

Neuromodulation in the treatment of chronic neuropathic pain and neurodegenerative diseases

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Abstract. Finding ways to treat chronic neuropathic pain and neurodegenerative diseases has been plaguing scientists for a long time. Pharmacological methods were firstly used to deal with these diseases. However, problems like drug overdose and addiction largely limit the efficacy of pharmacological treatment. With the rapid development of electronic devices and materials, scientists now have the ability to modulate nerve activities in a different way. Neuromodulation is a booming field of neurotechnology which use physical or chemical methods to exert modulation effects in the central or peripheral nervous system of the human body. Usually, neuromodulation is used as an alternative to long-term drug therapy for treating chronic neuropathic pain. This article discusses the mechanisms and methods of neuromodulation and reviews its applications in neuropathic pain, Alzheimer's, and Parkinson's. Different methods of neuromodulation are put together and their characteristics and advantages are discussed. This article provides a reference to current neuromodulation techniques, their possible mechanisms, and applications, helping future studies gain a clear overview of the field of neuromodulation.

Keywords: Neuromodulation, chronic neuropathic pain, neurodegenerative disease, bioelectronics, Alzheimer's, Parkinson's.

1. Introduction

Chronic neuropathic pain and neurodegenerative diseases persecute patients globally, bringing challenges to medical and health institutions in different nations. Neuropathic pain is often caused by damage to the somatosensory system or other diseases. Patients with neuropathic pain are likely to suffer from side effects like sleeping disorders, diet disorders, and even mental isolation, and their life qualities are thus significantly affected. Neurodegenerative diseases are caused by the degeneration of certain types of neuron cells. For example, Alzheimer's disease (AD) and Parkinson's disease (PD) are likely to be caused by pathological changes in the central nervous system. The high prevalence of AD and PD are struggling millions of families worldwide and effective treatment is eagerly needed. Until recently, huge efforts have been made both pharmacologically and physically to deal with neuro-related diseases. However, current pharmacological methods do not have a sustained effect. Problems like drug addiction and overdose are making patients suffer even more[1]. These side effects of pharmacological treatment cause researchers to focus more on other lasting and more effective methods. Compared with pharmacological treatments, neuromodulation is found to have a stable and effective clinical effect and is considered a promising way to deal with neuropathic diseases in the future.

Neuromodulation comes with the development of bioelectronics. With the rapid development of semiconductor physics and material science, scientists are gaining power in combining electronic devices with biological tissues and applying the methods from electronic engineering to organisms to cause biochemical and bioelectrical responses. This combination opens the door of bioelectronics, a brand-new tool for scientists to investigate and modulate biological activities inside a living creature. Numerous methods were created to modulate the human body in different ways. Among them, one most powerful method that can be created artificially is the firing of neuron cells. Having the ability to modulate the neuro cells provides scientists with an unprecedented power to deal with numerous neuropathic diseases. Since then, attempts to apply this artificial firing or inhibitory effects onto

neuron cells in the treatment of neuropathic diseases have never stopped. These attempts form the various methods of neuromodulation.

Neuromodulation targets modulating the nerve activities artificially. Early in the eighteenth century, Luigi Galvani's experiment revealed the close relationship between motion and bioelectricity. The experiment reveals the potential of placing electrodes onto the nerve to act as readout and control devices. After that, more research has been focused on artificially interfering with the motion of nerve activities through numerous efforts, contributing to the birth of neuromodulation methods. Neuromodulation is a booming field of neurotechnology which uses physical or chemical methods to exert modulation effects in the central or peripheral nervous system of the human body. It is often realized by delivering electronic pulses or causing pharmaceutical responses to modulate nerve activities. Usually, neuromodulation is used as an alternative to long-term drug therapy for treating chronic neuropathic pain. Due to the reveal of the mechanisms of AD and PD and the success in clinical experiments, neuromodulation is now found to be promising in dealing with neurodegenerative diseases[2, 3]. Mechanisms of neuromodulation are still unclear apart from several existing hypotheses. For example, the Gate Control Theory introduced by Melzack and Wall in the 1960s[4], partly explained why neuromodulation method like spinal cord stimulation (SCS) is effective in treating chronic neuropathic pain. The theory of circuit dysfunction in AD proposes that neuromodulation is a possible tool for its treatment[5]. New researches continue to focus on revealing the complex effects that neuromodulation provides.

