Comparing Wired and Wireless Optogenetic Control Systems: Impact on Behavior and Efficiency

Hongzhen Pan, Yitong Zhang, Yiran Lang, Dingjie Suo, Chunyu Zhang,
and Jian Zhang(✉)

Beijing Institute of Technology, Beijing 100081, China
`{3120231966,zhangyitong,yiran.lang,suo,zzccyy1977,`
`zhangjian2023}@bit.edu.cn`

Abstract. In optogenetics, light-sensitive proteins introduced into specific cells can only be activated by light of specific wavelengths. Therefore, it is possible to precisely modulate the functionality of neural cells by activating or inhibiting ion channels with light of the corresponding wavelength. Experimental setups often require electrodes or optical fibers implanted on or in the brains of animals. Wired connections between the animal's head and the equipment can pose some challenges to the experiment. In this study, we compared wired optogenetic control systems with battery-powered wireless optogenetic control systems. We found that the wired optogenetic control system outperformed the battery-powered wireless system in terms of both the impact on the natural behavior of the experimental subjects and the efficiency of optogenetic control. We also proposed some improvements in both aspects.

Keywords: Optogenetics · Fiber · Wireless · Efficiency

1 Introduction

Optogenetics is a novel technique that combines optics and genetics. It involves introducing light-sensitive proteins into specific cells using viral vectors for expression. These introduced proteins can only be activated by light of specific wavelengths. Thus, it allows for precise modulation of neuronal function by activating or inhibiting ion channels with corresponding wavelengths of light. Neuroscientists can precisely control the excitation or inhibition states of specific neurons in tissue cultures or live animals in a non-damaging or minimally damaging manner. They achieve this by implanting different types of optogenetic proteins into different neurons, allowing them to adjust the brightness, wavelength, and frequency of implanted light sources. This sophisticated control enables complex manipulation of biological neural activity [8, 9]. Researchers have conducted numerous biological experiments using optogenetics, including studies on chronic brain diseases like Parkinson's disease, epilepsy, and complex neural circuits (Fig. 1).

H.-H. Chen and W. Meng (Eds.): WiSATS 2024, LNICST 606, pp. 309–318, 2025.
https://doi.org/10.1007/978-3-031-86203-8_24

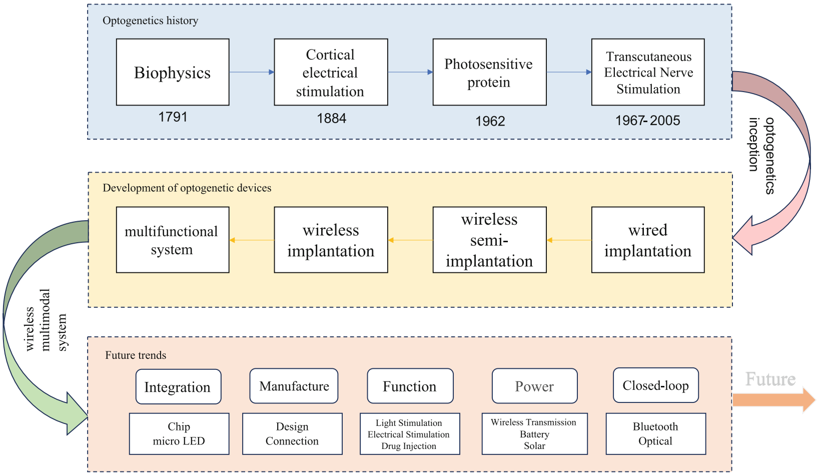

Fig. 1. The history of optogenetics and progress in the development of optogenetic devices

The advancement and clinical application of optogenetics are expected to be propelled and facilitated by the continued development of laser technology in the field of biomedicine. Common techniques used in neuroscience research on live small animals include in vivo electrophysiology, fiber optic recording, and optogenetic stimulation. In vivo electrophysiology involves recording brain electrical activity by fixing electrodes on the animal's skull or implanting electrodes into the brain. The former can capture electroencephalogram (EEG) signals, while the latter typically detects local field potentials (LFPs) and action potentials (spikes). During experiments, optical fibers are implanted into the animal's brain to deliver light stimulation and collect fluorescence signals from cells, thereby detecting changes in intracellular calcium ion concentrations and indirectly reflecting neuronal activity.

