

## Review Article

# Neuroprosthesis Devices Based on Micro- and Nanosensors: A Systematic Review

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**Background.** A neuroprosthesis (NP) is a medical device that compensates and restores functionality of neural dysfunctions affected by different pathologies and conditions. To this end, an implantable NP (INP) must monitor and electrically stimulate neuronal small structures in the peripheral and central nervous system. Therefore, one of the most important parts of INPs are the sensors and electrodes since their size, resolution, and material are key for their design and performance. Currently, most of the studies focus only on the INP application but do not show the technical considerations of the sensors. **Objective.** This paper is a systematic literature review that summarizes and synthesizes implantable micro- and nanosensors/electrodes used in INPs for sensing and stimulating tissues. **Data Sources.** Articles and patents published in English were searched from electronic databases. No restrictions were made in terms of country or journal. **Study Selection.** All reports related to sensors/electrodes applied in INPs were included, focusing on micro- and nanotechnologies. **Main Outcome Measures.** Performance and potential profit. **Results.** There was a total of 153 selected articles from the 2010 to June 2020 period, of which 16 were about cardiac pacemakers, 15 cochlear implants, 13 retinal prosthesis, 31 deep brain stimulation, 6 bladder implants, and 18 implantable motor NPs. All those INPs are used for support or recovery of neural functions for hearing, seeing, pacing, and motor control, as well as bladder and bowel control. Micro- and nanosensors for signal stimulation and recording have four special requirements to meet: biocompatibility, long-term reliability, high selectivity, and low-energy consumption. Current and future considerations in sensor/electrode design should focus on improving efficiency and safety. This review is a first approximation for those who work on INP design; it offers an idea of the complexity on the matter and can guide them to specific references on the subject.

## 1. Introduction

Nowadays, acquired cerebral injuries (e.g., stroke, traumatic brain injury, spinal cord injury, epilepsy, and Parkinson's disease), disability due to congenital disorders (e.g., deafness, blindness, cerebral palsy, muscular dystrophy, and spine malformations), or physiological damage by effect of age (e.g., brain degeneration, kidney failure, and cataracts) or by chronic disease (e.g., diabetes, heart rhythm disorders,

arthritis, and pain) have increased considerably, in addition to the population having a longer life expectancy than ever in the history of humanity. These facts have generated a larger number of patients with neurological disorders, which are chronic and progressive and constitute a global public health issue [1].

A neuroprosthesis (NP) is a medical device used to replace or compensate some lost body function when it is affected by an illness or accident of the central nervous

system or the peripheral nervous system. NPs can be of neurological, motor, sensory, or organic type, according to the function it intends to replace or support [2–6]. NPs can be used as a neurorehabilitation technique or as assistive technology.

The first commercialized NP was the cardiac pacemaker (CP) in the 1950s [7] and the cochlear implant (CI) for the deaf in the 1960s [8]. The statistics show that the number of CPs implanted in 2016 was 1.14 million units [9], and the new CP market research report indicates a production projected to reach USD 5,199 million by 2026 [10]. Currently, more than 45,000 CIs are sold worldwide each year [11]. Deep brain stimulation (DBS) is a treatment involving the implantation of a neurostimulator to deliver electrical pulses to targeted areas in the brain; this technique has been applied to over 150,000 patients with movement disorders who are treatment resistant to pharmacologic therapy [12]. The global DBS market size was USD 696 million in 2018 and is projected to reach USD 1,676 million by 2026 [13]. The bladder implant (BI) has been implanted in thousands of individuals with spinal cord injury and is both medically and cost-effective. A study showed in 2001 that more than 1,500 patients with spinal cord injury were benefited from a bladder implanted NP (BN); they compared the cost of this technology versus traditional management and concluded that BN reduces costs over time [14]. The global pelvic floor electric stimulator market size was valued at USD 123.67 million in 2018 and is anticipated to grow 11.1% [15]. Retinal prosthesis (RP) is a biomedical microchip that stimulates retinal neurons. The most important retinal prosthesis market is focused on the Argus II device and the implantable miniature telescope. The US, Canada, Germany, the UK, France, Italy, China, India, Japan, Brazil, and South Africa are the major countries where RPs are commercialized [16].

Most motor NPs (MNP) are intended for patients suffering from movement disabilities to restore walking, standing, or range of movement, and only a few of them are implantable. The rising prevalence of neurological disorders such as stroke, multiple sclerosis, cerebral palsy, or brain injuries has led to a market for devices (neurorobotics, brain-computer interfaces, wearable devices, and noninvasive stimulators) for motor neurorehabilitation valued at USD 915.1 million in 2015 and which is expected to grow over 15.1% by 2024 [17].

Electrical stimulation and biosignal sensing of living tissues are directly linked to the neuroprosthetic technique. The therapeutic use of electrical stimulation has been known in medicine for several centuries [18, 19]. It is common to apply electrical stimulation to relieve pain, reduce stiffness, and strengthen muscles. Unlike traditional electrical stimulation, new strategies, such as Functional Electrical Stimulation (FES), are used to activate the neural pathways that have been interrupted by the injury itself [1, 20], promote functional activity, and enhance neuroplasticity [21]. NPs are related to the improvement of movement, hearing, seeing, and bladder and bowel control, as well as recovery of sexual functions which always have a positive impact on the quality of life of people with disabilities.

NPs apply artificial electrical current impulses to the myogenic and neuronal small structures and cells of the peripheral, spinal, and central nervous system, including muscles, nerves, spinal cord, and the brain. Likewise, they may detect electrical activity or sensory information, e.g., texture, temperature, and position, thereby creating a bidirectional pathway or a closed loop. Both stimulation and sensing are carried out through lead wires and electrodes that can be either superficial or implantable ones. NP devices usually include a multichannel stimulator that can be activated externally or internally [22]. Activation is made through configurable parameters (current or voltage pattern, pulse amplitude, pulse frequency, pulse train, pulse width, and intervals) fully programmable to adjust to the site and aim of the application (therapy or assistive) [23, 24].

CP, CI, RP, DBS, BI, and MNP are typical implanted neuroprostheses (INP). These devices require arrays of several tiny implantable sensors for stimulation and recording, with the same number of channels as the functions that need to be stimulated and for each one, e.g., low-noise amplifiers, integrated analog-to-digital converters, and a processor controller module and power supply; all of these are located in a miniaturized package a few millimeters in size.

Another important aspect is to know the exact localization of anatomical structures in spaces as small as the order of microns [25], especially in the brain, ear, and eye, where the right place of registration and stimulation is of vital importance to achieve successful surgical implants and to avoid tissue damage, as well as motor, sensorial, or cognitive sequelae.

For this kind of invasive procedures, electrode type, material, and size are crucial. Micro- and nanosensor research has opened new possibilities to design implantable neuroprostheses which are required to work in biological environments avoiding tissue damage, while at the same time have a high degree of miniaturization; enhanced biocompatibility, sensitivity, and reliability; are light-weight; have multiple channels or include microelectrode arrays; and are reprogrammable and/or have a nanoscale power supply [26]. Reliable microsensors, implanted stimulators, telemetry and external control units, and transmitter/receiver coils, as well as micro-electro-mechanical systems, smart algorithms, and designs with minimal size and weight, are also a challenge [27].

