resonant THz field can enhance the permeability of voltage-gated calcium channels, sodium channels, and potassium channels to manipulate their conduction, which has potential applications in therapeutic interventions, such as regulating osmotic pressure, rectifying ion deficiency, and inducing apoptosis of tumor cells with overloaded ions (Romanenko et al., 2017; Li et al., 2021b; Liu et al., 2021a; Guo et al., 2022; Hu et al., 2022b; Wang et al., 2022c; Ding et al., 2023; Zhao et al., 2023b, c; **Figure 12**). This regulation may potentially be applied for suppressing pathological pain due to peripheral neuropathy (Wang et al., 2016). On the other hand, such changes in permeability are reversible, and antioxidants can be applied to manage this process, providing a protective effect against excessive THz radiation (Zapara et al., 2015).

Neuroendocrine function and neuronal growth and apoptosis are also considered to be sensitive to electromagnetic radiation. Tan et al. (2019) explored the effects of THz radiation on primary cultured neurons from the hippocampus, cerebral cortex, cerebellum, and brainstem of the rat brain. The results showed that exposure to THz radiation induced an obvious decrease in the level of glutamate and an increase in the levels of glycine and alanine in the hippocampus, cerebellum, and brainstem regions, while an increase in level of glutamate and a decrease in level of alanine were observed in the cerebral cortex area. This phenomenon may be related to the cognitive function. Yi (2018) also explored the biological effects of THz radiation on primary neurons from the rat hippocampus. They found that the frequencies, output powers, radiation times, and sample collection time points can affect the activities of primary neurons. THz radiation for 30 minutes at 30 mW led to immediate increases in levels of methionine and valine (essential amino acids), glutamate (an excitatory amino acid), and tyrosine (the precursor of serotonin), which contributed to enhancing the synaptic plasticity; however, the output power of 10 and 50 mW were found to cause mitochondrial injury and promote cell apoptosis. A recent THz study on neuromodulation found that dozens of THz photons can resonate with a variety of typical neurotransmitter molecules, resulting in them absorbing photon energy to activate the transition to a high energy state (Tan et al., 2022a). THz radiation with power of 30 mW, pulse width of 2 μs, and repetition rate of 200 kHz can modulate postsynaptic currents, including the excitatory post-synaptic current, inhibitory post-synaptic current, miniature excitatory post-synaptic current, miniature inhibitory post-synaptic current, and evoked currents. Thus, THz is a potential novel method of neural regulation. Zhao et al. (2009, 2023a) investigated the effects of THz radiation on morphology, cellular activity, apoptosis, and neurotransmitter release in rat primary hippocampal neurons. They found no significant effect of THz radiation on neuron growth and differentiation; however, THz sources with specific power intensities could induce apoptosis and alter the cellular activity of primary hippocampal neurons, as well as regulating the release of different amino acid neurotransmitters, which in turn affect the homeostasis of neuronal excitability. Another study found that 0.138 THz waves can modulate dynamic neuronal growth and synaptic transmission (Ma et al., 2023). Additionally, a cumulative effect of THz radiation on the promotion of neuronal growth has been demonstrated (Ma et al., 2023). Ma et al. (2020) explored the non-thermal effects of cell injury induced by THz radiation at a frequency of 0.22 THz in Neuro-2a cells. They found an obvious reduction in neurite length and the number of branch points; furthermore, the mRNA levels of Tubb3 and Syp were notably downregulated when exposed to a power density of 50 mW/cm^2. Borovkova et al. (2016) showed a dose-dependent cytotoxic effect of THz radiation. They found that the number of apoptotic rat glial cells increased by 1.5, 2, and 2.4 times after receiving THz radiation (0.15 THz, 3.2 mW/cm^2) for 1, 3, and 5 minutes, respectively (Borovkova et al., 2016). Thus, THz radiation is considered to have a two-sided effect on neurons and their generated neurotransmitters. However, Sitnikov et al. (2023) recently investigated the effects of high-intensity THz radiation on human directly reprogrammed neural progenitor cells and neuroblastoma cells. They found that the exposure of non-tumor and tumor cells to THz pulses (0.1–3 THz) with an intensity of 21 GW/cm^2 and an electric field strength of 2.8 MV/cm for 30 minutes induced neither a noticeable genotoxic effect nor a statistically significant change in the proliferative activity and cell differentiation. The non-thermal effects of THz radiation on neurons and neuroendocrine function are summarized in **Tables 1** and **2**, respectively.

