

Modalities of Neuromodulation for Neurological Diseases

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Abstract. Neurological diseases have attracted much attention as they have become the second leading cause of death worldwide. Several works on neuromodulation were reported to improve patients' quality of life or the body's functionality. After the early discovery of the gating theory, electrical stimulation was used to relieve chronic pain. In recent years, several other neuromodulation techniques, including thermal, and pharmacological stimulation, were proposed to improve the effectiveness. In this paper, some of the related researches on electrical, thermal, and pharmacological stimulation are summarized. Scientists are searching for more suitable therapies for neuromodulation now, including improving probe and electrode materials based on existing protocols. In terms of thermal stimulation, light-induced heating of heat conversion materials are introduced. The three administration routes of oral, intravenous and micropump in pharmacological are also mentioned. It also highlight the researches that combine some new cutting-edge technologies (e.g. nanotechnology) with the neuromodulation technique. In the end, the advantages and disadvantages are discussed, and the prospects are forecasted.

Keywords: neuromodulation; electrical stimulation; thermal stimulation; pharmacological stimulation.

1. Introduction

According to the overview of the “Global Burden of Diseases, Injuries, and Risk Factors Study 2016” on neurological disorders, neurological disorders is the second most significant cause of death, with 16.5% of global death, following heart disease [1]. And neurological disorders are the main contributor to disability [1]. It can be seen that neurological disorders will cause significant harm to human health, severely threaten people's life safety, and significantly impact people's life qualities.

People started to try to relieve the chronic pain brought by neurological disorders through neuromodulation, especially electrical stimulation, in ancient times [2]. Until the 1950s, scientists started to try brain stimulation to control pain [2], making breakthroughs in deep brain stimulation (DBS) technologies, which are quite effective and frequently used nowadays. In 1967, C. N. Shealy et al. created the first spinal cord stimulator, which to some extent, effectively relived the chronic pain of the patient [3] and became a milestone in the emerging, development and practical application of neuromodulation. Schmidt and Tanagho proposed the possibility of electrical stimulation of the sacral nerve as a therapy for chronic pain in the 1980s; before Craggs, Fowler demonstrated the specific mechanism of neuromodulation [4], making the theoretical framework of neuromodulation preliminarily formed. Since the advent of neuromodulation, chronic pain and neurological disorders, which have been a problem for thousands of years, have been solved in a way.

Besides electrical stimulation, the most mature modality of neuromodulation with the longest history, there are many other modalities of effective neuromodulation, including thermal stimulation, magnetic stimulation, optogenetic stimulation, mechanical (acoustic) stimulation, pharmacological stimulation, etc. [5]. Whatever the specific modality, neuromodulation is based on the Hodgkin-Huxley equation. It works because a portion of the cell membrane becomes depolarized, which can change the polarization and electric potential of the cell membrane. There are numerous ways to start the depolarization, thus causing different modalities mentioned above [5]. In other words, all the modalities of neuromodulation can be achieved by changing the polarization of the cell membrane

and then changing the charge distribution and electric potential of the nerve membrane, thus finally achieving the effect of alleviating chronic pain and treating neurologic disorders. And the difference between them is the way the stimulus is produced or the type of the stimulus. For example, potential difference or current is the stimulus for electrical stimulation, heat for thermal stimulation, the magnetic field for magnetic stimulation, etc.

Over decades of development, neural modulation technology has become safer and safer with better and better efficacy. Scientists are searching for more suitable therapies for neuromodulation, including improving probe and electrode materials based on existing protocols and applying new cutting-edge technologies such as nanotechnology [6]. So far, neuromodulation has played a positive role in treating neurological diseases. Neuromodulation is of great significance for treating brain diseases and relieving chronic pain and has a broad development prospect.

This essay focuses on three of the most essential and promising modalities of neuromodulation, including electrical stimulation, thermal stimulation and pharmacological stimulation: Firstly, the working mechanism of electrical stimulation is introduced and the development of the selection of electrode materials used in electrical stimulation, including noble metal, inherently conducting polymers and nanostructured materials, is demonstrated; Secondly, the working mechanism of thermal stimulation is introduced and two ways to change the temperature and achieve thermal stimulation, including optically induced heating and heating associated with thermal conversion materials are discussed; Thirdly, the mechanism of pharmacological stimulation is introduced, with three routes of administration including oral, intravenous and micropump illustrated; Finally, advantages and disadvantages of the three modalities are discussed through comparison and development prospects of neuromodulation is predicted.

