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Cerebral Organoids Respond to Sub-Terahertz and Terahertz Radiation

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Abstract

Beyond their potential for broadband wireless communications, sub-terahertz and terahertz signals have recently been shown to interact with certain proteins in the human body. Some of these proteins, involved in ion channel function and neurotransmission, play a key role in regulating neuronal activity by modulating the generation of action potentials. This paper presents and analyzes the measured responses of cerebral organoids exposed to sub-terahertz and terahertz radiation. The results suggest that such radiation can alter neuronal activity, suggesting potential implications for neuroscience and biomedical applications.

1 Introduction

The sub-Terahertz (sub-THz) and Terahertz (THz) bands that jointly span the range of 100 Gigahertz (GHz) to 10 THz have received significant attention for their potential in wireless communications [1]. However, in addition to their advantages in wireless communications, THz signals have recently been shown to interact with certain proteins [2], including voltage-gated ion channels. These ion channels play a critical role in regulating the flow of ions across neuronal membranes, which impacts neuronal activity. Proteins, in turn, mediate nervous system functions, and many medical treatments target specific proteins to initiate or inhibit certain chain reactions in the human nervous system. Therefore, understanding the interaction of electromagnetic radiation with proteins could open new possibilities for biomedical applications, including non-invasive neuromodulation or targeted therapies.

One potential metric for determining the success of THz signals in inhibiting or activating a certain protein is by observing whether there are changes in how neurons are firing. A neuron's ability to fire (i.e. generate a signal to communicate with its neighbors) is controlled by specific proteins inside the cell (e.g., voltage-gated ion channels) and embedded in the cell membrane. By measuring the firing rate of neurons in controlled experiments, we can learn about the biological impact of THz signals on neuronal communications. When neurons fire, they generate action potentials or spikes, and by counting and observing the number of spikes over time, conclusions can be drawn about the activity level of the neurons.

In this paper, we present the first-ever measured response of cerebral organoids exposed to sub-THz and THz radiation. The results indicate that the neurons respond to radiation and motivate further study.

2 Related Works

A single terahertz (THz) photon carries significantly less energy than medical X-rays, minimizing ionizing damage to biological tissues. Therefore, the non-invasive interaction of THz waves with tissues and cells at the molecular level presents novel opportunities for biological and medical applications. Moreover, THz waves are highly sensitive to water content in biological tissues, making the brain, which has high water concentration, an exciting subject for THz-based studies.

Recent research has explored THz technology as a diagnostic tool, demonstrating its ability to differentiate between healthy and Alzheimer's-affected brain tissues based on β-amyloid presence [3], hydration dynamics [4], changes in THz absorption coefficient [5], and THz refractive index [6]. Additionally, THz spectroscopy has shown promise in studying demyelinating diseases by identifying contrasts in myelin-deficient tissues [7]. Beyond diagnostics, the potential of THz technology for therapeutic applications has gained research interest. Its effects could be utilized for thermal neuromodulation, influencing neuronal activity by altering brain tissue temperature, or for hyperthermia treatments. The controlled power levels and exposure times could provide a non-invasive alternative to traditional methods that may pose risks to healthy tissues [8].

Besides its impact at the tissue level, radiation also affects proteins, as many exhibit vibrational modes within this frequency band. This leads to resonance absorption, where the protein becomes excited upon sensing this frequency, resulting in an increased absorption of electromagnetic radiation compared to other frequencies. The resulting energy absorption may raise the protein's temperature, which can influence thermally gated ion channels or lead to denaturation, depending on factors such as exposure time and power [9]. These factors were also investigated on the neurons exposed to THz radiation in [10], and the results suggested that short-duration exposure to THz radiation did not cause neuronal death. Instead, this exposure promoted the growth of neuronal cell bodies and protrusions, suggesting that carefully controlled THz radiation can positively modulate neuronal structure. In addition to that, it was shown that terahertz electromagnetic fields can selectively modulate the conductance of potassium and sodium voltage-gated channels [11]. These changes can regulate the movements of ions across the membrane, thereby affecting the generation of action potentials and the spike activity of neurons. Specific terahertz frequencies can reduce neurotransmitter levels and enhance cognitive function by regulating glutamate levels [12], potentially helping in the treatment of anxiety disorders, hallucinations, and post-traumatic stress disorders.