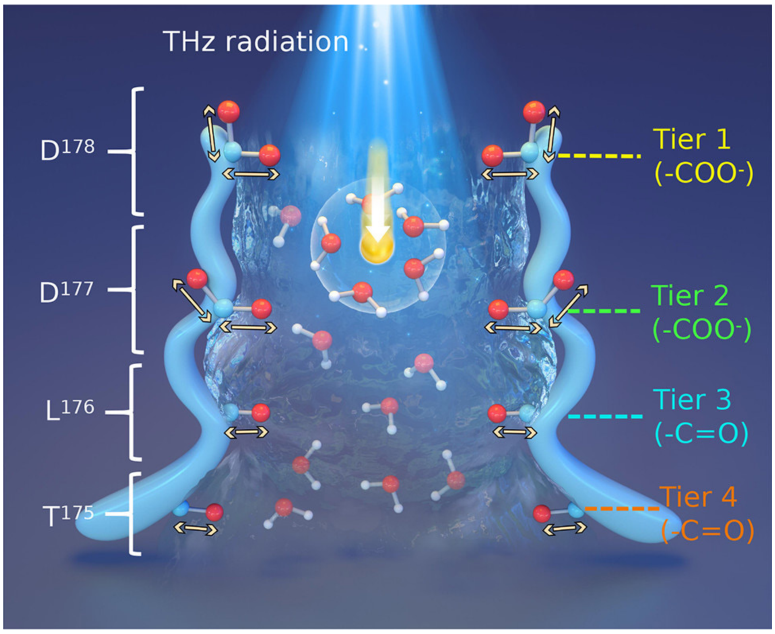

Figure 12 | Schematic illustration of accelerated Ca^{2+} permeation through the calcium channel under THz radiation.
The blue and red ball and stick models signify key functional groups; the red and white ball and stick models mean water molecules; the light from the top denotes THz field; the yellow ball indicates Ca^{2+} moving in the pore; the two-headed arrows denote the vibrations of C–O bonds. This figure shows that the resonant THz field can enhance the permeability of voltage-gated calcium channels. Reprinted with permission from Li et al. (2021b) Copyright © 2021 American Chemical Society, conveyed through Copyright Clearance Center, Inc. THz: Terahertz.

Table 1 | **Effects of terahertz (THz) radiation on neurons**

Frequency (THz)	Intensity (mW/cm^2)	Exposure time (min)	Effect	Reference
3.68	10–20	60	Neuronal growth disorder	Ol'shevskaia Iu et al., 2009
2.1	30	1	Decreased neuronal membrane potential, morphological disturbance, neuronal death after 2 h of radiation	Olshevskaya et al., 2010
2.1	3	1	Neuronal death after 3 h of radiation	
0.12–0.18	3.2	1–5	Increased neuronal mortality	Borovkova et al., 2016
0.05–2	5×10^{-4}–5×10^{-2}	3	Increased neuronal protrusions	Tsurkan et al., 2012
0.12	10	30	Structural injuries and cellular apoptosis	Zhao et al., 2023a
0.157	50			
0.12	10	10	Swelling of neuronal mitochondria, increased neuronal apoptosis	Yi, 2018
0.157	50	30	Mitochondrial impairment	
0.141	30	20	Increased neuronal activity and synaptic plasticity	Zhao et al., 2019
0.138	7	20 min/d, 3 d	Improved neuronal growth and synaptic transmission	Ma et al., 2023
0.22	50	5	Reduced neurite length and branch points	Ma et al., 2020
0.1–3	21×10^{12}	30	No effect	Sitnikov et al., 2023
0.05–1.2	928	3	Inhibited growth of neuronal protrusions	Sulatsky et al., 2014
	78		Promoted growth of neuronal protrusions	

