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Neuroengineering as an interface for therapeutic development

A neuroengenharia como interface para o desenvolvimento terapêutico

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ABSTRACT

Introduction: Nervous system's cells, particularly neurons, communicate through neurotransmitters and ionic exchanges that generate electrical currents when receiving an external stimulus or when the system itself transmits information through nerve impulses. Considering the principle that this information can be captured, decoded, and used by devices to restore motor and sensory functions, the field of neuroengineering has significantly advanced in recent years. As a multidisciplinary study area, its development requires aligning knowledge of the electrical functioning of the nervous system with engineering and circuits in order to optimize neuroprosthetics to be increasingly efficient, durable, and safe.

Objectives: To map the state of the art in neuroengineering and its nuances based on scientific literature, and to identify the main developments, challenges, and opportunities in the future of the field.

Methods: Literature review on the combination of engineering and neuroscience in therapeutic applications. English texts published between 2012 and 2022, that met pre-determined inclusion criteria, were considered/accepted using the following terms for the research: "robotic prosthesis, neuroengineering, electrophysiology, robotic movement, neural decodification, nervous system engineering, neurophysiology, neural prosthesis, and neuroanatomy.

Results: The review demonstrated that there are established therapeutic approaches based on neuroengineering, such as deep brain stimulation for alleviating Parkinson's symptoms. However, for some neurodegenerative diseases and nervous system injuries, therapeutic-focused neuroprostheses are still in experimental phases or require adjustments to meet user demands and thus achieving greater acceptance and accuracy.

Conclusion: Despite the numerous challenges faced in this early stage of the field's development, advances in research are already observable due to technological developments allowing the implementation of artificial intelligence, more modern microelectrodes, and a better understanding of the system and adaptation between organism and machine.

KEYWORDS: Electric stimulation therapy. Electrophysiology. Neural prosthesis. Neurological rehabilitation. Neurodegenerative diseases.

RESUMO

Introdução: As células do sistema nervoso, principalmente os neurônios, comunicam-se através de neurotransmissores e trocas iônicas que geram correntes elétricas ao receberem um estímulo externo ou quando o próprio sistema transmite informações através de impulsos nervosos. Considerando o princípio de que essas informações podem ser capturadas, decodificadas e utilizadas por dispositivos para restaurar funções motoras e sensoriais, o campo da neuroengenharia avançou significativamente nos últimos anos. Por ser uma área de estudo multidisciplinar, seu desenvolvimento exige o alinhamento do conhecimento do funcionamento elétrico do sistema nervoso com a engenharia e os circuitos, a fim de otimizar as neuropróteses para serem cada vez mais eficientes, duráveis e seguras.

Objetivos: Mapear o estado da arte em neuroengenharia e suas nuances com base na literatura científica, e identificar os principais desenvolvimentos, desafios e oportunidades no futuro da área.

Métodos: Revisão de literatura sobre a combinação de engenharia e neurociência em aplicações terapêuticas. Os textos em inglês publicados entre 2012 e 2022, que atendessem aos critérios de inclusão pré-determinados, foram considerados/aceitos utilizando os seguintes termos para a pesquisa: "robotic prosthesis, neuroengineering, eletrofisiologia, movimento robótico, decodificação neural, engenharia do sistema nervoso, neurofisiologia, prótese neural e neuroanatomia".

Resultados: A revisão demonstrou que existem abordagens terapêuticas estabelecidas baseadas na neuroengenharia, como a estimulação cerebral profunda para aliviar os sintomas de Parkinson. Porém, para algumas doenças neurodegenerativas e lesões do sistema nervoso, as neuropróteses com foco terapêutico ainda estão em fase experimental ou necessitam de ajustes para atender às demandas dos usuários e assim alcançar maior aceitação e precisão.

