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Research on the Application of New Flexible Electrode Materials in Implantable Spinal Cord Stimulators

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Abstract:
The spinal cord stimulator(SCS) is an implantable medical device based on the gate theory for pain management. Electrodes implanted in the human body receive signals from external electrical pulse transmitters. By precisely stimulating the dorsal column of the spinal cord or nerve roots, they interfere with the transmission of pain signals, achieving the purpose of pain management. However, traditional rigid electrodes may cause immune responses, signal attenuation and other problems due to their low biocompatibility, mechanical mismatch, significant increase in impedance over time, mechanical modulus being too high than that of biological tissues, and inability to change dynamically with the tissues. In recent years, flexible electrodes have provided new ideas for this problem. Flexible electrodes have better biocompatibility and flexibility than rigid electrodes, but they also face challenges such as balancing stability, durability, conductivity and flexibility. This article summarizes the new flexible electrode materials and their preparation for SCS. It conducts comparative experiments on biocompatibility with rigid electrodes, analyzes the electrical, mechanical properties and long-term implantation stability of flexible electrodes, aiming to provide ideas for the development of flexible electrodes for SCS in the future and promote the development of SCS in medical treatment.

Keywords: Flexible electrode materials; SCS; properties of flexible electrode.

1. Introduction

The current implantable SCS on the market are based on the gating theory, namely stimulation of large-diameter fibres inhibits the response to painful stimuli carried by small-diameter fibres of dorsal column neurons were designed and developed for the treatment of chronic pain, ischemic pain and pain related to nerve injury, and have many advantages [1]. On the one hand, when implanting electrodes, they can be implanted through puncture without damaging the nerve structure. On the other hand, the spinal cord stimulation includes Tonic SCS, HF SCS, and BurstDR multimodal stimulation, allowing patients to receive personalized treatment based on their own conditions. The SCS is composed of implantable electrodes and a pulse generator. Implantable electrodes are implanted into the epidural space of the human spinal cord to manage pain by transmitting stimuli to designated areas. The electrode needs to have excellent performance. First of all, it should have good electrical conductivity to ensure that the signal can be transmitted without loss. Furthermore, a high CIC is required to effectively stimulate neural tissue while supporting multimodal stimulation. On the other hand, it needs to have excellent biocompatibility to avoid triggering inflammatory responses; it should also have long-term stability, capable of preventing internal corrosion and electrode breakage or poor signal transmission quality caused by mechanical fatigue. Good ductility and flexibility are also indispensable, as the spinal cord needs to withstand certain tensile strains in daily life. Finally, an appropriate size is needed, which will make people more comfortable when providing electrical stimulation.

Due to the limitations of traditional rigid electrode materials, people have turned their attention to flexible electrodes. Flexible electrodes are developed based on flexible electronic technology, with the core lying in the use of flexible or extensible substrate materials to integrate organic or inorganic electronic components. Compared with rigid materials, flexible materials can be stretched, bent and compressed into any shape and still have stability. One of the commonly used flexible materials at present is hydrogel. Huang et al. combined PPY with hydrogel to develop a new type of hydrogel with excellent mechanical strength, electrical conductivity and biocompatibility [2]. In terms of mechanical strength, the network structure is reinforced and stability is enhanced through the mutual penetration of PPY and collagen. In terms of biocompatibility, the hydrogel has the same Young's modulus as the spinal cord, reducing mechanical imbalance and inhibiting inflammatory responses. Its electrical conductivity is similar to that of spinal cord tissue, which is conducive to stimulation conduction. Li et al. developed a rapidly self-healing low-modulus hydrogel-like elastomer [3]. Meanwhile, during the 100% strain cyclic stretching process, the signal response has no lag and can adapt to the deformation of the spinal cord during human daily life and movement. Another commonly used material is PDMS. Wang et al. developed an encapsulation layer with color adjustment, which has good biocompatibility and absorption properties [4]. It can effectively reduce the damage caused by thermal effects during processing and the inflammatory response caused by mechanical mismatch. Bao et al. used flexible material PI as the base, successively deposited Al2O3/HfO2/Al2O3 dielectric layers on it [5], and encapsulated them with PDMS to fabricate neuromorphic stimulators, which have excellent biocompatibility and non-cytotoxicity, and can directly emit electrical stimulation or be connected to other implantable flexible electrodes through anisotropic conductive films. Viana et al. proposed a graphene-based thin-film electrode material [6], namely EGNITE, which features low impedance and high CIL current pulse stability. However, flexible electrodes still have their own limitations. This article will explore the preparation of flexible electrodes and conduct a comparative analysis of rigid electrodes and flexible electrodes in terms of biocompatibility and electrical properties. At the same time, it will analyze the conductivity, stimulation accuracy, ductility and mechanical strength properties of flexible electrodes.