Table 2 | **Effects of terahertz (THz) radiation on neuroendocrine function**

Type of neurons	Frequency (THz)	Intensity (mW/cm^2)	Exposure time (min)	Effect	Reference
Primary hippocampal neurons	0.17	10	60	Increased levels of Gly and Ala	Tan et al., 2019
	0.16	50	6	Decreased levels of Glu	
	0.16	50	60	Decreased levels of Glu; Increased levels of Gly	
Primary cortical neurons	0.17	10	60	Increased levels of Glu; Decreased levels of Ala	
Primary cerebellar neurons	0.17	10	6	Decreased levels of Glu; Increased levels of Ala	
	0.17	10	60		
	0.16	50	6		
	0.16	50	60		
Primary brainstem neurons	0.17	10	6	Increased levels of Gly	
	0.17	10	60		
	0.16	50	6	Decreased levels of Glu	
	0.16	50	60	Increased levels of Gly and Ala	
Primary hippocampal neurons	0.12	10	10	Decreased levels of Arg, Ile, Leu, Lys, Pro, Ser, Phe, and Thr; Increased levels of Gly and Glu	Yi, 2018
	0.141	30	20	Decreased levels of Arg, Ile, Leu, Lys, Pro, and Thr; Increased levels of Gly, Glu, Ala, Met, Tyr, and Val	
	0.157	50	30	Decreased levels of Arg, Ile, Leu, Lys, Pro, Ser, and Thr	
Primary hippocampal neurons	0.12	10	30	Decreased levels of Leu, Lys, Arg, Thr, Phe, Pro, and Ser; Increased levels of Glu and Cys	Zhao et al., 2023a
	0.157	50			

Ala: Alanine; Arg: arginine; Cys: cysteine; Glu: glutamate; Gly: glycine; Ile: isoleucine; Leu: leucine; Lys: lysine; Met: methionine; Phe: phenylalanine; Pro: proline; Ser: serine; Thr: threonine; Tyr: tyrosine; Val: valine.

Recent studies have shown that endogenous THz photons released by phosphate bond breakage in adenosine triphosphate (ATP) or deoxynucleotide triphosphate can drive biological activities, such as DNA replication and polymerization (Li et al., 2021a; Zhang et al., 2022b; Yang et al., 2023). Tan et al. (2023) found that exogenous THz radiation can recover the reduced action potential emission frequency due to an inadequate ATP supply and alter the amount of ATP and reactive oxygen species in nerve cells. These findings suggest that THz photons may play a key role in neural activities, and the exogenous THz photons input can be used to regulate various brain activities (Tan et al., 2023).

In addition to the effects on neurons, THz waves may also modulate the binding between antipsychotics and their receptors. The application of antipsychotic drugs is a challenge in the treatment of psychiatric diseases owing to their adverse reactions, such as extrapyramidal symptoms, metabolic syndrome, anticholinergic effects, and postural hypotension. THz waves can potentially be used as a modulatory method to promote the dissociation of high-affinity antipsychotics and, thus, diminish their side effects. In a recent study, the 4.0 THz field was introduced to the dopamine-2 receptor-risperidone complex, which significantly weakened the salt bridge binding that anchors risperidone to the dopamine-2 receptor (Li et al., 2022c). The findings showed that the 4.0 THz waves reduced the affinity between the dopamine-2 receptor and risperidone by 71%; furthermore, via conformation modulation, it accelerated the dissociation of risperidone (Li et al., 2022c). It is estimated that enhancement of the dissociation rate due to THz radiation could be as fast as the enzyme's catalysis.

Although the non-thermal effects of THz radiation have been explored in living rats, mice, and fruit flies, there are some discrepancies among the findings. Continuous exposure of mice to high-energy radiation (0.15 THz, 3 mW/cm^2, 60 minutes) was found to induce depressive behavior (Kirichuk et al., 2009). A similar result was reported by Kirichuk et al. (2014). In addition, exposure of mice to 3.6 THz radiation induced signs of anxiety

(Bondar et al., 2008). However, other studies have found some beneficial non-thermal effects. For example, the antioxidant levels, electrolyte compositions, and hemodynamic parameters of rats were significantly improved after receiving THz radiation; the underlying mechanisms were reported to involve blockade of inhibitors of nitric oxide synthase (Kirichuk and Tsymbal, 2012).

Some researchers consider THz radiation as a potential treatment method for cerebrovascular diseases. A previous study has shown that THz radiation can be strongly absorbed by nitric oxide, which explains the improvement in hemorheological parameters (Ivanov, 2013). In patients with angina, THz radiation (0.24 THz, 1 mV/cm^2) was found to improve blood viscosity and the deformability of erythrocytes (Kirichuk et al., 2008). Kiryanova et al. (2021) reported that infrared radiation modulated by THz waves improved the cognitive function of stroke patients in the acute phase. The underlying mechanism was hypothesized to be restoration of an adequate blood supply in the affected hemisphere (Kiryanova et al., 2021). In a study by Reukov et al. (2016), a combination of infrared-THz radiation and acupuncture was found to improve the recovery of stroke patients during a 2-year follow-up. In addition to cerebrovascular diseases, THz waves may have potential applications for the treatment of hearing disorders without introducing any exogenous implants. Tan et al. (2022b) used THz waves to regulate hearing perception in guinea pigs by reversibly modulating the currents in cochlear hair cells. The study showed that THz waves reversibly increased mechano-electrical transducer currents and voltage-gated potassium currents in cochlear hair cells through the collective resonance of –C=O groups. Measurement of the auditory brainstem response indicated that THz waves increased the hearing sensitivity of guinea pigs by 10 dB (Tan et al., 2022b).