2. Electrical stimulation

Electrical stimulation is a kind of therapy for neurological disorders, including stroke, epilepsy, spinal cord injuries, etc., by implanting electrodes into human bodies and using electrical currents to conduct neuromodulation and change the potential on the surface of the neurons. Electrical stimulation, a frequently used neuromodulation modality, can significantly relieve chronic pain.

In the following part, specific types of electrical stimulation, including spinal cord stimulation (SCS), DBS, etc., will be taken as examples to discuss the mechanism of electrical stimulation for neuromodulation, the electrode materials, considering the advantages and disadvantages of them with comparison.

2.1. Working mechanism

The working mechanism of electrical stimulation for neuromodulation is based on the gate control theory of pain. When being electrically stimulated, the current can flow to the source of the chronic pain. The theory states that some spinal cord cells act as gates to block the passage of pain impulses to the brain, shielding the brain from pain [7].

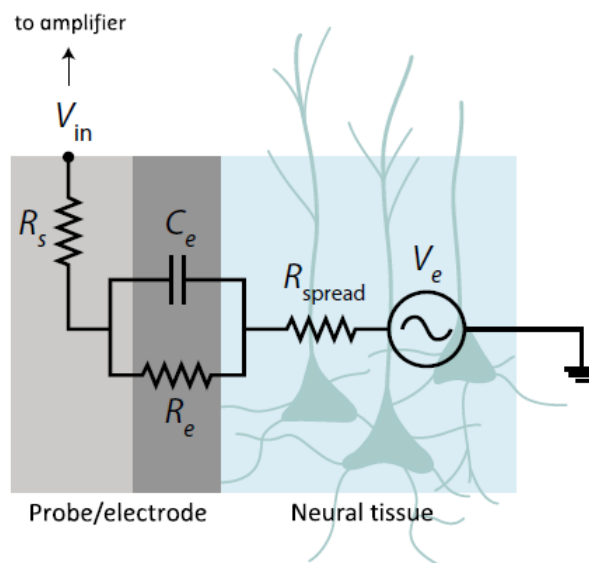


Fig 1. The equivalent circuit of electrode/tissue interface [6].

The equivalent circuit of electrode/tissue surface is shown in Fig. 1 [6]. In this instance, the neurons in the neural tissue serve as voltage sources, providing alternating voltage V_e . The circuit outputs a voltage signal V_{in} at the end of the electrode region, which is connected to an amplifier to achieve the recording function.

2.2. Electrode materials

2.2.1 Metal and inherently conducting polymers

Since the first stimulator for electrical stimulation was invented, scientists have been talking about which kind of electrode material is the most suitable for neuromodulation. With the development of electrical stimulation, the electrode materials have generally been improved and complicated, from precious metals to conductive polymers and microelectrodes.

As one of the most important types of electrical stimulation, SCS has been maturing through development for more than 50 years, which has led to more acceptance of electrical stimulation as a treatment and relief for more patients with neurological diseases. The first spinal cord stimulator designed in 1967 by Shealy et al. used Vitallium (Cobalt-Chromium-Molybdenum) as the stimulating electrode [3]. Their second device used a Platinum (Pt) electrode to improve the electrode's biocompatibility [8]. Since then, Platinum has been seen as an excellent biological electrode material because it is an inert metal, which is even less reductive than Argentum (Ag). With this property, patients are much less likely to experience rejection. Based on Platinum, scientists then substituted Platinum-Iridium (Pt-Ir) alloys for Platinum alone to improve the mechanical properties of the electrode. Iridium oxide (IrOx)-coated Platinum-Iridium alloys were then used to enhance the electrical properties of the electrode; more explicitly speaking, IrOx has a better charge injection capacity [9]. Being aware of the excellent properties, including electrical and biological ones, of the inherently conducting polymers (PPy, PEDOT: PSS, etc.), they have become alternative materials to metals or used as coatings for metal electrodes [10].