Due to the inability of visible light to penetrate biological tissues directly to reach neurons, early optogenetic experiments involved using wires to deliver micro light-emitting diodes (LEDs) or inserting optical fibers directly into the organism [10–12]. These methods had drawbacks such as large wounds, susceptibility to infection, and limitations on the normal movement of live subjects. In 2013, Kim developed a wireless optogenetic device powered by miniature batteries [13, 14], with the battery exposed externally due to its size relative to mice. In 2015, Park proposed an improved wireless power supply system using a small solar panel for long-term stable power [15], yet it still did not resolve the issue of complete implantation into the organism. Over the next two years, Park continued to refine the wireless optogenetic system, designing an implantable microsystem device (IMD) for precise neural control experiments [16, 17].

These experimental techniques all require the implantation of electrodes or optical fibers on or within the brains of animals, necessitating cables or fibers to connect the animal's head to the instrumentation. Wired designs pose several challenges to experiments: animal movements may sometimes cause entanglement or damage to the fibers or wires, leading to experiment termination or even wire damage; animals cannot move naturally, subject to dragging or tangling, which affects behavioral test results; behavioral software may make incorrect judgments or counts of animal behavior due to wire bundles on the animal's head; wire bundles are often chewed by small animals, especially in long-term unattended recordings such as sleep experiments, significantly increasing experimental costs; some special experimental designs, such as drilling, enclosed spaces, or simultaneous recording of several interacting animals, are greatly hindered by head wiring; cable movement and friction can cause significant motion noise, leading to unstable baseline recordings; during natural movement or during cable insertion and unplugging, forces applied to implants via related tethering can cause micro-movements between rigid bodies. Probes and soft tissues can cause tissue damage and artifacts, leading to decreased long-term stability [2, 3]. Unrestrained animals typically attempt to remove or disconnect cables, especially with advanced interfaces requiring multi-channel operations [3].

The remainder of this paper is organized as follows. The Materials and methods are presented in Sect. 2. Section 3 illustrated the specific experiments and the results. Corresponding discussions are presented in Sect. 4, and Sect. 5 concludes the paper.

2 Materials

Experimental animals-Male C57/BL6 mice (8–13 weeks old) were used. Mice were group housed (2–5 animals per cage) on a 12 h light cycle (light on from 7 a.m. to 7 p.m.) with free access to food and water until surgery or behavioral testing. The temperature was 24–26 °C, and humidity was 40–60%. All surgical and experimental procedures were approved by the Institutional Animal Care and Use Committee of the Beijing Institute of Technology in Beijing, China.

The viruses we use include the following: AAV2/9-hEF1a-DIO-hChR2(H134R)-EYFP (titer: 3.44 × 1012 vector genome (v. g.)/ml; Taitool Bioscience, Shanghai, China); AAV2/9- CamKIIa -EGFP-Cre (titer: 5.96 × 1012 vector genome (v. g.)/ml; OBIO, Shanghai, China); AAV2/9-hSyn-DIO-mCherry (titer: 2.3 × 1012 vector genome (v. g.)/ml; Taitool Bioscience, Shanghai, China).

3 Results

We compared the effects of wireless fiber optic cables and wired fiber optic cables on the locomotor activity of animals in optogenetic experiments, as well as their efficiency in optogenetic control. The behavioral method chosen for evaluation was an open field test. In the experiment, mice were placed in an open field test chamber measuring 400 × 400 × 200 mm. Each time, the mice were placed into the chamber from the same position and in the same direction. The mice's activity was recorded for 5 min. After the experiment, the mice were returned to their housing cages, and the experimental area was cleaned with alcohol to prevent any lingering odor from affecting the next mouse's test.