This article reviews the mechanism and common methods of neuromodulation and discusses several recent studies on the application of neuromodulation in treating chronic neuropathic pain, AD, and PD. Also, this article concludes the methods used in neuromodulation on different diseases and their characteristics and advantages in a chart, helping readers quickly get the gist of recent neuromodulation methods in treating neuropathic diseases. Overall, this review provides a reference for the current neuromodulation techniques and their applications for future studies.

2. NEUROMODULATION: MECHANISM AND METHODS

Neuromodulation is often realized by delivering electronic pulses or causing pharmaceutical responses to modulate nerve activities. In 1965, Melzack and Wall introduced the Gate Control Theory, which forms the fundamental of early neuromodulation methods. After that, new attempts have been made to look deeper into the factors that make neuromodulation a successful tool in treating neuropathic diseases. For example, A recent preclinical study showed that the inhibitory neurotransmitter γ -aminobutyric acid (GABA) plays an important role in the Gate Control Theory. Other possible factors related to neuromodulation include the concentration of glutamate, the release of acetylcholine, and an adenosine-dependent mechanism[6].

Physical neuromodulations include spinal cord stimulation (SCS), deep brain stimulation (DBS), transcranial magnetic stimulation (TMS), and photobiomodulation (PBM), while chemical neuromodulation contains methods like intrathecal drug delivery system (ITDD). Lately, new attempts like transcranial focused ultrasound (tFUS) are also proved to be effective[1]. Invasive Neuromodulation methods generally include SCS and DBS. Both use implantable devices to exert energy pulses onto the nerve cells. SCS, for example, requires the implantation of electrodes in the dorsal epidural space. DBS, on the other hand, implants electrodes into the deep brain. Apart from the invasive are noninvasive methods, TMS and PBM, for example. TMS uses coils to generate alternating magnetic fields and thus create eddy currents inside the brain. PBM transmits near-infrared wavelength light to be absorbed by intracellular chromophores. Ultrasound is another noninvasive method highly appraised by researchers. Low-intensity tFUS stands out for its noninvasiveness, high spatial precision, and adjustable focus[1].

Applications of neuromodulation traditionally focus on the treatment of neurodegenerative diseases. With the developments in the mechanisms of Alzheimer's Disease (AD) and the proposal of circuit dysfunction theory[5], neuromodulation is also found to be effective in treating AD. The

same happens to the Parkinson's disease, which is also found can be effectively treated with neuromodulation methods.

3. NEUROMODULATION: APPLICATIONS

3.1. Chronic Pain Treated with SCS

Chronic pain refers to pain that lasts longer than a month (3 months in the past). In China, over 10 billion patients suffer from chronic pain. Chronic pain leads to not only health problems but also sleeping disorders, diet disorders, and even mental isolation. Understanding the mechanisms of chronic pain helps us more accurately and effectively develop means to prevent people from suffering. Although thorough understandings of the mechanisms of chronic pain are still unclear, several theories have been put out. Among them, the Gate Control Theory by Melzack and Wall in 1965 plays an important role in tonic SCS[4]. In this theory, a certain type of stimulation would cause some cells to "close the gate" and thus inhibits pain. This type of stimulation can be created artificially and thus be utilized for pain relief.