Electrode materials used for different types of electrical stimulation are generally similar. A. Petrossians et al. reported an improved electrode for DBS, which uses a Platinum-Iridium alloy coating with low impedance as the electrode material [11]. Besides Pt-Ir alloy, J. Gimsa et al. used stainless steel (SS) as the electrode material for DBS in their experiments [11]. For other types of electrical stimulation, Tantalum (Ta) / Ta₂O₅, Titanium nitride (TiN), etc., are also used as electrode materials [12].

Table 1 lists some parameters and properties, comparing the electrode materials mentioned above to see the advantages and disadvantages of electrodes of different materials [9, 12, 15, 16, 17].

Table 1. Electrical parameters, advantages and disadvantages of the electrode materials (metals and inherently conducting polymers [9, 12 15, 16, 17].

Electrode materials	Electrical resistivity/ conductivity	Charge injection density	Advantages	Disadvantages	References
Pt	9.6×10^6 S/m	0.10-0.30 mC/cm ²	Good mechanical properties; good biocompatibility; chemically inactive; high electrical conductivity	Corrosion possible; may experience irreversible disintegration	9
Pt-Ir	25 $\mu\Omega \cdot \text{cm}$ (Pt-10Ir) 32 $\mu\Omega \cdot \text{cm}$ (Pt-25Ir)	-	High corrosion resistance; low contact resistance;	Low electrical resistivity; short service life	15
IrOx	0.75-1.67 m $\Omega \cdot \text{cm}$	1.2 mC/cm ²	Good mechanical and electrical properties; high charge injection capacity	Less biocompatible compared to Pt; chronic use may cause inconsistency	9
PPy	190 S/cm	5 mC/cm ²	Flexibility; high electrical conductivity; biocompatible	Fragile mechanical properties; degradation possible	9
PEDOT:PSS	5.8 S/m	1.2-3.9 mC/cm ²	High electrical conductivity; biocompatible	Water soluble; long-term unstable	9
SS	72 $\mu\Omega \cdot \text{cm}$	-	Widely used; good electrical properties	Mechanical damage possible if made small	16, 17
Ta / Ta ₂ O ₅	-	About 0.5 mC/cm ²	Good electrical properties	Requires large positive bias	12
TiN	-	About 1 mC/cm ²	Good electrical properties	Oxidized at positive potentials	12

2.2.2 Nanostructured electrodes

Based on traditional electrode applications and nanotechnology development, scientists have recently proposed a new concept of nanostructured electrodes for neuromodulation. Despite the strict demand for techniques and high cost, nanostructured electrodes have obvious advantages over traditional ones made of metal or conducting polymers.

Electrode miniaturization is one of the most effective methods for decreasing mechanical trauma during implantation [13]. Up to now, a few electrodes that combine flexibility with nanostructure have been proposed. For example, soft Platinum/Silicone electrodes with stretchable gold interconnect an electronic device with a bio-interface supported by silk fibroin bioresorbable substrates, etc., have been tried on the electrodes [14]. Except for the tip, where an electric charge exchange occurs, these electrodes, which range in diameter from 25 to 50 μm , are insulated with materials like polyimide [13].

Among those nanostructured electrodes, carbon microfibers are considered competitive materials in neuromodulation. The electrical resistivity of porous graphene is 303 S/m, and the charge injection density of porous graphene is 3.1 mC/cm², demonstrating that it has excellent electrical properties [9]. Moreover, porous graphene is mechanically flexible, biocompatible, and can record extracellular neuronal activity [9, 13]. Additionally, using nanostructured electrodes can help keep the voltage stable and avoid the occurrence of voltage overshoot. Fig. 2 shows that using carbon nanotube/graphene or conducting polymers permits close contact between the ions and the electrode, making the impedance drop significantly [6].

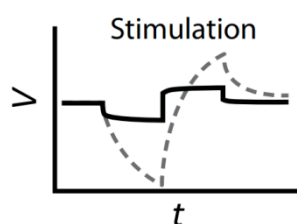


Fig 2. Getting stable voltage by nanostructured coating [3].