2. Comparison between flexible materials and rigid materials

2.1 Biocompatibility

2.1.1 Influencing factors and experimental methods

Biocompatibility is an important characteristic of flexible materials and one of the factors that make them superior to rigid materials in implantable electrode materials. It determines whether the material is safe, non-toxic, non-carcinogenic, and non-allergic when interacting with human tissues, the immune system, blood, etc. when implanted in the human body. Generally, it is determined through cytotoxicity tests and whether an inflammatory response occurs. Among them, cytotoxicity tests include indicators such as apoptosis, cell viability, and cell proliferation for judgment. The main material variables that affect biocompatibility include elastic constants, nanopores, moisture content, degradation characteristics, surface chemical composition, electronic properties, corrosion parameters, the toxicity of metal ions and so on [7]. Two common methods for testing biocompatibility are [8], on the one hand, to assess the substances that exude from biomaterials or devices and their impact on living cells or organisms; on the other hand, it is to measure the biological reactions that occur after the implantation of biological materials or devices in living organisms, which is conducted through in vivo or in vitro tests. In vitro testing can be conducted by directly culturing cells in vitro for in vitro cell biocompatibility experiments and in vivo testing

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is conducted through animal experiments, where incisions were made in mice and electrodes were implanted.

2.1.2 Comparison

In the past, the commonly used rigid materials for electrodes were mostly made of metallic materials. Such as Ti and Ti alloys, due to their corrosion resistance, but according to Kuwahara's research, Ti is a low-cytotoxic element. Thus, it can be seen that Ti is not suitable as an electrode material for long-term implantation in the body [9].

Zhu et al. conducted in vivo and in vitro biocompatibility experiments on the degradable metal Zn [10]. In indirectly cultured cells, the viability and proliferation of HCAECs decreased significantly with the increase of Zn concentration, but in directly cultured cells, HCAECs grew rapidly with the increase of Zn concentration. In response to the in vivo immune response, by implanting Zn biomaterials under the skin of mice, it was found that there were still a small number of immune cells between tissues and cells, and at the same time, fibrotic reactions occurred on the outer membrane side. Park et al. prepared four flexible electronic materials and conducted cytotoxicity tests in vitro and in vivo [11], as well as biocompatibility experiments after implantation in mice for four weeks. The results of the in vivo cytotoxicity test showed that no obvious cytotoxicity was detected even when the concentrations of the extracts of the four materials were 100%. Four devices were respectively implanted into mice and the immune spectrum of blood lymphocytes was analyzed. As can be seen from the immune spectrum. No significant changes were found in CD4+ T cells, B cells, NK cells and the percentage of neutrophils. Meanwhile, in the peripheral blood samples four weeks after implantation, the expression levels of pro-inflammatory cytokines remained relatively stable without obvious fluctuations. It can be concluded that these four devices have good biocompatibility as materials for long-term in vivo electrode implantation, are harmless to tissues and cells, and do not cause inflammatory reactions. They are excellent choices for long-term implant materials. In conclusion, flexible materials have better biocompatibility.

3. Properties of flexible electrode materials

3.1 Electrical conductivity

3.1.1 Experimental methods

High electrical conductivity enables electrodes to transmit electrical signals efficiently and is also one of the important characteristics of flexible materials. The principle of conductivity of conductive polymers is that current is generated by the movement of electrons in the conjugated double bonds within the polymer, but this does not make conductive polymers have high electrical conductivity. The main way for polymers to achieve high electrical conductivity is doping. The doping effect alters the carrier concentration and conductivity of semiconductor materials through oxidation (extracting electrons from HOMO) or reduction (injecting electrons into LUMO). The common method for measuring electrical conductivity is the four-needle probe method, and a digital ten-thousand-digit meter is used for detection. Before the test, the sample is cut into square specimens and silver paint is applied to the four corners to ensure good electrical contact. Then, the four probes touch the four corners and record the resistance. Calculate R according to the formula $R_s = \frac{\pi R}{ln2}$, and then calculate the conductivity according to the formula $\rho = \frac{1}{R_s \times t}$.