For this purpose, we have carried out a systematic literature review to analyze recent advances in cutting edge micro- and nanotechnologies applied to sensors used in the following implantable devices: cardiac pacemaker, cochlear implant, deep brain stimulator, retinal prosthesis, bladder implant, and motor neuroprosthesis. Additionally, aspects of biocompatibility, feasibility, complications, and limitations for applications in humans are considered. These devices were selected for their high impact on health, quality of life, and market demand.

Given the amount of literature on the subject, and the fact that time is always scarce and that professionals do not always have the time to track down all the original articles, critically read them, and obtain the evidence they need for their questions, this review may be their best source of

evidence. This review contains most of last year's available information on the topic and can be useful for those working on the subject. This review presents a systematic categorization of emerging technological developments for INP design, which are generally not considered in either review or research articles on INP. The study includes considerations to improve the spatial and temporal resolutions of the sensors, high-density arrays, and new techniques for low battery consumption. Also, it shows that multi-micro-electrodes are more effective than macroelectrodes and that a large number of electrodes and leads may improve both stimulation and recording capacities. Moreover, it highlights new recording techniques with implantable electrodes that are aimed at optimizing electrophysiological signals. Additionally, the topic of a proposed energy harvester produced by the human body is presented, that could represent a turning point for powering NPs. Finally, other important topics of nanotechnology applied to INPs are considered, including optogenetic and photobioelectronic techniques and nanostructures that comprise a variety of materials.

The rest of this paper is organized as follows: The methodology of the systematic literature review is presented in Section 2. The six selected implanted neuroprostheses are discussed in Section 3, including application, size, and materials of the electrodes. Section 4 is an outline of the main micro- and nanotechnologies available and under development used in implanted NPs. Finally, the importance of this technology for the restoration of walking, standing, hearing, and seeing, as well as the restoration of bladder and bowel control functions, are discussed, all being crucial for the quality of life of people with disabilities.

## 2. Method

The systematic search we used was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and was performed in the scientific databases PubMed/Medline, IEEE Xplore, ScienceDirect, Scopus, Google Scholar, EBSCO; patent searches were performed for article titles, abstracts, and keywords published in English. There was no lower limit for the time of publication, but literature was searched up to June 2020.

**2.1. Search Query and Strategy.** The strategy for selecting pertinent articles involves searching the literature sources in four steps. In the first step (Step 1—identifying), the titles of articles are identified from electronic databases, followed by the extraction of the abstract and keywords to exclude duplicates and studies that are unrelated to sensors for implantable neuroprostheses (Step 2—screening). The third step filters according to the inclusion and exclusion criteria during the full text review (Step 3—first eligibility), and only articles published in the period 2010–June 2020 are selected (Step 3—second eligibility). In the last step (Step 4—including), the studies considered relevant and belonging to recent advances are selected for analysis in this Systematic Literature Review (SLR).

The goals of the review were translated into research questions to understand and summarize evidences about

the micro- and nanosensors applied in implanted NP devices. In this context, the following research questions (RQ) were proposed:

- (RQ1) Is the neuroprosthesis implantable?
- (RQ2) What are the main requirements in implantable sensor/electrode design?
- (RQ3) What are the main technologies used in sensors/electrodes for implantable NPs?
- (RQ4) Do all neuroprostheses use implanted sensors/electrodes?
- (RQ5) Does the article describe the main issues to be solved?
- (RQ6) What are the challenges?

**2.2. Inclusion and Exclusion Criteria.** To ensure data quality, we further set the following criteria: the works were published in a reliable peer-reviewed conference, peer-reviewed journal, book, chapter of book, or scientific magazine.

Medical subheadings and free-text terms for “implantable neuroprosthesis,” “motor neuro prosthetic,” “therapy,” “motor rehabilitation,” “functional electrical stimulation,” “cochlear implant,” “retinal prosthesis,” “deep brain stimulation,” “bladder implant,” “cardiac pacemaker,” “microelectrode array,” “implanted device,” “micro- and nanotechnology,” “sensors,” and “electrodes,” were combined with “stroke,” “deafness,” and “spinal cord injury,” among others. In addition to the structured literature search, a manual search of the references from the included articles was also conducted. Thus, a number of articles not identified by the original search were included in this review after they met all other requirements. The level of evidence was not graded due to the exploratory nature of many of the studies.

We eliminated the studies that are not thematically relevant to the scope of this paper and those in which data quality is low by the selection of an inclusion and exclusion criteria based on the following: information provided in the abstract is thematically relevant to this paper, state-of-the-art information is included and the evaluation/validation thoroughly analyzed and explained, and the results of tests strongly support the ideas of micro- and nanosensors. Limitations of the proposed solution were considered.

**2.3. Data Extraction and Analysis.** 762 studies were retrieved from the electronic databases (Step 1—identifying) and 538 of them were initially selected based on the title, abstract, and keywords (Step 2—screening). From the set of 538 studies, the selection (inclusion/exclusion) criteria were applied, thus resulting in the exclusion of 174 studies during the full text review (Step 3—first eligibility). The remaining 364 articles underwent a quality screening where we eliminated 148 studies that did not meet the quality criteria.

Despite that the Systematic Literature Review (SLR) retrieved suitable studies since 2000, the most relevant contributions in terms of updating the state-of-the art on implantable sensors applied in NPs, including micro- and

nanotechnologies to manufacture sensors, come from 2010. Then, of the remaining 216 that were pertinent, only those from the 2010 to June 2020 period was selected (Step 3—second eligibility); thus, only 153 primary studies were considered as recent advances and therefore relevant to this SLR; these were then selected for data extraction (Step 4—including) and analysis.

Table 1 shows the studies that were considered as relevant for our SLR indicating the number of articles after the review of Step 3—first eligibility and Step 3—second eligibility. The total number of articles (Step 3—first eligibility) is shown in parentheses regardless of publication date. Only the references from those 153 articles that were considered for analysis (Step 3—second eligibility) are shown in Table 1. These references are classified by type of neuroprosthesis, as well as those studies that consider implantable sensors and electrodes manufactured with micro- and nanotechnologies and novel biocompatible materials.

The flowchart in Figure 1 shows the selections of the articles based on the PRISMA method for Step 3—eligibility that includes searches in EBSCO, Google Scholar, PubMed/Medline, Google Patents, and IEEE Xplore. Irrelevant and older boxes indicate the number of articles that were eliminated.

### 3. Results

The selected references are classified by type of neuroprosthesis, as well as those studies that consider implantable sensors and the electrodes manufactured with micro- and nanotechnologies, and with biocompatible materials. In the type of neuroprosthesis, information is reported on implantable motor neuroprosthesis, cochlear implant, retinal prosthesis, deep brain stimulator, cardiac pacemaker, bladder implant, and nonspecific applications. In the following paragraphs, we describe the method for selecting articles on INPs according to the type of application.

The first and second phases of Step 3—eligibility were concluded with the elimination of 211 studies due to irrelevancy, being older studies, and duplicated and inadequate sensor/material/technology data. Finally, 153 works which were published during the period of 2010-June 2020 were chosen: EBSCO—23, Google Scholar—37, PubMed—46, ScienceDirect—14, SpringerLink—18, Google Patents—3, and IEEE Xplore—12. Studies mainly originated in Europe, North America, and Asia. All publications were in English.