Indicators such as velocity, acceleration, angular velocity, sinuosity, and angle velocity during the experimental were processed by MATLAB 2021b. The results are as follows.

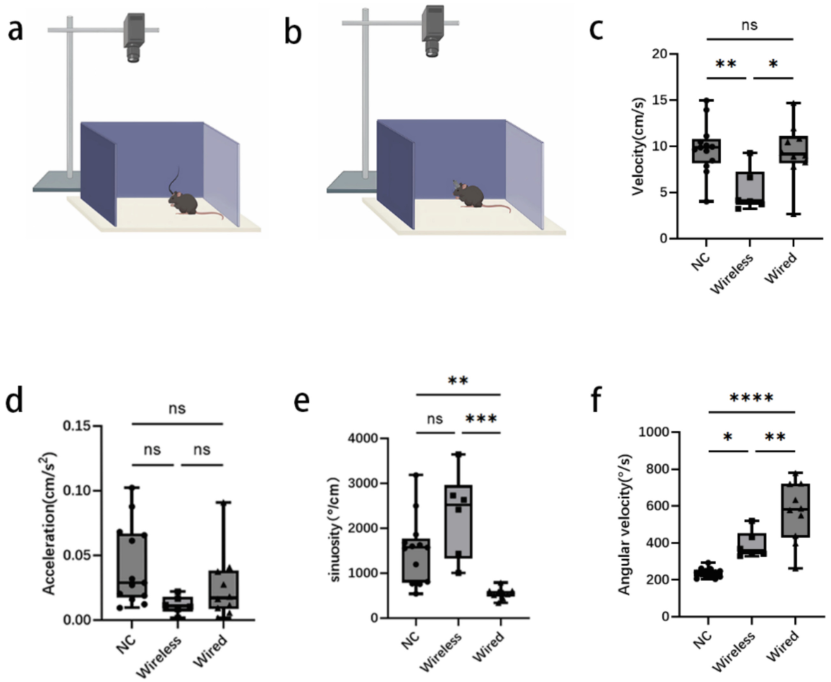

Fig. 2. (a) Schematic diagram of the open field test in the wired fiber optic modulation system. (b) Schematic diagram of the open field experiment in the wireless fiber optic modulation system. (c-f) Experimental indicators and results of different groups in the OFT (c)Velocity in the OFT (d)Acceleration in the OFT (e)Sinuosity in the OFT (f)Angular velocity in the OFT. Behavioral data in this and subsequent figures are presented as boxplots with gray dots representing individual data points, center lines denoting the median, open square dots denoting the mean values, the lower and the upper bounds of the box corresponding to the 25th and 75th percentiles, respectively, and the whiskers denoting the minimum and maximum values.

Figures 2(a) and (b) depict schematic diagrams of the open-field experiments of mice in the optogenetic wired fiber-optic control system and the optogenetic wireless fiber-optic control system, respectively. The former delivers laser stimuli with corresponding parameters via a wired fiber-optic cable from the laser generator, while the latter transmits light stimulation signal parameters via a Bluetooth controller. In studying the impact on locomotion ability, we divided the mice into three groups: the NC control group with no fiber-optic implantation on the head, the Wireless group with a wireless fiber-optic implantation on the head, and the Wired group with a wired fiber-optic implantation on the head. Figure 2(c) shows the average speed, calculated as the total path distance moved by the center point of the mouse's body divided by the total time. It can be observed that mice in the Wireless group exhibited significantly lower average speeds during the experiment compared to the other two groups, while the average speed of mice in the Wired group during the experiment showed no significant difference compared to that of the control group mice. Figure 2(d) shows the mean acceleration. After examining trajectory maps and eliminating trajectory noise, we obtained the mean acceleration of the center point of the mouse's body. During the experiment, a trend of lower acceleration was observed in the Wireless group compared to the other two groups, but our data showed no significant difference between the three groups. Figure 2(e) shows the mean sinuosity, calculated by dividing the angle by the distance moved to obtain the sinuosity value. Sinuosity is used to compare the turning ability of animals with different movement speeds. It can be observed that mice in the Wired group had significantly lower sinuosity than the other two groups. Although the median sinuosity of the Wireless group was noticeably higher than that of the control group, our data indicated no significant difference between the two groups. Figure 2(f) shows the mean angular velocity based on head direction. By dividing the angle by the sampling interval (25 frames per second in the video, sampling interval $T = 0.04$ s), the desired value was obtained. It can be seen that the angular velocity of the control group was significantly lower than that of the Wireless group, which was significantly lower than that of the Wired group.