Conclusão: Apesar dos inúmeros desafios enfrentados nesta fase inicial de desenvolvimento da área, os avanços nas pesquisas já são observáveis devido à evolução tecnológica que permite a implementação de inteligência artificial, microeletrodos mais modernos e melhor compreensão do sistema e adaptação entre organismo e máquina.

PALAVRAS-CHAVE: Terapia por estimulação elétrica. Eletrofisiologia. Prótese neural. Reabilitação neurológica. Doenças neurodegenerativas.

Central Message

This review emphasized established therapeutic approaches in neuroengineering, such as deep brain stimulation for alleviating Parkinson's symptoms and brain signal based motor prosthesis. However, for certain neurodegenerative diseases and nervous system injuries, therapeutic neuroprostheses are either in experimental phases or require adjustments to meet user demands, aiming for greater acceptance and accuracy. In this sense, researchers are developing solutions for problems such as biocompatibility and stability of sensors, proper translation and handling of the electrical signals and accessibility to collected data. Therefore, this multidisciplinary area brings hope to treat or even cure disfunctions as never did before with conventional medicine.

Perspective

Despite many challenges faced by neuroengineering, there are tecnologies emerging capable of revolutionize the field of medicine in the treatment of motor, sensory and neurological disorders. Thus, the mapping of the main needs of the field can guide the researchers towards innovative approaches to solve technical and conceptual problems of the existing devices, besides enabling the development of new techniques witch can be applied to more diseases, with greater ease and quality. Ergo, it becomes feasible to enhance quality of life of individuals with brain function loss and/or restore mobility to individuals with motor impairments.

INTRODUCTION

The brain contains an information processing network that coordinates the body using electrical impulses. This electricity generates nerve impulses among neurons induced by action potential, which after passing through the spinal cord, reach a specific limb. However, there's also the opposite direction, where limbs capture external sensory stimuli to adapt to the environment and enhance the nervous system, forming a closed loop. This system generates electric fields that can be captured by electrophysiology equipment, making it possible to decode them in order to understand the functional objective of each electrical signal or set of signals.[1]

In this scenario, the central nervous system can be divided into various organs, which are subdivided into regions responsible for specific functions that are essential to the functioning and maintenance of the organism. However, these regions are susceptible to neurodegenerative diseases and injuries that compromise their respective functions, causing symptoms that directly impact an individual's quality of life. Thus, by promoting a thorough understanding of neuroanatomy and electrophysiology for the practical application of engineering and electrical circuits, there's a promising possibility of overcoming these scenarios through the development of technologies aimed at restoring compromised motor and sensory functions.[2] As an example, there are experiments focused in a therapeutic approach to enable the movement of a robotic arm by individuals with tetraplegia through the monitoring and decoding of neuronal electrical activity in the motor cortex.[3]

Moreover, neuroscience can be combined with engineering in order to develop brain-machine interface technologies, which demonstrate potential in the medical field by allowing more efficient and specific treatments and alternatives for the symptoms and recurring consequences of neurological, motor, and sensory dysfunctions.[1,4] However, this is a recent and multidisciplinary area, and therefore, there are still challenges to be overcome such as equipment durability and efficiency, implant biocompatibility and safety, delineation of ethical standards for studying and implementing devices, as well as the consolidation of incentives for this research to disseminate the use of equipment outside the academic environment, among others.[2,5-7] Therefore, this context makes it relevant to map the current scenario of neuroengineering through a focus on existing literature about developing technologies, recent achievements, and the difficulties to be overcome. This mapping would allow fostering progress in this recent area with the potential to drive technological and biological advancements by proposing possibilities that enhance the quality of life for individuals with brain function loss and/or restore mobility to individuals with motor impairments.

This study aims to conduct a iterature review focusing on the interface between engineering and neuroscience, intending to highlight existing technologies and the challenges encountered within the research field. Thus, it seeks to identify the key areas requiring attention from researchers and governmental bodies, as well as explore prospects for the development of neuroengineering.