The selected articles were divided into two major categories, as shown in the proposed taxonomy of Figure 2. The first one (18/153; 11.76%) is the review cluster, in which researchers describe and provide a general overview of recording and stimulation electrodes used in implantable neuroprostheses, functional electrical stimulation, and their application in neurorehabilitation. The second category (135/153; 88.23%) is the three-tiered research cluster. Tier 1 contains articles on the development and clinical application of the six types of neuroprostheses considered in this paper. Tier 2 provides information on the most widely used and investigated material in the manufacture of sensors, electrodes, and cases. Tier 3 includes studies that are aimed at

developing and using sensors/electrodes for recording and stimulation.

In Figure 3, the number of selected articles is shown by each type of NP related with implanted sensors/electrodes, micro- and nanotechnologies, and materials, respectively, for the 2010-June 2020 period. 92 out of the 153 papers were concerned with micro- and nanosensors/electrodes, and 34 were concerned with the materials used. The rest (27) were concerned with power supply, NP application, or commercial use.

Data for device types (implantable or no implantable), sensor/electrode types (micro, array, tube), and material types (biocompatible, isolation) were recorded in a spreadsheet (Excel 2015, Microsoft Office). After analysis, data including the application for type of stimulation, causes of the disorder, size and type of sensor/electrode, and material for manufacture were tabulated and summarized in Table 2.

Nonimplanted NPs were excluded. 17.64% of the studies did not include either the size of the electrode or the type of material; however, this condition was not an exclusion criterion. Most of the cases (54-35.29%) were of nonspecific application and DBS (31-20.26%), while others were CI (15-9.8%), RP (13-8.49%), CP (16-10.45%), or implantable MNP (18-11.76%). The least reported was BI (6-3.92%). Most of the studies (126-82.35%) address the importance that electrodes should be manufactured in the smallest possible size and geometry and be made of biocompatible materials.

In the next sections, applications, materials, sizes, and electrodes/arrays used in the implantable NPs (MNP, CP, CI, DBS, RP, and BI) are described, and aspects of biocompatibility, security, and supply issues are considered.

#### 3.1. Implantable Neuroprostheses

**3.1.1. Implantable Motor Neuroprosthesis.** The aim of an implantable motor NP (IMNP) is to activate the upper and lower extremities. Five out of 18 works related to IMNPs used microelectrodes implanted in nerves [22, 104]. One study showed the activation of motor control and sensory feedback by stimulating a large number of independent neuronal pathways using a 96-multi-electrode array implanted in the median and ulnar nerves to control the fingers of a virtual prosthetic hand [32]. The second paper presented an improved power grip, fingertip pinch, and range of movement of the hand [105]. The third paper investigated if IMNPs can be used for controlling standing, stepping, and walking [106]. Finally, peroneal nerve stimulation in the drop foot syndrome was presented [107]. One of the major challenges of this technique is the implementation and adjustment of the electrodes [108].

Electrocorticography (ECoG), which captures signals from the cerebral cortex, has been used as a potential control signal to activate an IMNP providing information about movements and trajectories of the upper and lower extremities. ECoG offers higher spatial resolution, greater spectral frequency, and a generally improved signal-to-noise ratio in comparison to noninvasive EEG.

Commonly used ECoG sensors have grids (4-8 mm width) and/or subdural strip electrodes (8 mm width). Conventional ECoG grids are composed of stainless steel or

TABLE 1: Number and references of the articles selected for the 2010-June 2020 period.

Type of NP (number of articles)	Implantable sensors/electrodes	Micro- and nanotechnologies	Manufacturing materials
Implantable motor neuroprosthesis (18)	7/18 [5, 28–33]		2/18 [5, 31]
Cochlear implant (15)	6/15 [34–39]	4/15 [40–43]	2/15 [41, 44]
Retinal prosthesis (13)	9/13 [39, 45–51]		3/13 [39, 46, 52]
Deep brain stimulator (31)	10/31 [53–62]	9/31 [63–71]	6/31 [59, 72–76]
Cardiac pacemaker (16)	4/16 [77–80]	1/16 [81]	9/16 [78, 82–89]
Bladder implant (6)	3/6 [90–92]	2/6 [93, 94]	1/6 [95]
Nonspecific applications (54)	13/54 [96–108]	24/54 [42, 63, 65, 67–70, 75, 93, 106, 109–122]	11/54 [3, 55, 59, 66, 72–74, 76, 118, 123, 125]
153/364	52/153	40/153	34/153

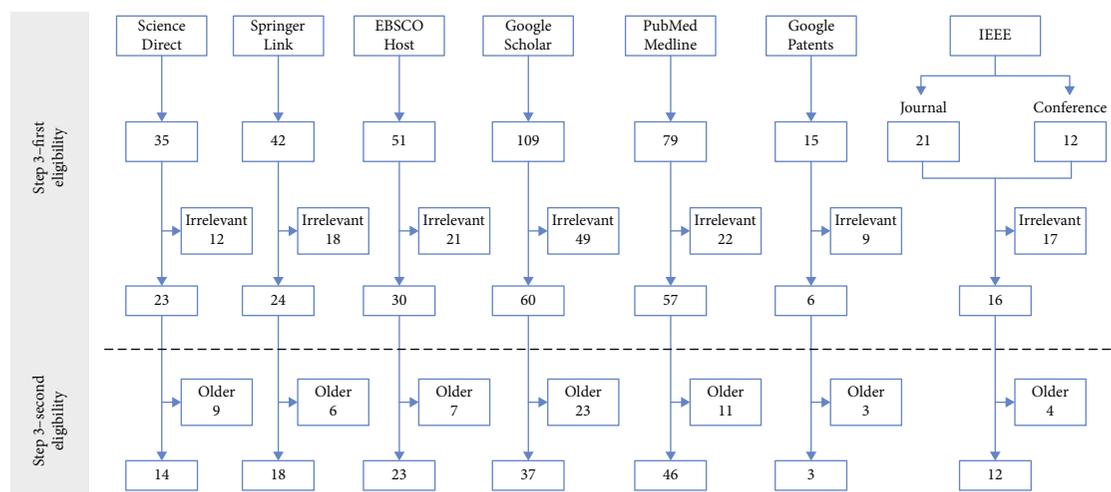


FIGURE 1: Flowchart of the Systematic Literature Review based on the PRISMA method.

platinum/iridium electrodes and wires embedded in a dielectric elastomer. We only found two papers that mention the size and material for the ECoG grid [5, 32].

Two out of 5 papers that use direct ECoG neural recording are focused on grasping and reaching therapy [109, 110] and another paper is focused on patients with partial or total loss of movement [111]. One paper published results of real-time control for a prosthetic limb [112]. Another ECoG grid application is the stimulation of the somatosensory cortex as reported in one paper [113].

Four papers investigate the potential of the IMNP as a solution for patients with spinal cord injury to restore full weight-bearing standing and assisted stepping by implanting stimulation electrodes in the dorsal epidural space of the spinal cord and by collecting neural signals using intracortical microelectrodes from the hand area of the motor cortex [28–30]. Also, the potential of the IMNP for robotic hand control for a patient amputee was investigated [33].

**3.1.2. Deep Brain Stimulator.** There are an extensive number of papers about DBS technology used in the nonpharmacological treatment of several nervous system diseases [114–118]. In this paper, we only consider some of these studies (23) for each disease considered. First, DBS has been applied for Parkinson’s control therapy [119–122]. The potential of the DBS technique is discussed in [123–125] for the recovery of and to ameliorate the symptoms in patients with stroke and movement disorders [126]. It has been reported that the DBS technique is useful for the treatment of refractory epilepsy [127–129], besides addressing pain, sensorimotor symptoms, and autonomic dysregulation associated with spinal cord injury [130–132] or even for resistant neuropsychiatric disorders [60, 133–135].