3.1.2 Achievements in scientific research

Li et al. conducted a gas-phase deposition of PPY on PPCL paper with the assistance of co-steam through the gas-phase deposition method [12]. During this process, the oxidation degree of the deposited PPY was adjusted, thereby altering the electrical properties of PPY and enhancing its conductivity. According to the results, it can be obtained that PPY has a higher electrical conductivity with the assistance of methanol. The four-needle probe method was used to observe that methanol increased the electrical conductivity of PPY to 0.74. Du et al. utilized CNF derived from PMS as the building block and prepared PEDOT: PSS flexible electrodes through in-situ polymerization [13]. At the same time, DMSO is used to treat the excessive PSS to prevent it from damaging the conductivity of PEDOT. Through the four-station exploration method, the maximum conductivity of PEDOT:PSS as the conductive matrix with CNP accounting for 62.5% reached 126.21S/cm, and the conductivity of PEDOT:PSS /CNP (53.5%) with better mechanical properties reached 66.67S/cm. After DMSO treatment, the conductivity of the PEDOT:PSS/CNP sample increased from 4.02 to 66.67 S/cm, with an increase of more than 16 times. In terms of flexible material carbon, improving electrical conductivity can be achieved either through sp2 hybridization of carbon or by doping carbon atoms to replace other carbon atoms in the lattice, or by utilizing graphene. Graphene itself has excellent electrical conductivity, with a carrier mobility of up to 15,000 $cm^2/(V\cdot s)$ at room temperature, far exceeding that of traditional materials and semiconductor materials. Qi et al. prepared an sp2/sp3 nitrogen-doped activated carbon material at 1000°C through solvothermal dehalogenation polymerization [14]. This material has an ultra-high electrical conductivity of 1.14*104S/m, which is more than three times higher than that of widely used conductive additives such as Ketenblack. WAHYUNI et al. combined graphene with excellent electrical conductivity [15], PEDOT: PSS materials that can prevent the stacking of graphene layers, and Au-Ag core-shell to prepare materials with electrical analysis performance and sensitivity of 3.24 μA μM within a wide linear concentration range (0.2-100 μM). In conclusion, flexible electrode materials not only possess excellent biocompatibility but also have superior electrical conductivity, facilitating efficient signal transmission and high sensitivity, ensuring that smile current signals can still be accurately captured.

3.2 Stability

3.2.1 Experimental methods

Stability is related to whether patients can use electrodes for a long time and reduce the trauma to the body caused by frequent electrode replacement during surgery. Therefore, it is also a very important characteristic. Stability mainly includes mechanical performance stability and electrical performance stability. The main testing methods for mechanical performance stability include tensile testing, dynamic fatigue testing, and high and low temperature cycling testing, etc. Tensile testing is carried out by measuring the stress-strain curve of materials through a universal material testing machine to obtain elastic modulus, tensile strength, etc. Dynamic fatigue testing can measure the lifespan of materials at specific bending angles and radii, such as when they break and develop cracks, by repeatedly folding them. High and low temperature cycling testing involves cycling materials within a certain temperature range to test their mechanical properties and verify the impact of temperature on flexible materials.

The stability of electrical performance can mainly be measured by two indicators: CSC and CIC. The CSC mainly includes EDLCs and pseudo-capacitors. The EDLCs charge storage of the conductive polymer depends on the non-Faraday adsorption of electrolyte ions at the extended electrode interface. The values of CIC and CSC can be accurately measured by the cyclic voltage method. A false capacitor is a Faraday reaction that stores charge in the electrode through REDOX reactions. The specific capacitance in the cyclic volt-ampere curve can be measured through this formula $C = \frac{1}{mv(V_b - V_a)} \int_a^b i dV$ [16].