The comparison between the effects of wireless and wired fiber-optics on the locomotion ability of mice has been made. Next, let's compare their efficiency in optogenetic modulation. The NC group was injected with AAV2/9-CamKIIa-EGFP-Cre virus and AAV2/9-hSyn-DIO-mCherry virus. The wireless fiber and wired fiber groups were injected with AAV2/9-CamKIIa-EGFP-Cre virus and AAV2/9-hEF1a-DIO-hChR2(H134R)-EYFP virus. After transfection of target neurons with viruses containing the cre gene, they express the cre recombinase enzyme. Viruses containing the DIO element have two loxP sequences flanking the functional gene in opposite orientations. The cre recombinase specifically recognizes and cuts the loxP sequences, resulting in a genetic inversion between the two inverted loxP sequences, placing the gene in an expressible orientation, thus expressing the target protein. The control group was injected with fluorescent viruses lacking light-responsive functional components and would not be activated by laser stimulation. The implanted fiber group was injected with viruses containing light-responsive functional components and would be activated by laser stimulation. Research has already demonstrated a significant relationship between the cerebellar deep nuclei (DN) and depressive-like behaviors [4]. We employed optogenetic technology to assess the regulatory efficiency of both the wireless fiber-optic control system and the wired fiber-optic control system on mice. It can be observed that in terms of regulating acceleration Fig. 3(b) and (f) and angular velocity Fig. 3(c) and (g), both systems showed no significant difference compared to the control group. However, in regulating average speed Fig. 3(a) and (e) and sinuosity Fig. 3(d) and (h), the efficiency of the wired fiber-optic control system was significantly superior to that of the wireless fiber-optic control system.

In summary, the current battery-powered wireless fiber-optic control system based on Bluetooth transmission signals, whether in terms of interference with the movement of experimental animals or the efficiency of optogenetic control, falls short of the existing wired fiber-optic control system.

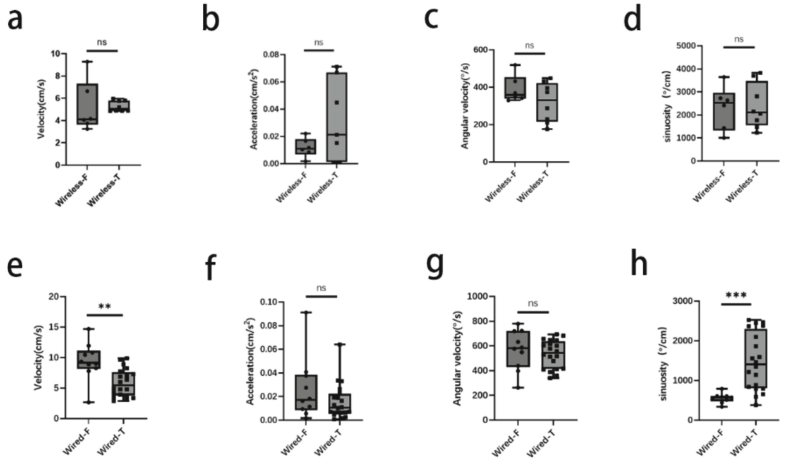

Fig. 3. (a-d) Experimental indicators and results of wireless groups in the OFT. In the wireless-F group, mice were injected with the fluorescent virus and implanted with wireless fiber optics. In the wireless-T group, mice were injected with the modulating virus and implanted with wireless fiber optics. (e-h) Experimental indicators and results of wired groups in the OFT. In the wired-F group, mice were injected with the fluorescent virus and implanted with wired fiber optics. In the wired-T group, mice were injected with the modulating virus and implanted with wireless fiber optics.