As the core pathological feature of neurodegenerative diseases, such as AD, the degradation or clearance of accumulated Aβ protein has been the most widely investigated therapeutic method. A recent *in vitro* study suggested that the thirties THz waves decreased the aggregation speed of Aβ fibrils to approximately 80% (Peng et al., 2023b). This was attributed to the fact that the infrared electromagnetic waves at this frequency could resonate with Aβ fibrils. The resultant loosening of the structure of β-sheets with more coil and bend regions may have altered the conformation of Aβ proteins to slow down the fibrotic process, rather than protein degeneration (Peng et al., 2023b; **Figure 13**).

Limitations and Prospects of Terahertz Technology in Neuropsychiatry

Although remarkable advances have been made in the application of THz technology in brain sciences, some limitations need to be acknowledged. Firstly, THz waves cannot penetrate deep-seated nerve tissues due to strong absorption by water (Ge et al., 2023). However, the penetrating ability of THz waves can be improved with the use of nanotechnologies, such as metal nanorods and superparamagnetic iron oxide nanoparticles, or other agents, such as glycerin (Tseng et al., 2010; Zhang et al., 2016a; Charkhesht et al., 2019). On the other hand, the strong absorption of THz waves by water is not devoid of any merit; the change in water content can be a source of THz signal contrast when exploring edematous tissues in the brain (Li, 2014; Bajwa et al., 2017; Zhao et al., 2018; Chernomyrdin et al., 2023; Ge et al., 2023).

Secondly, specific responses to THz radiation are often difficult to detect at the organism level, and related research findings have sometimes been inconsistent or even contradictory due to the complexity of organism structures and the diversity of biosystems. Other potential reasons may include the lack of standardized THz experimental procedures, insufficiency of appropriate THz sources, the use of particular THz techniques with different sensitivities, a diversity of research models and experimental environments, and the shortage of tools for the accurate assessment of the initial functional state of the biological samples. Thus, the establishment of homogeneous research models and standardized procedures is a key imperative to enhance the comparability of different studies (Cherkasova et al., 2020; Yu and Zhang, 2020; Zhang et al., 2021a).

Thirdly, the safety evaluation of THz radiation is the precondition for its further application in neuropsychiatry. However, most studies related to THz radiation and the nervous system have been confined to acute or short-term exposure effects, and the effects of long-term exposure and secondary hereditary effects