Neurostimulation and neuromodulation techniques require a larger number of electrodes for both neural signal recording and electrical stimulation to provide high-charge-density values and more spatially focused

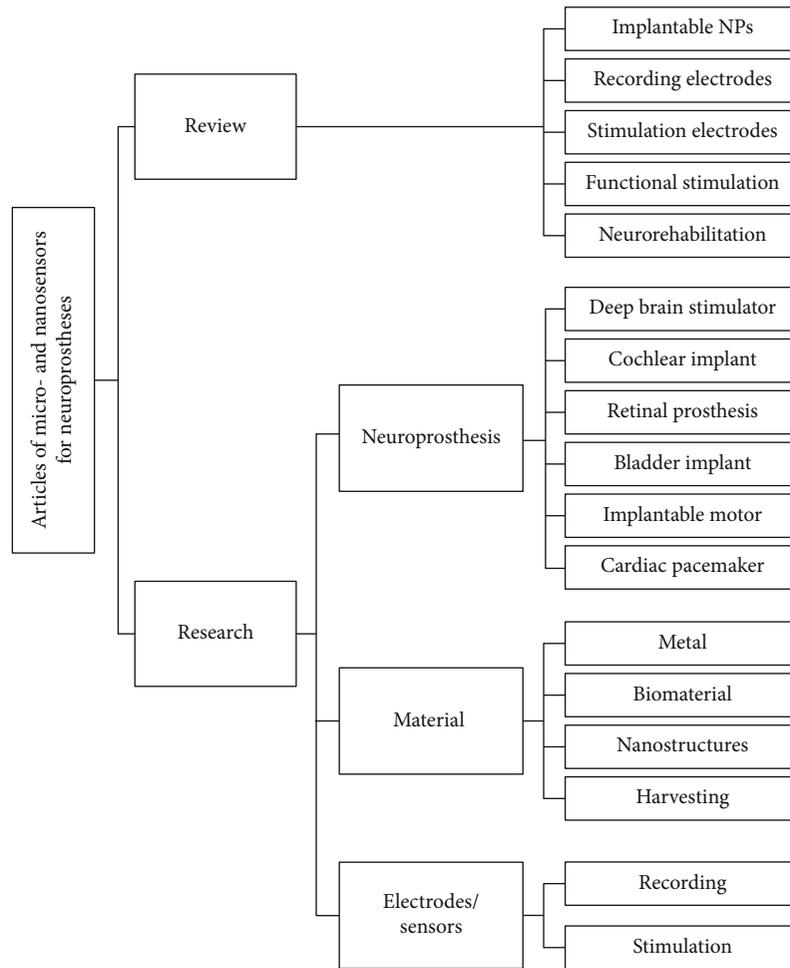


FIGURE 2: Taxonomy of research literature on micro- and nanosensors and electrodes used in implanted NPs.

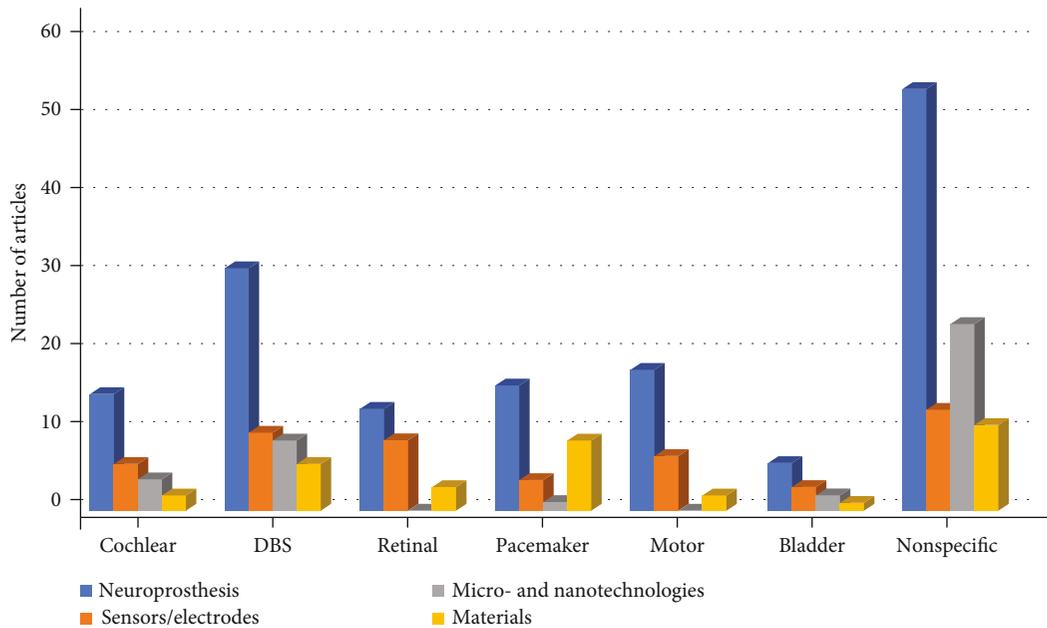


FIGURE 3: The blue bar indicates the total number of general articles by type of neuroprosthesis. The orange, gray, and yellow bars indicate the studies specific for sensors/electrodes, micro- and nanotechnologies, and materials, respectively, are shown for the 2010-June 2020 period.

TABLE 2: Dimensions and materials of microtechnology-based sensors/electrodes for neuroprostheses. Systematic review of the literature during the 2010-2020 period.

Application	Disorder causes	Material (lead, electrode, and case)	Sensor/electrode	Size range	References
Intracortical microstimulation	Brain lesion	Iridium	Deep electrode	Tens of $\mu\text{m}$ in diameter, 250–750 $\mu\text{m}$ between pins	[4] [25]
Stimulation of the motor and sensory thalamus, subthalamic nucleus, and basal ganglia nuclei	Parkinson Stroke Epilepsy	Platinum-iridium Iridium tungsten	Metal wire Electrodes and arrays Microprobe	Length: 15 mm or 25 to 50 $\mu\text{m}$ Width: 0.2 mm Diameters: 16 $\mu\text{m}$ to 1.2 mm Thickness: 5 $\mu\text{m}$	[56] [58] [57] [59]
Motor cortex stimulation	Stroke Spinal cord injury Traumatic brain injury	Platinum Stainless steel Silver nanoparticle	Electrocorticography grid	1–10 mm in diameter	[31] [5]
Retinal ganglion cell stimulation (photoreceptors)	Retinitis pigmentosa Macular degeneration Diabetic retinopathy Birth defects	Platinum CMOS	4 by 4 array of light-sensitive diodes 64 $\times$ 64 array consisting of 4096 electrodes	Diameters range from 30 $\mu\text{m}$ to 520 $\mu\text{m}$	[52] [49] [50] [46]
Cochlea stimulation (auditory nerve of the inner ear)	Genetic factors Trauma Bacterial or viral infections	Platinum-iridium	Array with 12–24 electrode contacts	Length: 31.5 mm Diameter of wires: 20 $\mu\text{m}$	[44] [101] [34]
Stimulation of heart chamber (sinoatrial node, septum)	Sinus bradycardia, tachycardia Blockages Cardiac arrest Conduction system disease	Platinum-iridium Platinum alloys Titanium Titanium-nitride Steroid Ferromagnetic	Array/electrode Epicardial, intramyocardial, and endocardial	Length: 4–8 mm Contact area: 10–28 $\text{mm}^2$	[77] [78] [82] [84] [87]
Sacral nerve root stimulation	Urinary incontinence Voiding dysfunction	NA	Quadripolar electrode Tripolar cuff electrode Electrode array	NA	[91] [90]
Recording neural activities	Brain lesions	Nanowire field-effect transistor	Nanostructure	1,100 nm	[70] [68] [99]
Stimulation of electrical activity	Not specific	Nanotube	Nanostructure	NA	[102]
Control, monitoring, and activation of action potentials	Brain lesions	Optogenetic	Nanostructures and nanoparticles	Nanometric scale	[103]

stimulation. The local field potentials (neuron's electrical activity) can be recorded using invasive multi-microelectrode arrays embedded into implantable chips with low impedance and very small size that are less invasive and also with ECoG [53].