METHOD

This is a review of scientific literature conducted using the PubMed and Scielo databases. The search utilized the following keywords: 'robotic prosthesis,' 'neuroengineering,' 'electrophysiology,' 'robotic movement,' 'neural decodification,' 'nervous system engineering,' 'neurophysiology,' 'Neural prosthesis,' and 'neuroanatomy.' Inclusion criteria for the review comprised review articles, experimental studies, pre-clinical and clinical research published between 2012 and 2022, written in English, and available in full text. The articles selected were analyzed based on the technologies addressed, future perspectives and challenges mentioned, diseases referred and main idea of the article.

RESULTS

Quantitative analysis of verified articles

There were 56 articles collected, with 43 of them being review articles, 9 being experimental articles, and 4 being research articles. From this, it is possible to visualize the occurrence of various technologies related to machine-brain interfaces discussed in this article (Table 1).

TABLE 1 — Correlation between types of technology and mention frequency in the analyzed articles

Technology	Number of articles that mention the technology
Microelectrodes/arrays	45
Computacional and mathematical methods/ software/ data	44
Brain stimulation	40
Nanotechnology/materials	31
Motor prostheses/exoskeleton	29
Electroencephalography (EEG)	27
Optogenetics	18
Wireless devices	17
Local Field Potentials (LFP'S)	16
Retinal neuroimplants	13
Cochlear neuroimplant	8

In this sense, 51 of the articles analyzed present a promising future for neuroengineering, with several growth potentials. None of the remaining 5 articles presented negative growth prospects for the area. To achieve this potential, efforts and research are required to overcome the technical and regulatory challenges listed by the articles in which: 32 of them refer to challenges in an operational and technical aspect, such as the improvement of systems, data volume, decoding and noise; 7 of them infer to issues in the biocompatibility of sensors and equipment and 18 mention ethical implications, user suitability, user safety and approval by regulatory bodies.

DISCUSSION

Structure and electrical functioning of the nervous system

The nervous system can be divided anatomically into central and peripheral. The latter concerns nerves and nerve ganglia that connect the central nervous system

(CNS) to the rest of the body for the transmission of nerve impulses. The central nervous system is composed of the spinal cord and the brain, which is the set of the brain, cerebellum and brainstem.

The basic functional unit of the nervous system are cells called neurons, composed of dendrites, cell body, axon and axon endings. These cells communicate through electrical signals, that is, electric currents originated by ion exchanges between the extra and intracellular environment, which cause a brief reversal of electrical charges and depolarize the cell membrane, which, upon reaching an excitability threshold, generates a potential of action. Thus, the transmission of this stimulus and its respective decoded information between the neurons occurs at synapses and is accelerated by a structure of lipids and proteins called myelin sheath, which coats the axon and acts as an electrical insulator.[8] In this sense, the CNS is visually distinguished in two regions with distinct colorations, the gray and white matter. The first one, which constitutes the cerebral and cerebellar cortex, is formed by many cell bodies of neurons, in addition to the dendrites, glial cells and non-myelinated portion of axons. The white matter basically consists of myelinated axons, which gives the whitish coloration.[8] These two portions differ functionally because white matter is related to communication and information transport between regions, while the gray matter is associated with motor control and linguistic and sensory processing.

Additionally, the gray matter is divided into four lobes: frontal, parietal, occipital, and temporal. Each of these lobes has a specific function and differentiates itself in the gyres and sections of the cortex. For example, the temporal lobe is associated with sensory functions in addition to memory and emotions. Within this are the average temporal gyres, related to the perception of movement, and the lower, linked to the distinction of visual forms and colors. Therefore, lesions in each of these areas have different consequences. Thus, neuroengineering resides in the understanding of the specificity of the electrical activity of neuron populations, so that the use of microelectrodes for recording or stimulation is assertive for the dysfunction to be treated or recovered, according to its nature.[1] Associated with this, the development of prostheses and techniques should consider all the transmission of action potential from the region of the cortex in which action planning occurred, through the bone marrow and the subsequent nerves to the determined limb and muscle in which there is the conversion of movement.[8] The same notion applies to the inverse sense of information, that is, to the external stimuli that are processed by a specific arrangement of areas of the cortex involved in, for example, the vision or hearing.