3 Experimental Set-up and Data Analysis

Brain organoids grow from stem cells into three-dimensional structures that include neurons that can mimic the molecular, cellular, and structural functions of human brains in their early developmental stages [13]. Within the last decade, these organoids have emerged as a model through which to study human brain development and disorders [14].

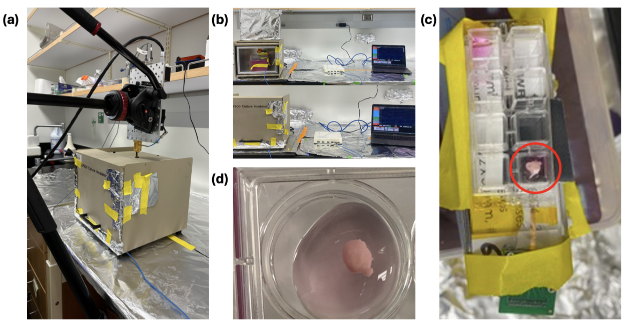

Figure 1. Experimental set-up: (a) Closed 37°C incubator with a sub-THz radiation source positioned above to deliver radiation. (b) The incubator set-up with the door open, showing the apparatus inside. The MEA and organoid are positioned on a slider directly below the opening, where the radiation antenna is inserted. The door is then closed to mitigate external environmental noise affecting measurements. (c)Eight-chamber slides with a cerebral organoid positioned on a Microelectrode Array (MEA) in the circled bottom right chamber. (d) An organoid surrounded by Brain Ephys medium.

For this study, brain organoids that had been grown for 12 months were placed on a custom-made multi-electrode array (MEA) [15] inside a 37°C incubator to isolate the experiment from exterior noise. The MEA was connected to an Open Ephys Acquisition Board, and the Open Ephys GUI was used to save the data read from 16 channels into a raw binary format.

There was an opening with a radius of 5 mm at the top of the incubator. The sub-THz and THz radiation were directed through this opening, and the MEA with the organoid was placed directly beneath the opening to irradiate the organoid while maintaining an environment with minimal noise and interference. The TeraNova testbed [16] was used to generate electromagnetic radiation at 130 GHz with a power density of 16 $\mu W/mm^2$ and 1 THz with a power density of 4 nW/mm^2 for the sub-terahertz and terahertz experiments, respectively.

In Figure 1a, the closed incubator with the 130 GHz radio positioned above it is shown. Figure 1b presents the measuring setup with the interior of the incubator, including the stand and slider where the organoid was placed. The incubator door remained closed during measurements to mitigate external noise. Figure 1c displays the organoid positioned on the MEA within the slider, while a zoomed-in image of the organoid is shown in Figure 1d.

To analyze the data, we used the SpyKING CIRCUS algorithm, presented and verified in [17]. To calibrate the algorithm to our measurement system, we first performed the analysis on control measurements taken without an organoid present. We adjusted the parameters of the SpyKING CIRCUS algorithm on the obtained "no organoid" recordings to eliminate noise currents and establish a threshold for the remaining organoid recordings.

4 Results and Discussion

An initial set of experiments measured the organoid response over 10 minutes under three conditions: no radiation, continuous 130 GHz radiation, and continuous 1 THz radiation. During each experiment, not all 16 electrodes in the MEA detected signals from the organoid. This could be due to the organoid's placement on the MEA or the neurons in contact with certain electrodes being less active. Hereafter, "active electrodes" refer to electrodes that detect spikes, while "inactive electrodes" refer to those that show no spike activity during the whole 10 minutes.