In 1965, Melzack and Wall introduced the Gate Control Theory which form the fundamental of the earliest spinal cord stimulation (SCS) technic. In SCS, electrodes were applied onto the dorsal column, with an implant pulse generator (IPG) connect to it. Nowadays, SCS was proven to be clinically effective, but the Gate Control Theory was found to be only partially right[6]. A recent preclinical study showed that the inhibitory neurotransmitter γ -aminobutyric acid (GABA) plays an important role in the Gate Control Theory. A high concentration of extracellular GABA was detected during SCS, so it can be concluded that SCS induced the release of GABA into the extracellular space. This conclusion may form the core mechanism of the pain-relieving treatment of the SCS system[7, 8]. Other theories on the mechanisms of SCS include Supraspinal Inhibition and Anti-ischemic mechanism[6].

An early stimulation paradigm introduced by Shealy et al. is the tonic SCS. It generates a simple pulse within each cycle with a frequency of about 40Hz and a pulse width of about 200us. Problems and drawbacks of tonic SCS are poor pain-relief rate and uncomfortable paresthesia experienced by some patients. High-Frequency SCS, which delivers pulses from 1 to 10kHz, to some extent increases the pain-relief and reduces paresthesia. Another advancement is the burst SCS. Unlike the tonic SCS, which delivers only one pulse in each cycle, burst SCS produces a cluster of pulses (often 5 pulses) with a frequency of about 500Hz and a pulse wide of around 1000us inside each cycle. These clusters are separated for a long period and the frequency of the cycle remains at about 40Hz[9].

In addition to the innovations in waveforms and frequency, novel SCS methods also target differently: the dorsal root ganglion (DRG). The DRG collects sensory information from the peripheral nerves to the central nervous system and is an appealing site for pain treatment recently. SCS targeting the DRG usually requires less stimulation current and has a more focused effect. Another breakthrough in SCS development is the application of wireless charging. In this case, an IPG with coils is implanted on the flank. The charger is belted on the patient's waist and magnetically coupled to the IPG through the skin. The wireless charging system frees patients from open traumas at the implanting site and largely reduces the possibility of infection.

3.2. Neuromodulation on Alzheimer's (AD)

Alzheimer's disease (AD) is a progressive neurodegenerative disorder with a latent onset. It affects 10% of people over the age of 65 in the US[5]. Clinically, symptoms of AD include loss of memory, aphasia, impairment of visuospatial skills, executive dysfunction, personality, and behavior changes. Due to AD's high mortality and significant damage to people's living qualities, effective diagnosis and proper treatment is needed. There are many hypotheses on the mechanisms of AD. To list a few of them, genetic factors, senile depression, and head trauma, for example. Currently, the two crucial chemical factors that help us identify AD are the presence of extracellular amyloid- β ($A\beta$) plaques and intraneuronal tau neurofibrillary tangles (NFT). In 2018, the NIA-AA set a new criterion, making

biomarkers the most important factor in defining the disease. As a result, the definition of AD altered from certain clinical symptoms to the presence of A β plaques and NFT[3, 10]. The alternation of the criterion helps us recognize AD from a pharmacological perspective at a much earlier stage than when we use clinical symptoms for diagnosis. The benefits of this alternation are earlier detections and intervention strategies, bringing a new promise for tools targeting early intervention.

As is mentioned above, neuromodulation applies physical or chemical impacts on the nerve to modulate nerve activities. Different neuromodulation methods always target differently and have diverse effects on nerve cells. Consequently, certain types of neuromodulations may target emotional and physical dysfunctions in AD at the same time[3]. Existing neuromodulation methods to treat AD include deep brain stimulation (DBS), transcranial direct current stimulation (tsDCS), transcranial magnetic stimulation (TMS), and focused ultrasound (FUS).

DBS is a neuromodulation approach that implants electrodes into a specific area in the deep brain. Common DBS targets include the Subthalamic Nucleus, the Pedunculopontine Nucleus, the Cuneiform Nucleus, and a combination of the above. The efficacy of DBS on AD is proved by understanding the role of circuit dysfunction. Investigation at structural, functional, electrophysiological, and neurotransmitter levels provides evidence of circuit dysfunction in AD patients, meaning that DBS, which succeeded in treating some diseases relate to circuit dysfunction, is also promised for treating AD[5].