Technical characteristics and materials of the microarrays and electrodes are reported in six articles; the spatial res-

olution (50 to 350  $\mu\text{m}$ ) and high temporal resolution using a platform of 0.13  $\mu\text{m}$  is described [54]. The length of an implantable chip varies from 25 to 50  $\mu\text{m}$ , reaching values up to 1.5 mm, 10 mm, and 14.9 mm; the number of multiplexed channels has reached up to 384 and the number of detectors up to 960 [55, 56]. Diameters (1.27-1.8 mm) and smaller widths (0.2 mm) are reported [57]. Another

approach is the implantable micromachined neural probe with a rough three-dimensional microstructure on the electrode surface to maximize the electrode-tissue contact area. The flexible arrays are composed of a long shaft (in length) and 16 electrodes ( $5\ \mu\text{m}$  thick and diameter of  $16\ \mu\text{m}$ ) [58]. Iridium/tungsten is the material more used in metal wire electrodes/arrays, although silicon-based arrays are also employed, as a polyimide-based intracortical electrode [56].

New microfabrication processes and efficient materials such as the ultra-low-impedance platinum-iridium alloy coating not only significantly improve the electrical properties of the DBS electrodes but also enable the increase of the number of electrodes implanted into the chip as presented in [57, 59].

Geometry (a high-perimeter electrode increases surface current density), polarity, materials (lower impedance), and the electronic design have an important role for both increasing the efficiency and effectiveness of the electrodes and reducing power consumption (inducing fewer side effects associated with high voltage); these features are considered in [60–62].

**3.1.3. Cochlear Implant.** Regarding the treatment of deafness or severe hearing loss, in 1989, a solution arose with CIs [136], which are NPs used to stimulate the auditory nerve of the inner ear, the cochlea, for auditory rehabilitation [137].

Mechanical flexibility, atraumatic straight, miniaturization, and arrays of several microelectrodes [138] for hybrid electric and acoustic stimulation are key factors for preserving residual hearing. Perimodiolar electrodes with small diameter wires of  $20\ \mu\text{m}$  each and designed to lie adjacent to the modiolar wall can provide more spatially focused stimulation of the spiral ganglion cells. Platinum is used in the conventional CI [41], and the platinum-iridium alloy has shown good results [44]. Electrodes inserted to a depth of 18–22 mm has a good chance of contact closer to the neural elements of the cochlea to perform an effective stimulation [101, 139]. One of the longest known electrode arrays used in CIs is the FLEXSOFT, with an overall length of 31.5 mm from the tip to the stopper marker and an active stimulation length of 26.4 mm [34]. The importance of the length, the number of contacts, and the type of electrode for the optimal stimulation has been demonstrated in several studies [35–37] such as the 26 electrodes embedded into the CI device with multiple amplitude resolutions that not only are compatible with perceptual capability but also allow interleaved or simultaneous stimulation. A decrease in electrode impedance was observed within the first month of using the device but was stable until a slight increase at the end of two years [38].

In addition to improving CI functionality, [140] proposed to regenerate auditory nerves delivering a neurotrophic factor into the cochlea by using the CI electrode array. This led to electroporation, a technique to temporarily open the cell membrane which allowed passage of genetic material into the mesenchymal cells lining the scala tympani [140].

Ohta et al. reported in 2009 their findings about implantable CMOS chips that can be used in RPs [141]. Although this paper does not meet the inclusion criteria (2010–June

2020 period), we find it important and interesting to present. The imaging sensor uses standard  $0.35\ \mu\text{m}$  2-poly 4-metal CMOS technology and has a submillimeter and subsecond spatiotemporal resolution. The developed device has functions of imaging and electrical stimulation. The chip size is  $2\ \text{mm} \times 2.24\ \text{mm}$ . The pixel structure is a three-transistor-type active pixel sensor with a parasitic photodiode, with a pixel number of  $216 \times 144$  and a pixel size of  $7.5\ \mu\text{m} \times 7.5\ \mu\text{m}$  [141].

The CI, like the CP, is one of the most widely used NPs in patients. In Google Patents, we can find some publications on the multiple electrode array used in a CI system [138].

**3.1.4. Retinal Prosthesis.** RPs are focused on interfacing with four main structures in the eye: the retina, the optic nerve, the lateral geniculate nucleus, and the visual cortex [142, 143]. The first-generation of RPs contained 50–60 electrodes [45].

Published papers show that a RP should take into account adaptation to light and darkness, visual fields, pupillary reflexes, and binocular fields, among others [48]. One paper presents recent advancements in modeling spatiotemporal light information to encode and decode visual scenes based on artificial intelligence methods [51].

The implanted electrode arrays reported for RP devices are equivalent to a matrix where an image is projected, each slot in the matrix can change its value within a range, depending on the value of the matrix elements that are translated to electrical signals [52, 144]. Electrodes are placed through the vitreous space in order to be in contact with the inner retinal layer.

According to the literature, the size of the electrodes is important for effective stimulation; one study described that when the size is increased from a diameter of  $30\ \mu\text{m}$  to a diameter of  $300\ \mu\text{m}$ , there is variability of charge density [50]. Other diameters reported were  $520\ \mu\text{m}$ ,  $400\ \mu\text{m}$ , and  $260\ \mu\text{m}$  and a 1 mm separation among electrodes, center-to-center [52].

The size of the electrodes of  $21 \times 21\ \mu\text{m}$  provide light patterns of  $664 \times 664$  pixels, covering an active stimulation area of  $2.67 \times 2.67\ \text{mm}^2$  or  $3.5\ \text{mm}^2$  [39]. A microelectrode array has been used for retinal stimulation [47] or as the 44-channel array of electrodes of a high-density  $64 \times 64$  multi-electrode array consisting of 4096 electrodes to study how the hundreds of retinal ganglion cells that encode the visual scene have been developed [46].

We found three papers that mention platinum as the main material to build electrodes and arrays for CI [39, 46, 141]. The CMOS-MEAS technology has also been reported as the material to manufacture a high-resolution photostimulation system [46]. A micrometer spatial resolution to project visual stimuli over the entire retina and record simultaneously light-evoked responses is achieved. The Argus II RP system was the first of its kind to receive regulatory approval for commercial use in Europe and the US [145].

We also found inventions related to an artificial RP system in Google Patent. For example, [146] use an intraocular retina chip that includes a solar cell to convert image information into optical pulse signals.

**3.1.5. Cardiac Pacemaker.** The sinus dysfunction syndrome is a set of alterations of the heart rhythm that includes sinus bradycardia, tachycardia, and bradycardia/tachycardia [48]. CPs for cardiac resynchronization therapy represent effective tools in the treatment of cardiac arrhythmias and heart failure by electrical stimulation; these devices replace and/or regulate the function of the electrical conduction system of the heart [147].