3. Thermal stimulation

In addition to electrical stimulation, proper thermal effect regulation can be viewed as a different approach to neuromodulation. Recent studies demonstrate thermal stimulation related to treating epilepsy, neuropathic pain, and peripheral neuropathy. Neuromodulation occurs when temperature changes cell membrane capacity and the thermosensitive transient receptor changes the passage of a potential ion channel [18]. There are some well-known heat-sensitive ion channels, including TRPV1, TRPV2, TRPV3 and TRPV4, which can be activated at 43 °C, 52 °C, 32 °C and 27 °C, respectively.

There are two main options to change the temperature: one is the targeted tissues absorb light and visible light, and another is thermal conversion materials. Infrared neuromodulation (INM) for optical-induced fever was studied about 15 years ago and gradually aroused scientists' interest in this field. Raising temperatures in the spatially constrained target area allows direct or indirect regulation of cell activity. Repeated application of the technique won't harm tissues. It is also MRI-compatible and insensitive to magnetic fields [19]. INM can be used to research brain disorders, regulate peripheral nerves, and restore auditory perception. Lanthanide-doped nanocrystals, which have been employed in some areas, for example, molecular sensing, bioimaging, and therapy, are excellent methods for converting NIR into visible emission [20].

In the field of heating using heat conversion matter, there are some studies on indirect optical modulation by infrared light. In this part, IR light is used to expose micro- and nanoscale transducers, which ultimately takes advantage of NIR radiation's advantageous tissue-penetrating propagation capabilities. The materials that can be used are polymer materials and upconversion nanoparticles. The magnetic susceptibility of biological tissues is very low, and the magnetic field can enter the brain without generating signal attenuation and side effects. Magnetic fields open ion channels depending on the magnetic field itself or MNPs. Microwave/radiofrequency (RF) heating has shown that magnetic nanoparticles can absorb high-frequency radiation. The tissue nearby will then become heated by the nanoparticle. This approach is promising in the field of cancer treatment [21]. Due to the magnetic nanoparticles' shown capacity to attach to particular protein targets on the neural cellular membrane, focused heating of the target cells is made possible by this technique, enabling high spatial resolution.

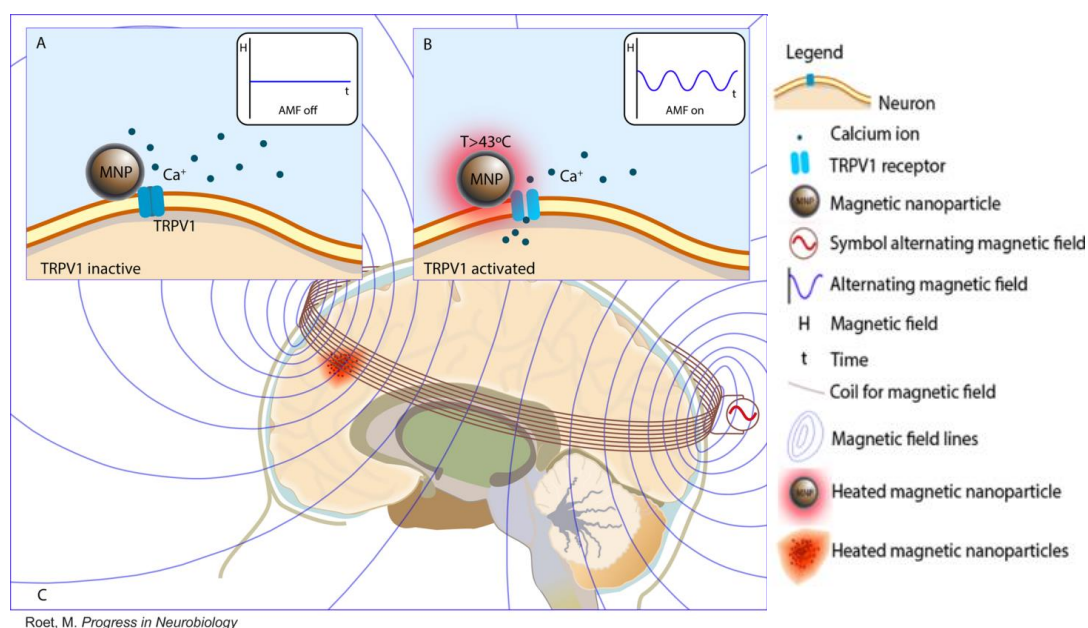


Fig 3. A conceptual representation of magnetothermal DBS in the human brain [21]. Part A and Part B show the change of TRPV1 in AMF from closed to open. MNP near the TRPV1 receptor is heated, the TRPV1 receptor is opened, and calcium ion influx activates neuronal cells. Part C is a schematic diagram of the magnetic coil worn on the head.