Current therapeutic panorama of neuroengineering

Each clinical case of loss of body functions due to neurological disfunctions or lesions in the nervous system extension, including the absence of limbs, involves specific affected areas. Thus, in order to attenuate symptoms or recover functions, there are brain-machine interfaces already available for use. These technologies rely on the implementation of microelectrodes in regions of the CNS and in specific neuronal populations for communication with the prosthesis, in the case of signal recording technologies, which will perform the action with a certain level of naturalness.[1,9]

Neuroengineering, since its beginning, has followed a linear understanding of nerve circuits, which neglects the feedback of the organism's interaction with the environment. However, despite the proportion of electrophysiological understanding obtained from this, simplification brings failures that reduce the safety for the therapeutic use of neuroprostheses.[10] Thus, several researches describe in vivo, with humans and animal models, and in vitro nerve networks that simulate and study the functioning of the bidirectional pathway of nerve stimuli. From these, rises a focus in research to create closed loop neuroprostheses and brain stimulation equipment that are more reliable for the body, which explains the meaningful adoption and expansion of this perspective.[10,11]

From this, the academic scope has interest in developing neuroprostheses with a focus on recovery of movement and limb replacement, once this modality is not yet well established due to the difficulty in recreating voluntary movements from electrical signals captured directly in the cortex. After all, motor prostheses on the market operate myoelectrically, that is, robotic movement occurs from contractions of the muscles of the residual part of the limb.[9] However, there are already experimental tests which aim to increase the naturalness of prostheses in everyday activities. These experiments can be made with individuals with disorders that interfere with the communication of electrical signals from the brain to the body, such as paralysis after spinal cord injury and amyotrophic lateral sclerosis (ALS).[3] In this sense, researchers were able to two people with tetraplegia perform with high accuracy movements of reaching and grasping with a robotic arm, and one of them, with microelectrodes already implanted five years ago, was able to drink coffee in a bottle.[3] There are also studies for therapeutic use of robotic exoskeletons with non-invasive electroencephalogram in the rehabilitation of patients who suffered stroke in order to train sensory and motor skills.[12] Despite being simple tasks, this type of technology allows people with certain movement limitations to rescue some level of motor independence.[3]

Another example of neuroengineering in therapeutic treatment is deep brain stimulation (DBS) to reduce symptoms of Parkinson's disease. This is the second most common neurodegenerative disease and the fastest growing worldwide.[8,13] It is caused by the degeneration of dopaminergic nerve cells, and, with this, there is a reduction in the production of dopamine, generating the symptoms of the disease, such as tremors and bradykinesia. The treatment by neuroengineering consists in the surgical implantation of neurostimulators that provide an electric current to the region where the loss of neurons occurred, usually in the dorsolateral motor part of the subthalamic nucleus or in the posteron-internal pale, relieving symptoms of Parkinson's disease.[8,14] In addition, this technology, which is also used in patients with other movement disorders such as epilepsy and Tourette's syndrome, served as the basis for a deep adaptive closed-loop stimulation that uses artificial intelligence for the application of point electrical discharges rather than continuous in anticipation of the onset of a symptom.[14]

With this, it is remarkable that the brain-machine interfaces are in a context of accelerated improvement, exploring the machine's ability to learn and adapt, in order to enable equipment and software for reading and storing electrical signals progressively more efficient and natural in their functions. In this sense, future challenges for neuroprostheses mainly involve the user's levels of freedom, such as allowing movements to reach and grasp, the calibration of the prosthesis so that it presents an optimized performance, besides allowing the quality of the signal transmitted/received by the prosthesis over time.[15]

Technologies for capture and decoding of electrical signals

The signals emitted by the nervous system can be captured in different ways, each being indicated for cortical regions and specific contexts in order to assimilate and decode a category of signal and information transmitted. At a more basic level, readings can be divided into invasive and non-invasive technologies, both with intrinsic advantages and disadvantages.