Apart from invasive neuromodulation like DBS, noninvasive ways are also applied. tsDCS combined with cognitive training also shows efficiency in improving attentional and executive functional abilities of AD patients[11]. TMS uses coils to eddy currents inside the brain. Animal studies on TMS correspond with findings in human studies, showing that TMS does reduce AD pathology[3]. Focused ultrasound (FUS) can target both shallow cortical and deep brains. By using MRI-guided FUS (MRIGFUS), the size of the A β plaque is seen to be significantly reduced. At the same time, MRIGFUS increases the level of endogenous immunoglobulin and glial activation[12].

3.3. Neuromodulation on Parkinson's (PD)

Patients with PD always show a series of symptoms including abnormal posture, postural instability, and gait disorders. Current neuromodulation targeting PD largely focuses on dealing with gait disorder problems. Clarifying the mechanisms of walking is difficult. Four gait components contributing to functional aspects of walking can be described: straight walking, gait initiation, turning and gait flexibility, and adaptation to environmental requirements[2]. All four components are to some extent affected by PD. It is believed that a loss of automaticity causes walking problems in PD[13]. Freezing of gait (FoG) is a typical type of gait disorder and is defined as a “brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk”. Over half of PD patients suffer from FoG and it is now a common feature of Parkinson's plus syndromes. Another syndrome of PD is the significantly increased pain in PD patients. One possible reason for this is the decreased threshold of pain due to abnormality of the dopaminergic system in the basal ganglia of PD patients[14].

DBS is mostly used to deal with refractory motor fluctuation in PD, especially for younger patients. A combination of traditional DBS target and the predominantly cholinergic pedunculopontine nucleus (PPN) causes stable improvements in gaiting parameters[15]. SCS applies electrodes onto the spinal cord to modulate the activity of nerve cells and is clinically proven to be effective in treating chronic pain. An increase in pain is found in PD patients, making SCS an ideal tool to deal with this syndrome of PD[14]. However, most of the time, SCS is used to manage posture control of FoG in PD patients[16]. TMS creates focused electromagnetic fields near the target area for modulation. Different target sites and frequencies have been tested and the generation of a believable sham stimulation was found to pose the main difficulty. The supplementary motor area (SMA) is believed to be the best target for TMS[17]. Another neuromodulation method, tsDCS, has been proved to provide a low-cost, portable, and effective way to treat PD patients with FoG[17].

Table 1. Characteristics and advantages of different neuromodulation methods on different diseases

Type of Disease	Modulation Methods	Characteristics	Advantages
Chronic Neuropathic Pain	Tonic SCS	Simple pulse, frequency of 40Hz.	\
	High-frequency (HF) SCS	Simple pulse, frequency of about 10kHz.	Increase pain relief, and reduce paresthesia (compared with tonic).
	Burst SCS	A cluster of (usually 5) pulses, each pulse about 500Hz, with a full cycle of about 40Hz.	Increased pain-relief and more subjective preference (compared with tonic), lower pain intensity (compared with HF).[9]
	DRG-Targeted SCS	Target at the dorsal root ganglion (DRG): an appealing site for pain treatment.	Require less stimulation current and a more focused effect.
Alzheimer's disease (AD)	Deep Brain Stimulation (DBS)	Targeting different places in the deep brain, tackling circuit disfunction.	FDA-approved DBS show marked improvements in PD patients, indicating its promising application in AD.
	Transcranial Direct Current Stimulation (tDCS)	Non-invasive, a weak direct electrical current (1-2 mA) on the skin, influences at the cortical level.	Influence the sensorimotor areas, can be combined with cognitive trainings in AD patients.[11]
	Transcranial Magnetic Stimulation (TMS)	Non-invasive, effects are frequency-dependent (inhibition when <1Hz and excitation when >1Hz).	Beneficial effects on hippocampal function[3], potential for becoming a biomarker.
	Focused Ultrasound (FUS)	Non-invasive, able to target both shallow cortical and deep brains, able to disrupt the blood-brain barrier (BBB).	Flexibility and accuracy in targeting different areas, FUS BBB opening benefits drug delivery.
Parkinson's Disease (PD)	Spinal Cord Stimulation (SCS)	Dealing with chronic pain of PD patients, managing posture control of FoG.	FAD-approved products and successful clinical cases.
	Deep Brain Stimulation (DBS)	Dealing with refractory motor fluctuation in PD.	Combination of traditional DBS target and the predominantly cholinergic pedunculo pontine nucleus (PPN) causes stable improvements in gaiting parameters.
	Transcranial Magnetic Stimulation (TMS)	Create focused electromagnetic fields near target area, sham stimulation poses the main difficulty.	Noninvasiveness. (SMA is tested to be the best stimulation area, however, larger cohort randomized studies are needed)
	Transcranial Direct Current Stimulation (tDCS)	Non-invasive, a weak direct electrical current (1-2 mA) on the skin, unclear for its long-term retention.	Low-cost, noninvasiveness, and portable.