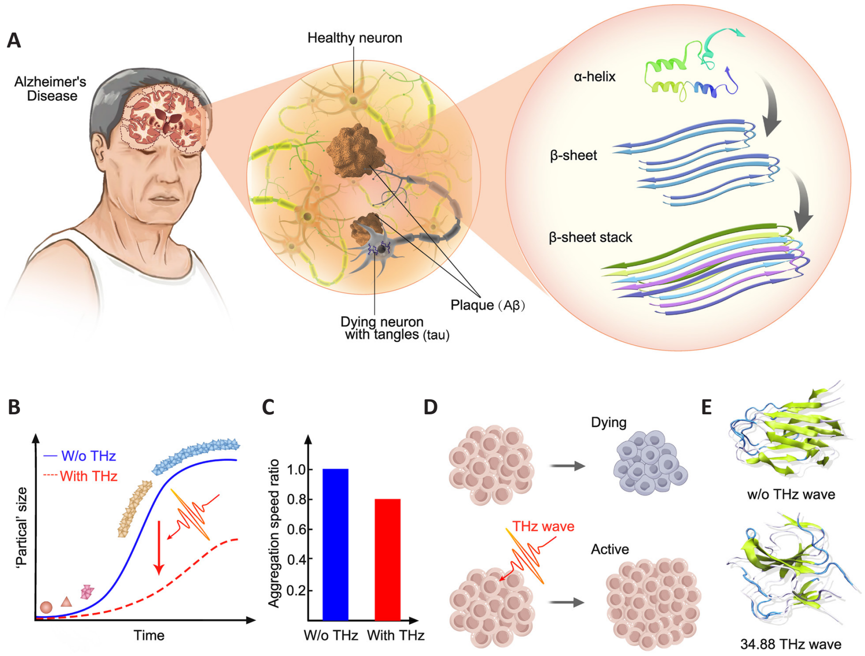

Figure 13 | **High-frequency THz waves disrupt amyloid-beta (Aβ) fibril formation in Alzheimer's disease.**
(A) Two primary neuropathological features of Alzheimer's disease. (B) THz waves delay the fibrosis dynamic curve. (C) THz waves decrease the aggregation speed to 80% in cases without the waves. (D) THz waves promote cell proliferation. (E) THz waves loosen the dense protein conformation with transformed β-sheets to a structure with more coil and bend regions. Reprinted with permission from Peng et al. (2023a), under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/lisceses/by/4.0/). THz: Terahertz.

are not yet clear. In addition, most THz studies on neuropsychiatry have been conducted at the cellular level or in excised brain tissues. Consequently, the dose-effect curve cannot be clearly charted, and there is no clear consensus regarding the safety of THz radiation on biological objects (Cherkasova et al., 2020; Yu and Zhang, 2020; Zhang et al., 2021a). The safety of THz radiation should be further verified at more macroscopic levels, or even in live patients or normal individuals.

Fourthly, the scale of THz wavelengths is usually similar to or even larger than the dimensions of the structural components in neural tissues (Chernomyrdin et al., 2023). Thus, the scattering characteristics of individual pathological structural elements may be overlooked. However, modern THz super-resolution imaging techniques enable the visualization of brain tissue at a sub-wavelength resolution, enabling detection of the heterogeneity between healthy and diseased neural tissues at the sub-wavelength level (Chernomyrdin et al., 2021). For example, super-resolution microscopy can unravel the heterogeneity of intact tissues and glioma tissues (Kucheryavenko et al., 2021).

Lastly, most studies on the applications of THz technology in brain sciences are confined to laboratories, with expensive and complex equipment. Despite the remarkable advances in laboratory investigations, THz technology is still far away from neuropsychiatric clinical transformation and application.

Technically, the development of appropriate THz sources, ultra-sensitive detection devices, as well as spectroscopic and imaging techniques with specific identification and higher sensitivity *in vivo* are worthy of endeavor and exploration. For example, the combined use of THz techniques and other imaging or detection methods, such as THz quantum cascade laser (Darmo et al., 2004), THz near-field microscopy (Geng et al., 2019; Li et al., 2020b; Yang et al., 2021), and THz images based on metamaterials (Ou et al., 2020; Roh et al., 2022; Wang et al., 2023a), to realize a higher sensitivity or resolution is a promising research area. Another exciting point is that THz photons are released in the tricarboxylic acid circle and in the process of ATP hydrolysis, providing researchers with a new method to explore the quantum mechanisms of brain activities (Song and Shu, 2020; Li et al., 2021a; Peng et al., 2023a; Tan et al., 2023). A remarkable development is the implantable, degradable, and therapeutic metamaterial devices at THz frequencies proposed recently, providing an appealing choice for *in vivo* sensing and in situ treatment (Sun et al., 2020). Currently, the application of THz technology in brain sciences, especially in the diagnosis and treatment of neuropsychiatric diseases, is still in the initial stages. Further studies are required to characterize the optical properties of THz signals in different pathological tissues and to unravel the relationship between THz signals and the nervous system.

Conclusion

THz technology has the potential to be a promising method in the field of neuropsychiatry. The brief overview of the applications of THz technology underlines its unique advantages. The progress in research made to date provides some directions for future studies, despite certain limitations. However, there also exists some limitations in the review design; as indicated in a recent review by Leitenstorfer et al. (2023), the advances and underlying mechanisms of the applications of THz technology in neurosciences thus far represent the proverbial tip of the iceberg. Almost all related studies have been confined to animal models and *in vitro* studies; thus, the effects of THz radiation on living patients with neuropsychiatric diseases remain unclear. The precise underlying mechanisms of the interaction between THz waves and the nervous system are not fully understood. The parameters, such as frequency, power, and treatment duration, which can affect the results of THz radiation need further study. Although THz radiation is generally considered to be safe, it may still induce some changes at the genetic level. Overall, the development and progress of THz technology in the past few decades suggests bright prospects for its application in brain sciences.

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