4 Discussion

Conventional small, lightweight batteries, while capable of meeting the power requirements of intricate wireless devices, often exceed storage capacities of 3 cm3^3 and weigh more than 2 g, limiting their practicality for numerous real-world applications. This necessitates percutaneous wiring when used in small animals. Moreover, the need for battery recharging interrupts experimental continuity and can influence animal behavior. While a battery-powered optical stimulator enabled unrestricted movement of mice, the need for repeated brain surgeries to replace intermittent batteries impeded continuous and long-term usage [5]. Batteries typically occupy 90% of the volume and over 60% of the weight of implantable devices. Therefore, reducing their size and weight or eliminating them entirely offers substantial advantages. Wireless power delivery allows devices to be lightweight, compact, and potentially have unlimited lifespans. Options include utilizing bodily energy such as kinetic energy from bone and visceral movement, chemical energy from blood glucose, thermal energy from body heat, or external sources via wireless radiofrequency (RF) electromagnetic field transmission, light, or ultrasound.

The impact of wireless fiber optics on the movement of experimental animals in this study can be improved by altering the power supply scheme. Here are two improvement strategies proposed here. Firstly, by harnessing internal energy for power collection. Piezoelectric and triboelectric effects can convert the kinetic energy of voluntary movements (e.g., skeletal muscles) and autonomous movements (e.g., cardiovascular, respiratory, and gastrointestinal) muscle cells into electrical energy. This would allow devices to operate autonomously without the need for separate power sources.

Secondly, harvesting power through external energy emissions offers distinct advantages over energy storage approaches in terms of both power output quantity and stability. Specialized power delivery methods, such as electromagnetic radiation, acoustic vibration, or other transmission means, can reliably transmit significant power amounts (up to approximately 500 mW), with various design options available for deployment. Remote power transmission technologies primarily fall into several categories: far-field radio frequency (RF), near-field magnetic resonance coupling, photon energy transfer, and ultrasound conduction.

Far-field radio frequency (RF) refers to the electromagnetic radiation that propagates as waves through space over long distances from a transmitting antenna to a receiving antenna. The radio frequency (RF) radiation emitted by far-field RF power transmission (with frequencies ranging from 420 MHz to 2.4 GHz and wavelengths from 0.1 to 1 m) can be captured by harvesting antennas and converted into direct current by rectification circuits to drive electronic devices [6]. In summary, far-field RF is essential for a wide range of communication and sensing applications that require reliable transmission of electromagnetic waves over long distances.

Near-field wireless power transfer refers to the technology that enables the transmission of electrical energy from a power source to a device without the need for physical connectors or direct contact. Unlike traditional far-field electromagnetic radiation, which propagates over long distances, near-field wireless power transfer operates over short distances, typically within a range of a few centimeters to a few meters.Near-field wireless power transmission utilizes non-radiative electromagnetic energy and relies on inductive coupling between transmitting and receiving coils. In this method, a primary coil generates a time-varying magnetic field, which induces a voltage in a secondary coil placed nearby. This induced voltage can then be used to power a device or charge a battery. For example, implantable medical devices such as pacemakers can be powered wirelessly using near-field technology to avoid the need for frequent surgical procedures to replace batteries. Near-field wireless power transfer offers a promising alternative to traditional wired charging and power supply methods, particularly in situations where convenience, safety, and durability are prioritized.