Accurate sensing, pacing threshold, and impedance are the three critical parameters of CP and defibrillators [148]. CPs not only stimulate the heart but also monitor and record its electrical activity using one or more pacing electrodes within the heart chambers to control and synchronize the heartbeat on demand. There is an estimated 50–75% probability that CP users will be indicated for a magnetic resonance imaging (MRI) study. All components of the active implantable device must be safe to use at the MRI environment [149].

In three papers, it has been reported that CP efficiency is influenced by the tip-cathode material and the design of the surface and electrode-tissue interface configuration. High impedance decreases the stimulation threshold to create a large electrolytic surface area of contact for reduced polarization voltage, thus improving impulse and signal transmission [82–84]. One of these articles has mentioned that due to the incorporation of steroid elution to the electrode-tissue interface, a reliable and significantly low stimulation threshold cardiac pacing became possible [82]. Even improvements in manipulating the technique of the applied force over a self-adhesive electrode may reduce the transthoracic impedance, and so, may be useful in improving electrical cardioversion [85].

We found few papers in the literature that describe the technical characteristics of electrodes. Today, CP devices are much smaller than traditional pacemakers, roughly the size and shape of a pill. One of the articles presents an endocardial electrode with a multiedged tip (contact area  $28 \text{ mm}^2$ ), which gives high-electric-field strength and low thresholds; the spreading-tip electrode guarantees better stability. The efficacy, safety, and suitability of a multielectrode array has been tested to enable noncontact mapping of cardiac arrhythmias [77, 78].

Due to the important role of the material in the efficiency of the CP, we report nine articles that we found in the literature on this topic [78, 82–89]. Titanium nitride (TiN), iridium oxide-coated titanium, platinum, and platinum-iridium are the more commonly used materials in the manufacture of currently available pacing electrodes; studies in the early 21st century showed that certain physical features at the tissue-electrode interface appears to be more important in determining polarization signals than electrode tip size and fixation method [86].

Other important issues to consider in implanted CP design are the electromagnetic field and radio frequency emissions (produce, e.g., by headphones or cell phones) that can cause interferences to the device and disrupt normal functions [150, 151]. Electronic components such as ceramic feedthrough capacitor electromagnetic interference broadband filter has shown to be useful to protect CPs against electromagnetic interferences. In addition, the antibacterial

coating to reduce infections and the polymer coatings to facilitate extraction make the leads conditionally MRI safe [88].

To prevent tissue-lead fibrosis, pacemaker leads are built with steroid-eluting collars, which reduce electrode displacement and mitigate the requirement current that may be increased over time [78, 87].

Since 1957, when the first wearable battery-powered cardiac pacemaker was available, and in 1958, when it was implanted in a patient, long-term energy source has been an essential issue to solve. High impedance is a goal to be achieved to decrease chronic stimulation thresholds and current drain, as well as wastage of energy for preserving battery performance and longevity [83, 84]. Lithium-iodide or lithium anode cells for batteries and titanium as the encasing metal became the standard materials since the mid-1970s [151].

Recent studies about piezoelectric energy harvest design for generating energy from the bending CP's lead have been carried out. The proposed energy harvester combines a flexible porous polyvinylidene fluoride-trifluoroethylene thin film with a buckled beam array for potentially harvesting energy from cardiac motion [152].

The latest generations of CPs include sensors for hemodynamic endocardial acceleration. The detector is embedded at the tip of an implantable pacing lead allowing measurement of the myocardial mechanical vibrations occurring during systolic and diastolic periods of the cardiac cycle [79]. Temperature and breathing sensors, as well as implantable cardioverter defibrillators are now built into the CPs [80].

**3.1.6. Bladder Implant.** In patients with thoracic spinal cord injury, the bladder and bowel are organs with high dysfunction, characterized by loss of bladder control, slow colonic transit, and loss of compliance; in consequence, they can present discoordination of both anal sphincter [153] and urination function. The management protocols for these dysfunctions are minimum use of pharmacology, self-management of regular bowel emptying, and prevention of accidents and complications [154].

Electrical stimulation of the sacral nerve root using a BI is a therapeutic alternative reported in the literature to regain bladder control and to diminish the number of involuntary bowel movements [155].

Six works have studied the potential of the BI treatment [90–95]. Lee et al. [94] reported a flexible neural clip interface combined with a triboelectric nanogenerator implanted for direct electrical stimulation of the bladder pelvic nerve for direct modulation of bladder function. The high-density Utah Slanted Microelectrode Array (48 microelectrodes;  $200 \mu\text{m}$  spacing), designed by Mathews et al. [90], was placed intrafascicular of the pudendal nerve trunk to stimulate the nerve and inhibit reflexive detrusor contractions. And a quadripolar electrode was used to treat the fecal incontinence [91].

In an *in vivo* experiment, it has been demonstrated that changes in bladder pressure occur (from 5 to  $20 \text{ cmH}_2\text{O}$ ) when different parameters of electric stimulation are applied to the pelvic nerve. This approach suggests that sensing the bladder pressure is desirable for chronic detection of bladder events.

Encapsulating the sensor in silicone oil and isolating the pressure-sensing membrane from the physiologic environment can help avoid sensor drift or loss of accuracy over time [95].

Stimulation should only be applied when it is detected that a pressure level has been exceeded in the bladder walls. An ultrasmall and highly sensitive pressure sensor for the detection of pressure in the bladder walls has been investigated. The optimum geometry dimension, frequency of sensing, and location are analyzed in order to assess the sensitivity of the sensors. The results show a high-quality factor, making this sensor appropriate for bladder-pressure-sensing applications [92].

### 3.2. *Micro- and Nanotechnologies Applied to Neuroprostheses.*

We found in the literature 48 articles directly related to the materials and micro- and nanotechnologies used to manufacture implantable sensors/electrodes for biomedical applications [66, 156]. None of them mention their application in a specific implantable NP or that they are in the stage of animal testing.

Recording and stimulation of neural tissue activity are two of the main tasks of NPs. Efficiency of electrodes depend on their geometric surface area (GSA) divided in macroelectrodes (GSA in  $\text{mm}^2$ ), microelectrodes (GSA in  $\mu\text{m}^2$ ), and nanoelectrodes (GSA in  $\text{nm}^2$ ). They have contrasting characteristics related to charge phase and charge density thresholds, stimulation signal pulse width, and selectivity, which are important parameters for different types of prosthetic applications [157].

The place in which sensors/electrodes are implanted determines the material type and fabrication method. Metals alone could cause inflammation, because of discrepancy with soft tissues. Novel hybrid biomaterials have been developed to fulfill the basic needs for efficient NPs. For instance, metal-polymer hybrids are able to diminish the disparity between soft tissues and electrodes in which the polymeric part can regulate the metal modulus [158].

A silicon probe compatible with CMOS technology (a neuropixel with 384 recording channels) opens a path toward recording with high spatiotemporal resolution and large volume coverage [55]. Studies have been conducted on thermo-mechanical properties of smart polymers that show the potential to address critical problems at neural interfaces [74].

An organic electrode interface applying tissue engineering through encapsulated neurons within hydrogel coatings are being studied for activating tissue at the cellular scale. However, several technological challenges must first be resolved to demonstrate the feasibility of this innovative idea [76].