The long-term stability of pseudocapacitors is challenged by the material expansion and cracking caused by the exchange of charges through REDOX reactions, which leads to the destruction of the conductive polymer structure and the deterioration of mechanical and electrical properties. Two major evaluation criteria for the performance of energy storage devices, namely power density and energy density, can be obtained through cyclic current charging and discharging, and they can be calculated by formula $E = \frac{1}{2} C \text{\DeltaV}, P = \frac{E}{\text{\Deltat}}$ [16]. The continuous CV method is a technical means to study the behavior,rate and control steps of electrochemical reactions at the electrode interface. The principle is to apply a pulsed voltage to the closed loop formed by the working electrode and the counter electrode,and change the potential at the working electrode/electrolyte interface at a certain rate, forcing the active substances on the working electrode to undergo oxidation-reduction reactions. Thereby obtaining the magnitude of the response current when electrochemistry occurs on the electrode.

3.2.2 achievements in scientific research

Lu et al. prepared pure PEDOT: PSS hydrogels. By dry heat treatment and the addition of DMSO solution [17], the growth interconnection of the PEDOT region was promoted, enabling it to maintain a good permeation network and provide excellent mechanical stability. The Young's modulus of pure PEDOT: PSS hydrogel in PBS is 2-10 mpa, which is lower than that of PDMS and traditional rigid materials, and decreases with the increase of DMSO concentration until it reaches a constant order of magnitude. Fig.1 indicates that the stretchability increases with the increase of DMSO concentration until it reaches 20vol.%, after which it begins to decrease. Its ultimate tensile strain in deionized water can reach 40%, which is very similar to the stretchability of neural tissue. Pure PEDOT: PSS (13vol.%DMSO concentration) also exhibits excellent electrochemical stability in a humid physiological environment. The value of CSC was measured by the CV cycle method. Fig.2 indicates pure PEDOT: PSS hydrogels on Pt electrodes in PBS CV curves after different cycles. After 20,000 CV cycles, the value of CSC did not decrease significantly, with a reduction of less than 9%, and it also has a high CIC value. The stable CSC, high CIC, low Young's modulus, good mechanical stability and excellent mechanical compliance provide stable and long-term biomechanical interaction with biological tissues such as neural tissues, making it suitable as an implantable biological stimulation electrode material.

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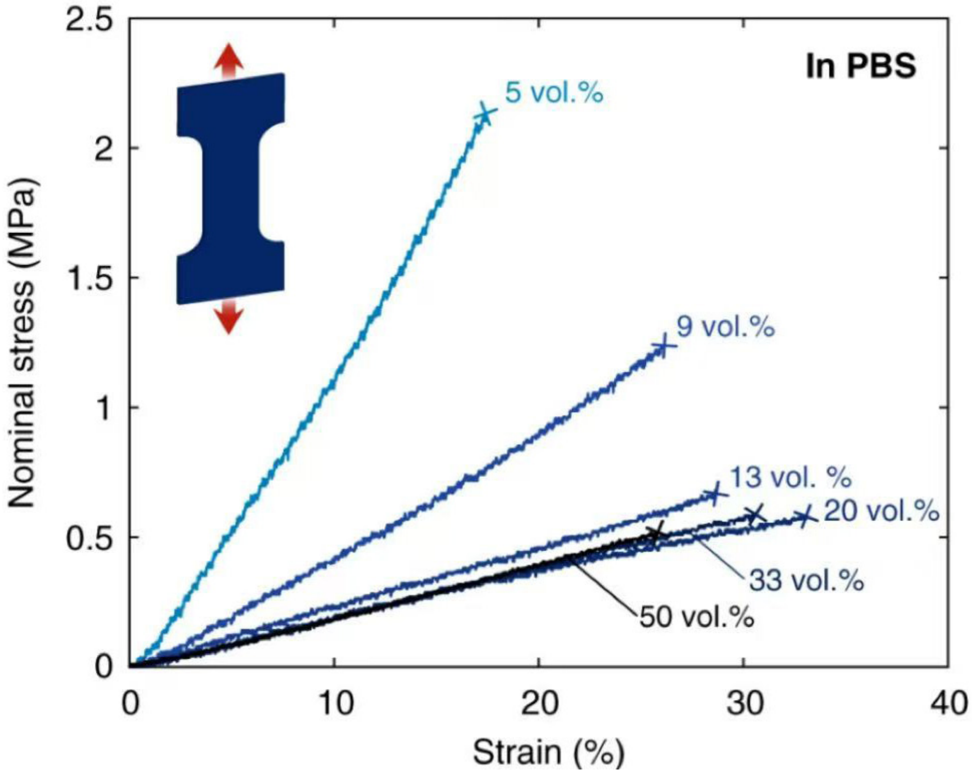