4. Discussion

This article reviews the mechanism and common methods of neuromodulation and discusses several recent studies on the application of neuromodulation in treating chronic neuropathic pain, AD,

and PD. Also, this article concludes the methods used in neuromodulation on different diseases and their characteristics and advantages, helping readers quickly get the gist of recent neuromodulation methods in treating neuropathic diseases. Overall, this review provides a reference for the current neuromodulation technics and their applications for future studies.

The past half-decade has seen the rapid development of neuromodulation methods and technologies. Their applications in neuropathic disease provide scientists with a brand-new tool to observe and modulate nerve activities. With the development of SCS, DBS, tDCS, TMS, and FUS, clinical trials on these methods are showing progressing results. In treating chronic neuropathic pain, HF-SCS, Burst SCS, and DRG-Targeted SCS were developed, helping SCS to become a more effective and focused neuromodulation method. As for treating AD and PD, most major neuromodulation methods including DBS, tDCS, TMS, and FUS were tested and have shown positive results and a promising future. Apart from finding out the most effective way of neuromodulation, researchers have also spent huge efforts on investigating the mechanisms of these methods. For example, GABA was found to play an important role in chronic pain relief in addition to the Gate Control Theory. Circuit dysfunction theory in AD help scientists tackles this disease in a way of neuromodulation. However, despite all these mechanisms scientists have found, people still don't know the exact mechanism that how neuromodulation works. Animal and clinical experiments are the only way to make sure innovation is properly conducted and on the right track. Problems brought by the ignorance of the mechanisms are that time and money may be wasted because of superficial success and the limitation of sample size. On the other hand, even current successful applications of neuromodulation aren't achieving the best results. Even though several clinical experiments have shown to be positive, actual effects are still unstable when these methods are applied to patients. For example, only about 50% of patients say that they get pain relief after having applied SCS for chronic pain treatment. About 20% of patients receiving SCS say that they need revision surgeries[18]. Combining bio tissues with electronic devices needs to consider factors like electrical overshoot, inflammatory responses, and probe degradations, exerting higher standards on materials and waveform design. As a result, development in neuromodulation methods highly relies on the advancement in materials and a deeper understanding of neuroscience and pathology.

5. Conclusion

To conclude, neuromodulation can be applied to neuropathic diseases like chronic neuropathic pain, AD, and PD. Research in this field largely focuses on innovative methods of neuromodulation, discussions on the mechanisms of neuromodulation, and animal and clinical trial results. Most studies reserve their estimation of the effectiveness of a certain neuromodulation method because of a lack of clinical data, calling for more clinical trials and research on a certain type of neuromodulation. Consequently, it is hard to find out the best option of neuromodulation methods for a certain disease. For future studies, more research should be done on revealing the mechanisms of neuron activities and the theoretical principles for applying neuromodulation. Also, sufficient clinical trials are still needed to further prove the efficacy of a certain neuromodulation method.

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