Magnetothermal genetics is also related to this. On the neural membrane, superparamagnetic nanoparticles are heated using alternating magnetic fields. By expressing TRPV1, neurons become heat-sensitive. When a magnetic field is applied, the neurons become active. Walking was induced by magnetothermal genetic activation in the motor cortex [22]. For example, NIR-sensitive gold nanorods (AuNRs) have been shown in research to modulate neural activity. It must have good biocompatibility. Moreover, it has significant photothermal conversion properties, which enable it to use the surface plasma reaction to transform NIR light energy into thermal energy. This nanotechnology method may be an effective minimally invasive treatment tactic in the future.

4. Pharmacological stimulation

An explanation for chronic pain can be established in the existence of the descending pain modulation system [23]. Blocking the central or peripheral pain transmission pathway through drugs or physical methods can relieve pain for a short time or sometimes a long time. Nerve destruction (pathway destruction) is rarely used, except in patients with advanced diseases with short survival. For some patients with pain caused by autonomic nerve abnormalities, a local autonomic nerve block can effectively relieve pain, so such patients can further undergo physical therapy. Some oral analgesics (NSAIDs, opioids and other auxiliary drugs) can effectively reduce pain so that patients can further undergo rehabilitation treatment.

There are multiple administration methods of drug stimulation, for example: oral, intravenous, and micropump. For drug-based therapy, increasing blood-brain barrier permeability is still a barrier. Among them, the micropump is a relatively new method, which now pays much attention.

Oral medicine is a primary therapeutic technique for neuromodulation. For patients with long-term use, an oral preparation or transcutaneous administration is preferred, and in use, both are effective and maintain stable blood concentrations. If oral or percutaneous sustained-release practices can reduce the number of doses, it can provide analgesia all night.

Venous preparations can reach the blood concentration quickly, thus having an immediate effect but a short duration. The blood drug concentration has large fluctuations (rapid infusion effect), which can lead to the early toxicity reaction when the peak blood drug concentration is reached, and the fulminant pain after the later efficacy decline. Continuous intravenous infusion, sometimes with dose-

controlled devices, avoids these adverse effects but requires an expensive drip pump, most commonly applied in postoperative analgesia. Drug injection can provide a more lasting effect than an intravenous injection, but it is more painful, and the absorption site is uncertain, so it is not recommended. Especially for cancer pain, a long-term continuous subcutaneous injection can be used.

Although the most common form of administration is systemic, if this method is applied to some diseases, there may be adverse consequences. Because the drug is distributed all over the body, it may cause serious side effects in healthy parts [24]. Therefore, accurate drug delivery is one of our needs. The traditional administration methods are oral and intravenous injections through blood circulation. Due to the blood-brain barrier, it is difficult to deliver drugs directly to the brain. The endogenous transporters in the brain only allow some types of nutrients and drugs to enter [25]. Suppose we use an implanted pump to deliver drugs since it does not need to be metabolized and passed through the body before reaching the designated area. In that case, it can be administered in a small dose, which means fewer side effects on the body compared with traditional methods, and can improve patients' comfort and quality of life [26].

The foundation of chemical neuromodulation is the delivery of nerve-healing micropumps. Nerve repair can help people overcome the blood-brain barrier's restrictions so that a sufficient concentration of drugs can enter brain tissue and regulate neurons. Chemical transmission and regulatory neurons can perform their functions directly in the intrathecal space, the nerve parenchyma, or a nearby peripheral nerve. The regional selectivity of chemical transmission is often more significant than electrical stimulation. The capability of the micropump places a limit on it. For micropumps to operate correctly, given their geometric and anatomical limitations, additional microdevices are needed [27, 28].

5. Discussion

Based on the three stimulation methods introduced before, this part will discuss the advantages and disadvantages of the three stimulation methods, and their development prospects will be analyzed and forecasted.