Fig. 1 Nominal stress and strain curves of standalone pure PEDOT: PSS hydrogels in PBS with different DMSO concentrations [17]

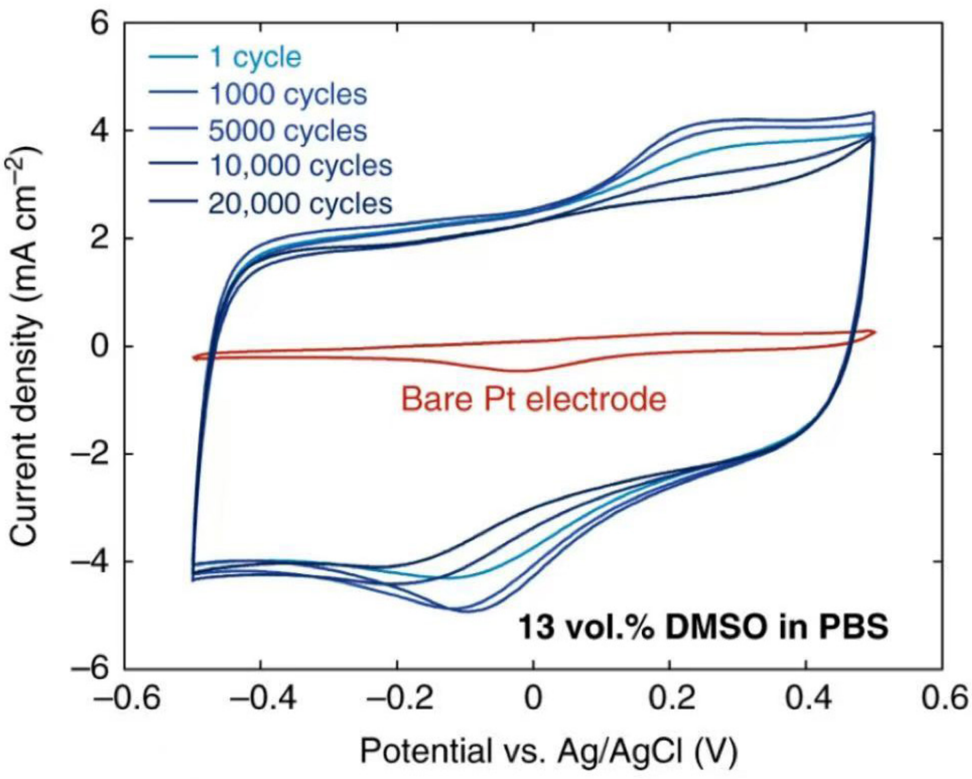

Fig. 2 CV curves of pure PEDOT: PSS hydrogels on Pt electrodes in PBS. The red curve represents the CV curve of the bare Pt electrode as a reference [17]

The Young's modulus of carbon nanotubes is approximately between 270GPa and 950GPa, and they have a tensile strength as high as 63GPa. This is because the hollow configuration of carbon nanotubes absorbs more energy during deformation [18]. Meng et al. first obtained thin carbon nanotube membranes by filtering uniformly dispersed MWNTs in ethanol through microporous membranes [19], and then immersed graphene paper in aniline /HCl solution for vacuum impregnation to ensure full infiltration of MWNTs. Subsequently, APS solution was added dropwise. Finally, the product (BP/PANI) was washed with distilled water, acetone and ethanol, and then vacuumed at 80°C for 12 hours. Fig.3 indicates that the specific capacitance of the CNT/PANI and BP/PANI composites measured by the CV cycle method was much higher than that of the original PANI. After 1000 cycles, it could be observed that the specific capacitance of the composites decreased by 20.6% compared to the 30% of the original material, with only about 10.6% of the loss. In conclusion, the flexible electrode, due to its excellent mechanical properties, adaptability and iodine chemical stability, has become the best choice for the electrode of the SCS.