Thus, invasive methods involve the surgical implantation of microelectrodes directly on the intracranial surface, which, in general, capture signals with high quality and low noise. Some examples are recording microelectrodes, spikes, local field potential (LFP) recordings and electrocorticography (ECoG).[16] On the other hand, non-invasive readings take advantage of greater acceptance by the scientific community and medical organs due to the lower risk to the user. However, such techniques as electroencephalography (EEG), transcranial electrical stimulation (TES) and transcranial magnetic stimulation[16,17] are challenged regarding the time needed by the records and lower efficiency in capturing the signals and translational properties in daily use.[1]

Among invasive technologies, those based on LFPs have gained notoriety. Its principle is associated with the recording of synaptic potentials that occur at the tips and near the implanted electrodes. The main advantages of LFPs are the amplitude of recording that allows a lower influence of the healing of neural tissue in the signals and less noise compared to the ones with the presence of sweat and electrode paste, for example. In addition, the durability and volume of information obtained with these devices is greater.[4,16] However, the sources of noise are more difficult to control, and the specificity of the signals is reduced, since a region of neurons is recorded. The signals transmitted by LFPs have been used mainly in the study of the mechanism of action of DBS.[4] As the signals are evaluated in frequency bands, it is possible to associate changes in oscillations with the symptoms of neurodegenerative diseases such as Parkinson's and dystonia and thus the understanding and modulation of neurological activity is facilitated.[16]

In addition, an approach that is already widely used and has excellent growth potential is DBS, although its mechanism is not yet fully known.[17,18] This consists of implanting electrodes in specific areas of the brain and a neurostimulator under the skin of the patient's chest. When the neurostimulator is activated, it can transmit electrical currents to target regions of the nervous system and thus act on the symptoms of neurological disorders such as Parkinson's, severe depression, epilepsy and Tourette's syndrome.[10,16,19] There are several branches of DBS, but the main classification is in closed or open loop systems. In the closed loop ones, the electrodes are connected bidirectionally, which provides a feedback mechanism that allows the monitoring of the course of symptoms and the use of neurological activity patterns to adapt the stimulation in real time. The open loop system does not have this feedback system and is based only on electrical stimulation configured by the previously measured activity patterns of the patient and other studies.[10,16,19] One of the main and most common recording methods is EEG. It is based on electrodes located on the scalp of the user, which identify oscillations in neurological activity. Because they are surface electrodes, the main advantages of this method are their simplicity and non-invasibility, which also brings a limitation: the area of access to brain activity.[20] Thus, EEG is relevant for its sensitivity to neurological dysfunctions and, mainly, because it can be used as a tool for diagnosis and evaluation of the course of the disease, as well as treatment management,[21] being widely applied in brain- machine interfaces in stroke recovery.[22] On the other hand, EEG-based devices show weaker signals, more noise and less spatial definition of signals.[23,24]

Moreover, starting from the classical recording methods, it is intended to improve such technologies in the context of fully implantable microelectrodes for application in brain-machine interfaces. Thus, the miniaturized evolution of electrocorticography, called microelectrocorticography, presents advantages, such as the lower invasibility and consequent reduction of inflammatory response and scarring, as well as the high spatial definition, higher density and long-term durability of recordings and fewer manufacturing limitations. Given these conditions and the increased ability to detail the data, it is intended a refinement of DBS devices and responsive neuromodulation, in addition to its application in optogenetic stimulation.[24]