In these experiments, the number of active electrodes was 6, 14, and 12 for the no-radiation, 130 GHz radiation, and 1 THz radiation conditions, respectively. The total number of spikes detected by the SpyKING CIRCUS algorithm throughout the 10-minute measurement period is displayed in Figure 2. This initial analysis suggests that the sub-THz radiation is causing an increase in activity. The total number of spikes observed by the organoid subjected to

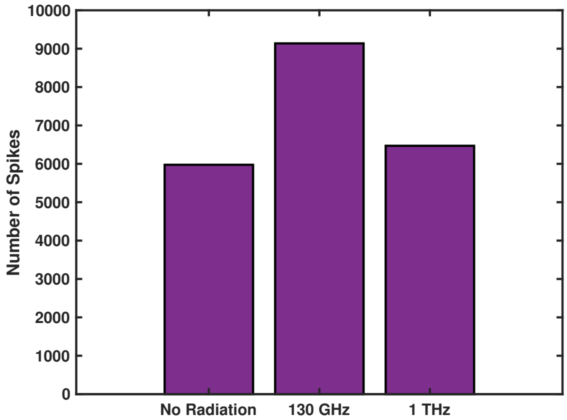

Figure 2. Total number of spikes in constant radiation experiments.

130 GHz radiation was 52.94% higher than that of the no-radiation condition. For the 1 THz radiation experiment, the organoid exhibited a similar number of spiking activity to the no-radiation condition, with only an 8.29% increase. This suggests that the 1 THz radiation may have had no measurable impact on the spiking activity, unlike the 130 GHz radiation which increased the organoid neuronal firing. The lack of activity could be due to the fact that the 1 THz radiation is at a much lower power than that of the 130 GHz case.

The second set of experiments involved delivering radiation after the first minute, lasting for four minutes, followed by five minutes without radiation. These experiments aimed to assess the impact of radiation on the same organoid under radiation and no-radiation conditions. Figure 3 presents the spike count per 1-second window from three different organoids. The first minute of recording is omitted, as the set-up required time to stabilize after closing the incubator door, and this initial period was typically noisy.

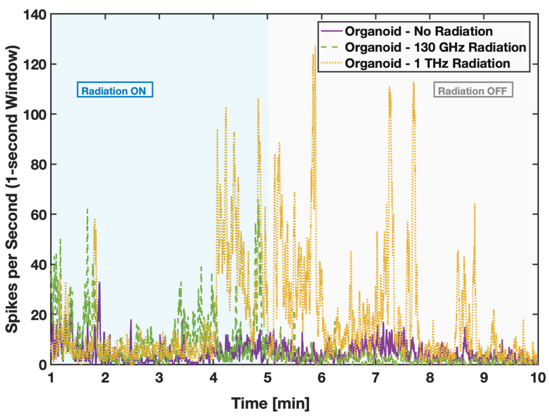

Figure 3. Spike count per second, using a 1-second sliding window, in experiments with intermittent radiation exposure.

Baseline activity was recorded in an organoid that was not irradiated throughout the experiment. In this case, with 6 active electrodes, spiking activity remained relatively steady across the nine-minute recording. For the 130 GHz and 1 THz experiments, radiation was applied at minute one and turned off after four minutes. In the 130 GHz experiment, with 12 active electrodes, the organoid exhibited increased spiking activity during radiation exposure, returning to lower activity levels once the radiation ceased.

In contrast, during the 1 THz experiment, with 13 active electrodes, the organoid initially showed a slight increase in activity from the onset of irradiation and a further increase in the fourth minute. Spiking activity then continued to increase and persisted into the post-irradiation period. This suggests that 1 THz radiation had a delayed but sprolonged effect on neuronal activity, extending beyond the irradiation period.

Organoids are brain-derived tissues, and since each person's brain is unique, with different regions exhibiting distinct functions, we observed varying responses between the continuous and time-varying radiation experiments. However, these results suggest that sub-THz and THz radiation can potentially influence neuronal activity in human cerebral organoids in a complex manner. More thorough studies should be conducted to determine the extent of these kinds of interactions.

5 Conclusion

In this paper, we have presented measured neuronal activity of brain organoids exposed to sub-THz and THz radiation. The responses of the organoids indicate some response from the neuronal activity to the radiation. Further studies are warranted to determine if there is potential for these frequency bands to be used in brain-machine interfaces or therapeutic treatments.

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