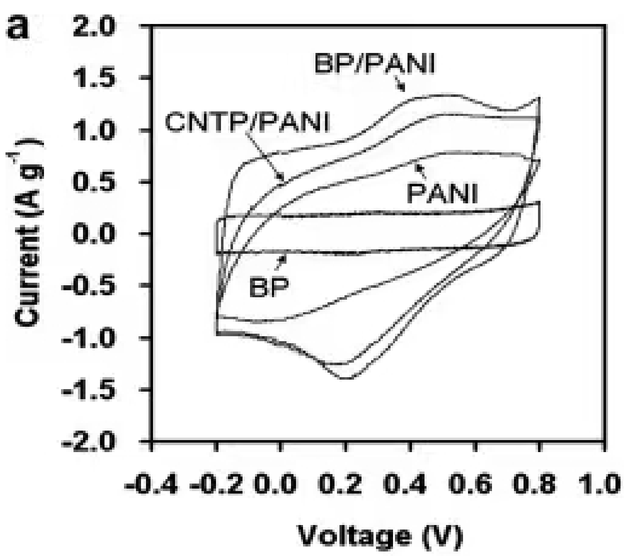

Fig. 3 CV curves CV curves at 5 mV s^{-1} [19]

4. Limitations and Future outlooks

Although the application of flexible electrodes in SCSs shows great potential due to their superior biocompatibility, conductivity,mechanical and electrochemical stability, the following challenges still exist. The flexible electrode implantation device, as a component of the SCS, should possess the properties of stability, long-term activity, and high power density. However, at present, some conductive polymers still have structural degradation during continuous oxidation cycles and will degrade under specific conditions.False capacitors cannot maintain high power density and energy density for a long time. Moreover, although materials such as graphene, carbon nanotube and conductive polymers have low Young's modulus, can adapt to the complex deformation of biological tissues and have good biocompatibility, they will self-damage when bent and stretched, so their stability and long-term activity still face challenges. Moreover, the difficulty in large-scale production at low cost and high quality, as well as the tendency to damage materials during the preparation process. The preparation process of composite materials such as graphene and carbon nanotubes is complex and costly, making it difficult to achieve large-scale production. At the same time, the market prices of raw materials for graphene, carbon nanotubes and conductive polymers are also relatively high, and their costs will be high during the development process and the electrode manufacturing process. Thirdly, electrodes composed of carbon nanotubes need to be supported by elastomers or combined with other materials to ensure the stability of the carbon nanotube structure, but this will reduce the energy density of the carbon nanotubes.

In the future, to enhance tensile properties, maintain long-term stability and reduce fatigue rates, the influence of fatigue and cracks under multiple tensile tests can be reduced by developing new materials such as self-healing conductive hydrogels or composite materials, thereby improving the long-term stability of the electrode. Appropriate geometric shape structural designs can also be adopted to enhance tensile strength, such as two-stage wave structures, serpentine structures, etc. For electrodes based on carbon nanotubes and elastomers, it is also necessary to consider how to enhance the adhesion between the carbon nanotubes and the base, so that the cracks are evenly distributed rather than directly breaking. Good stability and long-term usability can enable the electrodes to be implanted in patients for a long time, reducing the damage to patients caused by frequent surgical electrode replacement. At the same time, it is also necessary to explore how to further reduce the electrode resistance and enhance the CIC under the premise of maintaining a certain mechanical strength. This can not only reduce signal attenuation, enabling precise targeting of the target nerve, but also support multimodal stimulation such as high-frequency stimulation, meeting the treatment requirements of using suitable stimulation modes in complex pain states. In terms of manufacturing processes, it is also necessary to consider how to reduce costs, not cause damage to electrode materials, be environmentally friendly and capable of large-scale production to meet market and patient de-

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mands.

5. Conclusion

In conclusion, compared with traditional rigid electrodes, flexible electrodes exhibit superior biocompatibility, electrical conductivity and mechanical stability, and thus have become the most promising material in the implantable electrode part of SCSs at present. In this paper, by implanting flexible electrode materials into mice, it was found that no inflammatory response occurred and they had good biocompatibility. The methods for improving the electrical conductivity of commonly used flexible materials were explored and the current flexible materials with high electrical conductivity were discussed. The main factors affecting the stability of flexible electrodes and the testing methods were discussed, and the current research progress was reported. Finally, the limitations and challenges faced by current flexible materials were discussed. Through the research on flexible electrode materials, it provides ideas for the future development of SCSs, improves the therapeutic effect on patients, and meets the needs of patients.

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