**3.2.1. *Microtechnology.*** Metals, such as tantalum, iridium, titanium, and their alloys [100], and a variety of biocompatible polymers are among the most prevalent materials used to manufacture not only the stimulating and recording microelectrodes but also the critical parts of the implanted NPs [98].

The fact that the dimensions of sensing/stimulating microelectrode sites are being scaled down from micron to submicron scale (smaller than  $50\ \mu\text{m}$ ) has generated wide interest in creating tiny, small enough, less invasive, and high-density electrode-tissue interfaces.

Different types of microsized electrodes have been designed; we can mention thirteen papers related to microelectrodes [97, 118] that reported the cuff electrode, the Longitudinal Intrafascicular Electrode (LIFE), the thin-film Longitudinal Intrafascicular Electrode (tLIFE), the Transverse Intrafascicular Multichannel Electrode (TIME), and the Flat Interface Nerve Electrode (FINE). All these types of electrodes go around the nerve; touch or surround the fascicle; or like the FINE electrode, go around, but also squash the nerve to make it flat and increase spatial resolution. The Utah Slanted Electrode Array (USEA) has an array of 10-by-10 electrodes with  $400\ \mu\text{m}$  interarray spacing and has the capability of touching multiple fascicles for simultaneous recording and stimulation [97].

The 25-electrode/ $\text{mm}^2$  penetrating electrode array with electrodes of varying lengths has been designed to access nerve fibers that are found at different depths in small peripheral nerves [159]. The needle-shaped probe of a  $160\ \mu\text{m}$  thick SU-8 substrate contains four planar platinum microelectrodes for monitoring the electrical impedance of living tissues [160, 161]. And the ceramic-based multisite electrode array was developed for long-term recordings of a single-neuron activity. It has a vertical arrangement for simultaneously recording across the different layers of brain areas such as the cerebral cortex and hippocampus [162].

Cylindrical microarrays of electrodes embedded on biocompatible plastic or polymer materials are used in epidural spinal cord stimulation [163]. One of the most commonly used commercial epidural stimulation systems is the RestoreADVANCED stimulation unit, developed by Medtronic® [164, 165].

Planar arrays comprised of a crystalline, ceramic, or polymeric structure and prosthetic microcolumns are alternatives for neural activity recording and tissue reparation that can be used for creating the next generation of implantable NPs [64, 99, 166, 167]. Three-dimensional neural-firing microelectrode arrays allow the recording of interlaminar and/or regional neural circuits [168].

Finally, the promised array for intraspinal microstimulation of the lumbar spinal cord has been reported to selectively activate muscles and afferent nerve fibers; it is made of titanium/iridium and microwires of tens of  $\mu\text{m}$  in diameter [4].

**3.2.2. *Nanotechnology.*** Nanotechnology applied to NPs can be divided in two main categories: optical techniques and nanostructures. Optical techniques include optogenetics and photobioelectronics. Nanostructures are comprised of a variety of materials based on carbon, gold, and other materials, such as nanotubes, nanowires, and nanoparticles [73, 169].

Microelectrode arrays with an increased active surface, built by means of depositing nanostructured materials, have been developed to access the brain cortex for NP applications and basic neuroscience research [170].

In neural prosthetic systems, a low-impedance electrode-tissue interface is important for maintaining signal quality during recording; for this propose, nanostructures (materials or structures of 1 and 100 nm) have been incorporated into the electrode to increase the effective surface area [171].

Carbon nanotubes [172] and silicon nanowire field-effect transistor (Si NWFET) arrays fabricated on transparent substrates can reliably offer a small active surface ( $\sim 0.06 \mu\text{m}^2$ ), material stability, and low electrical impedance in bioelectrical interfaces for the nervous system. Si NWFET provides highly localized multiplexed measurements of neuronal activities with demonstrated sub-millisecond temporal resolution and significantly better than  $30 \mu\text{m}$  spatial resolution [70].

(1) *Nanostructures*. Nanostructures are novel materials based on carbon, metals, and other materials, with unique shapes and properties that confer them special properties that provide electrical and interfacing advantages over classical metallic materials at very low dimensions. These structures and their properties are important, since their size is similar to biological molecules and optimal as manipulation tools at nanoscales, allowing the creation of sensors, conductors, and other structures [99].

Five papers reported the use of carbon nanotubes to repair the damage of brain tissue using a single-wall carbon nanotube [173] or probe for neural recording [69]; 3 out of 5 present a multielectrode array based on carbon nanotubes for interlaminar recording and microstimulation for cortical microcircuits [65, 67, 99]. The last is related with a flexible carbon nanotube microelectrode array for recording ECoG [68].

On the other hand, three researches study the potential of carbon nanowires as interface materials for neurons to record and stimulate electrical activity [102] and to perform intralaminar brain recording and stimulation of cortical microcircuits [99], and also for recording brain activity using nanotube architectures [174].

Gold nanoparticles have shown interesting performance characteristics for implantable electrodes when used to generate conducting films layer by layer and for extracellular recording [175]. They have a high potential of being produced, in comparison with carbon nanostructures, because they can be created from microtechnology techniques [98].

New nanotechnologies are being studied to improve implantable biomedical devices such as the one presented by Bazard et al., who show an implant comprised of a nanoelectrode coated with an array of gold nanoparticles configured for modulating the firing patterns of electrically excitable cells to improve the spatial resolution and fidelity of transduction of electrical stimulation using visible wavelength light and metallic nanoparticles [176, 177]. Also, the biocompatibility, reliability, and the long-term tissue response of nanoparticles that release medicines such as dexamethasone and anti-inflammatory drugs during implantation of microfabricated cortical NPs has been investigated [178].

(2) *Optogenetic Techniques*. Optogenetics is a strategy for modulating neuronal activity, which uses genetic and optical stimulation to activate ion channels in neuronal cells. A variety of nanoparticles and/or nanostructures have been used for this purpose: upconversion nanoparticles (UCPs), quantum dots, gold nanoparticles, and piezoelectric sensors made of carbon nanotubes [169]. In addition, studies of an elec-

trode array based on graphene have demonstrated its utility in optogenetic activation of focal cortical areas [75]. Recent advances in optogenetics increase the feasibility to apply it for DBS and neuromodulation [179].

Six optogenetic researches are focused on the restoration of motor function using animal models; one investigates the efficiency of cervical optical spinal cord stimulation for the activation of hind limb muscles of rodents with induced spinal cord injury [180]. Other works explore the optical control in vivo of brain activity and behavior in rodents using the UCPs [63]. In another study, it is shown that the photoluminescence properties of quantum dots, which are the proper nanostructures for monitoring neural cell activity in vivo, could be considered as some type of nanosensors that in the future can be applied to INP [169].

Optical neural interfaces include implanted  $\mu\text{LEDs}$  and passive array waveguides, which are in the micrometric scale. In the nanometric scale, there are nanomachined tapered fibers and optically active colloidal nanoparticles, which allow control of neural activity, monitoring, and activation of action potentials [103].

In contrast to electrical stimulation, optogenetics does not interfere with the recording of tiny neural electrical signals, enabling simultaneous closed-loop control. There are possibilities that optical stimulation could someday be used for DBS in Parkinson's disease, epilepsy, and depression, as well as other hearing and organic applications [179].

Finally, one paper presents the neurohybrid devices that interface brain-inspired devices with actual natural brain structures and are thought to be the base of future "intelligent NPs" for augmentation of brain functions. Memristors are nanometric elements that can act as interfacing elements in neurobiohybrids, since they can be used for simulating artificial synapses [181].