Electrical stimulation for neuromodulation has received wide world recognition as an effective and safe modality in managing chronic neuropathic pain, making every nervous tissue in the human body able to be reached with a stimulating lead directed by a good strong arm [29]. Electrical stimulation technology for neuromodulation has been developed for several decades and tended to mature over the years, making it able to satisfy most situations. And the efficacy of the electrical stimulator is comparatively high [30]. Moreover, as the nanostructured electrodes are emerging and more frequently used, The pain experienced by the patient during the electrical stimulation is also significantly reduced.

However, there are also disadvantages to this method. One of the most prominent disadvantages is the high complication rate. For example, 30-40% of patients report complications after spinal cord stimulation, including hardware complications, biologic complications, etc., mainly because of wrong lead location, inadequate technique familiarity, and surgeon experience [31]. Furthermore, there is a 1.6-3.7% absolute chance of cerebral bleeding and a 2%-4.5% risk of perioperative infection following deep brain stimulation, let alone less severe side effects like mood swings, muscle twitching, and dizziness more frequently [30].

Thermal stimulation often relies on specialized ion channels like TRPV1 that can be opened by heat and initiate pain-relieving countermeasures [32]. Thermal stimulation, including optical and nanoparticle stimulation, enables the precise control of neural activity [33], and it has cellular specificity and might have successful applications in this area [5].

However, this kind of therapy hasn't emerged until recent years, with a much shorter history as a way for neuromodulation compared with electrical stimulation. Therefore, thermal stimulation is not a therapy that is mature and perfect enough to be as widely used as electrical stimulation [5]. The materials used for thermal stimulation must also meet strict criteria since they must stay close to the

target cells without dispersing or migrating through the tissue [26]. Also, the temperature mist is tightly controlled in thermal stimulation to achieve activation without harming cells [5].

Pharmacological treatments are the most well-established and time-tested approaches for cell-specific neuromodulation. Pharmacological treatments can target specific endogenous systems to either promote or inhibit activity at specific chemical junctions without carrying the hazards associated with genetic modifications [26]. Additionally, the new method for pharmacological stimulation, using devices with microfluidics, has avoided many problems brought by traditional drug delivery methods, including oral and intravenous ones, which can cause pressure imbalance and harm organs. There are also challenges for microfluidics used in pharmacological stimulation, including the fact that specialized equipment is needed and microfluidics are sensitive to operational parameters and materials used [34].

All three stimulation methods are promising neuromodulation modalities for chronic pain and neuro disorders. Each of the modalities discussed above has its advantages and disadvantages. Therefore, combining two or even more modalities to treat the same neuromodulation is desirable, where different modalities can compensate for their shortcomings, thus giving it a good development potential [6]. For example, integrating electrical stimulation with microfluidics can reduce stimulation thresholds [35], and it might make it possible to observe directly how quickly and locally medication administration affects tissue responses [6].

However, many studies on combinatorial modalities mentioned above are only in the laboratory stage. Due to some limitations, they cannot be put into practical application. There is a long way to go to make neuromodulation a mature technology and completely solve neurological disorders.

6. Conclusion

Electrical stimulation is the most well-established technology. We have looked into its electrodes, including metal and inherently conducting polymers and nanostructured electrodes. The latter has been put forward recently, which has an obvious advantage over the former and can reduce mechanical trauma during implantation. Carbon microfibers are considered to be competitive materials in neuromodulation; porous graphene is highly effective in recording extracellular neural activity. For thermal stimulation, two methods are usually used to change the temperature: the target tissue absorbs light and visible light and thermal conversion materials. Infrared neuromodulation can be applied to tissues repeatedly without damage and can be used to restore auditory perception, investigate brain diseases, and control peripheral nerves. Nanotechnology has also been used in this area; lanthanide-doped nanocrystals are popular systems nowadays used in molecular sensing, bioimaging and therapy that can convert NIR into visible emission. The capacity of magnetic nanoparticles to capture RF energy and then warm the tissue around appears promising in cancer therapy due to the emphasis on heating the target cells. On the neural membrane, superparamagnetic nanoparticles are heated using alternating magnetic fields. For pharmacological stimulation, there are oral, intravenous injection, and micropump three ways of administration, micropump in which has attracted much attention as it can be administered in a small dose, which means fewer side effects on the body compared with other methods.

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