Photon energy transfer refers to the process by which photons, which are quanta of electromagnetic radiation, transfer their energy to other particles or systems. This transfer occurs through interactions between photons and matter, and it plays a crucial role in various physical phenomena across different scales, from atomic and molecular interactions to macroscopic processes. Photons from the sun transfer energy to solar cells, where it is converted into electrical energy. And radiation from visible and near-infrared light can also be exploited for power delivery [7].

Ultrasonic power transfer is a method of wirelessly transmitting electrical power using ultrasonic waves. This technology utilizes acoustic waves with frequencies above the human audible range (typically above 20 kHz) to transfer energy from a transmitter to a receiver. Ultrasonic power transfer operates on the principle of converting electrical energy into mechanical vibrations (ultrasonic waves) at the transmitter. These waves travel through a medium (such as air or water) and are captured by a receiver where they are converted back into electrical energy. The system typically consists of a transmitter that generates ultrasonic waves using a piezoelectric transducer or similar device. These waves propagate through the air or another medium and are picked up by a receiver equipped with a similar transducer that converts the acoustic energy back into electrical energy. Ultrasonic power transfer can be efficient over short distances, typically up to a few meters. The efficiency of power transfer depends on factors such as the frequency of the ultrasound, distance between the transmitter and receiver, and environmental conditions that may affect wave propagation. It can be used for wireless charging of small electronic devices like smartphones, wearables, or sensors. And in medical devices, ultrasonic power transfer is explored for implantable medical devices where wired power connections are impractical or pose a risk of infection. Overall, ultrasonic power transfer offers a promising alternative to traditional wired and other wireless power transmission methods, particularly in applications requiring small-scale, flexible, or implantable power solutions.

In terms of modulation efficiency, laser light sources exhibit higher efficiency due to their highly focused nature, high energy density, precise directional control, and accurate temporal and spatial manipulation. Although LED light sources offer characteristics such as broad spectral coverage and lower light energy density, which can help reduce thermal damage and phototoxic effects on experimental subjects, as well as the ability to be directly inserted into brain tissue for long-term stable stimulation [7], their modulation efficiency is not as high as laser light sources.

5 Conclusion

In optogenetic research, minimizing the impact of light control systems on the movement of experimental subjects is crucial. Battery-powered wireless optofiber control systems may introduce additional weight and volume, thereby affecting the natural behavior of experimental subjects. This impact can be effectively mitigated by adopting lighter, more compact wireless power supply solutions or selecting implants with greater tissue compatibility. These improvements can reduce the burden on experimental subjects while maintaining their behavioral naturalness to the greatest extent possible.

On the other hand, in terms of light control efficiency, choosing the appropriate light source is essential for the accuracy and reproducibility of experimental results. Light-emitting diodes (LEDs) and lasers each have their own advantages and disadvantages. LEDs provide relatively uniform illumination and lower light energy density, suitable for long-term stable stimulation of experimental subjects while reducing thermal damage and phototoxic effects on biological tissues. However, the light control efficiency of LEDs may not be as high as that of laser sources, especially in cases requiring high energy density or precise spatial control. Laser sources offer highly focused, high-energy density, and precise directional illumination, suitable for experiments requiring high sensitivity and precise control. Therefore, in experimental design, it is necessary to flexibly select LEDs or lasers as light sources based on specific experimental requirements and research purposes to achieve optimal experimental outcomes.

In summary, by optimizing wireless power supply solutions and implant selection, as well as selecting appropriate light sources according to experimental needs, the issues of motion impact on experimental subjects and light control efficiency in battery-powered wireless optofiber control systems in optogenetic research can be improved, thereby enhancing the accuracy and reproducibility of experiments.

Funding. The authors declare financial support was received for the research, authorship, and publication of this article. This work was supported by the Key-Area Research and Development Program of Guangdong Province of China to Jian Zhang (Grant Nos. 2023B0303030002); the National Natural Science Foundation of China to Yitong Zhang (Grant Nos. 82302341); and the National Natural Science Foundation of China to Dingjie Suo (Grant Nos. 12104049).

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