## 4. Discussion

Implanted-type NPs are promising medical devices for restoration functions. The cochlear implant (CI), deep brain stimulation (DBS), cardiac pacemaker (CP), retinal prosthesis (RP), and bladder implant (BI) are NPs whose sensors and electrodes are fully implantable. Most of today's motor NPs are not implantable.

The wide market of implantable NPs [10, 13, 15, 16] shows their effective use in humans. Concerning the technology, we found 48 articles in the literature that mention that most of the sensors and electrodes used in INPs for humans are manufactured with microtechnology (see Table 2). Nanotechnology has been applied in some sensors/electrodes used for neural recording and microstimulation [65, 67, 68, 99, 173]. Recent research uses animal models to study the potential of optical and optogenetic technology such as carbon nanowires [99, 102, 174], gold nanoparticles [175], or metallic nanoparticles [176, 177] to promote and to encourage their use in implanted NPs for humans. None of them mention its application in a specific implantable NP.

In reference to micro- and nanosensors/electrodes, we found that we needed to comply with four special requirements for stimulation and recording signals: biocompatibility (which implies minimal tissue damage), long-term reliability,

high selectivity (mainly but not only by size reduction), and low-energy consumption.

Regarding the main issues remaining to be solved, we can mention insufficient strength, nonlinearities, poor repeatability, electrochemical degradation, excess encapsulation, infection or rejection, and surgical risks [182, 183]. Other requirements such as geometry, materials, and hardware have an important role for both increasing the efficiency and effectiveness of the sensor/electrodes and reducing power consumption [60–62]. Also, arrays of several microelectrodes [138] are key factors for sensing and recording. The importance of the size ( $\mu\text{m}$  and nm order) [184], the number of contacts (up to 500 microelectrodes), and the type of sensor/electrode for optimal stimulation and sensing has been demonstrated in several studies [35–37]. This is particularly true for retinal prosthesis, where several thousands of retinal ganglion cells must be stimulated to expose the retina to well-controlled visual scenes [39] and encode the visual scene [46]. It is also similar to CI, where multiple amplitude resolutions are needed using multiple electrodes built into the CI device for efficient sound discrimination and speech understanding. However, available arrays do not yet have sufficient high density to mimic vision and hearing or to stimulate all areas of the brain necessary to control or inhibit injuries. On the other hand, impedance of the electrode-tissue interface is a critical parameter for accurate sensing and signal quality transmission [148]. By accomplishing a large electrolytic active surface area of microelectrode arrays, high impedance is achieved to reduce polarization voltage, thus decreasing the stimulation threshold. This characteristic is even more crucial in nanosensor technology [82–84, 169–171].

Traditional electrode materials (silver and gold) do not allow manufacturing of small-sized sensors that support current levels for stimulation; now, new materials have been developed as possible solutions [59]. Thin-film platinum and platinum/iridium electrodes are used in micromachined neural interfaces to ensure highly selectivity, high channel count, and top miniaturization. During biphasic stimulation, a temporarily and fully reversible oxidation of this type of electrode has been observed; this fact allows concluding that the electrode integrity must be maintained during electrical stimulation. For clinical applications, high longevity and integrity of electrode metallization are important for safe and reliable long-term stimulation [72, 185].

Given the experimental advancements that have been made in micro- and nanotechnologies, it is now possible to record and stimulate a large population of neurons simultaneously. For this purpose, nanostructures (materials or structures of 1 and 100 nm) have been incorporated into the electrode to increase the effective surface area [43, 65, 67–70, 99, 169, 170, 172–174, 183].

Long-term-use materials and biocompatible materials present manufacturing issues that need to be addressed. Implantable NP devices must incorporate components of high reliability, medical grade, and biocompatibility to isolate the package from fluid and tissue reactions and avoid the foreign body rejection phenomena. The micro- or nanoscale power supplies must sufficiently and continuously meet the power needs for stimulation, recording, and wireless com-

munication functions. Other important issues to consider are the loss of electric current due to the deterioration of the insulator and the perforation of the leads by corrosion, abrasion, and stress cracking.

Although batteries based on lithium have been used for implantable devices during the last 4 decades, recent advances in materials have led to new classes of batteries such as the bio-fuel cell (the fuel can come from glucose and oxygen, being highly biocompatible) and nuclear power (can provide long service of over 15 years, is stable, but has potential danger of radioactivity). There are other types of electrical supplies that have advantages and disadvantages. One is thermoelectricity that offers unlimited lifetime but low output power. Another is the electrostatic source that produces high output power but requires an additional voltage source and has high output impedances. Lastly, there are electromagnetic batteries that have unlimited implantable locations but their fabrication is highly complex and expensive [26]. Additionally, harvesting the energy produced by the human body [46] could represent a turning point for powering INPs [152].

*4.1. Challenges and Future Directions.* Currently, the usage of micro- and nanosensors in INPs is still limited. Limitations remain, such as the proper monitoring of the cell functions, accurate stimulation, mimicking the functions of the peripheral and central nervous system, and the timely detection of responses to stimulation. Even though high-density arrays are available, they are still used in research. High density increases the spatial resolution and improves the power efficiency, and it is crucial especially in INPs such as CI, RP, and DBS where it is necessary to process a large amount of information that allows imitating vision, hearing, and brain functions for the control of diseases such as Parkinson's and epilepsy. The next generation of implantable neuroprostheses is likely to come in the form of nano-electromechanical systems that can pick up the signals in real time with microenvironmental resolution.

New miniature implants could push the boundary of signal collection even further and ultimately promise to provide records and stimulation capabilities with a far greater spatial and temporal detail than available at present. The use of electrophysiological signals may be a promising biomarker to improve the efficiency of neuroprostheses.

Looking forward, brain-computer interfaces and adaptive closed-loop stimulation systems could be incorporated to neural implants as feedback signals since they could ideally be able to rapidly respond to real-time patient needs.

Furthermore, nanosensors to detect changes can serve as a quality assurance to monitor the occurrence of adverse response arising from implantation and stimulation.

## 5. Conclusion

Micro- and nanotechnologies are key elements at present and in the future to improve the design of implantable sensing and stimulation sensors/electrodes for INPs. They have enabled great improvements in the four main design requirements identified from this systematic literature review: biocompatibility, selectivity, reliability, and power efficiency.

Moreover, research on the potential of novel concepts and materials that can be used in the design of the six INPs is presented. We can mention the following: high-density microarrays to increase resolution and obtain precise stimulation, optogenetic and photobioelectronic techniques or nanostructures, biologically inspired materials to achieve biocompatibility and low impedance, and energy harvesting to extend the lifetime and effectiveness of the INP.

Further research efforts should be made to further advancements in electronics, microfabrication, material science, and new technologies. This will enable a better understanding of functional processing and gain wider acceptance and accessibility of implantable neuroprostheses to the public, and at a low cost. However, there are still great challenges in high-density manufacturing and integration, low invasiveness, lower power consumption, and better biocompatibility of implantable sensors/electrodes for a long-term operation within living tissues in the future.

Ultimately, the relevance of this work as a reference guide of micro- and nanotechnologies for sensors/electrodes used in INPs is more evident when considering that invasive neuroprosthetic devices may be the only real and permanent functional assistive technology for many people suffering a variety of disabling conditions that result in chronic sensory and motor impairments that diminish their independence and quality life.

## Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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