However, the monitoring of neurological signs in the therapeutic context requires an accurate and organized positioning of several microelectrodes that work together.[25,26] From this, microelectrode arrays (MEAs) are made, allowing amplitude in the reading of electrical activity in specific regions. One of these is the Utah Array, a silicone arrangement with high practicity consisting of 100 spikes that can be deployed both for monitoring communication between neurons and for application of stimulating electrical loads.[9,27] Using spikes capable of recording activity of individual neurons and their networks, signal separation is achieved through the analysis of waveform, activity frequency and correlation with the activity of nearby neurons.[28] Thus, this MEA popularly known as BrainGate, has already been applied as a by-pass, mimicking dysfunctional nerves in the transmission of signals from the motor cortex captured by the Utah Array to muscles of the arm and hand with paralysis. Also, its use brought success to the world's first bionic man through the reinnervation of nerves in the upper pectoral arm, causing electrical signals from the limb movement intention to generate controlled prosthetic movement.[9] Similarly, in another system, electrical signals generated by the user's brain were transmitted via surface electrodes to stimulate muscular nerves of the paralyzed arm and thus generating movement.[23]

From this, it becomes possible to collect a vast amount of biological data in real time, which requires appropriate software to handle and translate such data. So, in addition to the relevance of sophisticated hardware, small in size, stable and easy to handle and maintain, it is important to have algorithms capable of making the electrical signal understandable from the interpretation of neuronal origins of the signal for action conversion.[26,28] In this sense, the improvement of algorithms capable of learning and adapting contextually can take advantage of the benefits that nanotechnology brings to brain-machine interfaces.[29] There are several softwares, bioamplifiers and processors developed for research in neuroengineering. Voitiuk et al.[28,] developed the Piphys platform, which consists of a processing system for recording and transmitting data based on a minicomputer (Raspberry Pi). This system allows the visualization of data and control of experiment parameters via dashboards. In it, the Intan RHD2132 bioamplifier chip converts the analog signals detected by the electrodes into digital values for storage within the Raspberry Pi computer. In addition, the use of this computer model, as well as the concept of the platform, allows this system to have a low associated cost and a wide application.

In this context, an approach that has been explored is the use of data-based models, from which it is possible to use information that encompasses biological complexity to better understand the neurological system and the dysfunctions associated with it, in addition to developing simulations and designing better solutions for neuroengineering. Deep Learning is one such model and has proven useful in increasing performance in the decoding of electroencephalogram.[30]

Also, in order to improve the functioning of the device and adaptability to the user, the implementation of artificial intelligence (AI) in different existing technologies has been explored, being applicable for both invasive and non-invasive technologies.[29] As an example, the adaptive deep brain stimulation (aDBS) relies on artificial intelligence for discontinuous application of electrical discharges in anticipation of the onset of the symptoms of the disease, preventing them from happening and reducing patient wear. The main contribution of AI would be the ability to evolve from a computational system based on deep learning to artificial neural networks optimized to predict needs and adapt the operation of the neurodevice in real time.[14,29]

Main challenges faced by neuroengineering

The devices proposed by the field of neuroengineering carries the highly coveted possibility of overcoming barriers in various neurological and motor dysfunctions as never imagined before. However, considering the high degree of complexity and invasiveness intrinsic to these devices, it is essential to thoroughly assess the user's safety in the short and long term, as well as the lifespan of these devices and the actual benefits that can be derived from them.[5]

Therefore, a factor frequently highlighted in studies is the biocompatibility of prostheses, leading to an important aspect: the study and production of microelectrodes using materials that minimize or eliminate rejection by the immune response and encapsulation of the device by brain tissue.[31] These factors should be avoided as they reduce the specificity and quality of signals, as well as the long-term viability of the equipment.[24] Carbon-based nanomaterials[32] and biocompatible polyamides[33] have excellent potential for biomedical use and for a new mode of interaction between systems and the body, along with possessing unique pharmacological properties. However, attention is needed regarding purification processes to avoid potential toxicity and to validate the levels of biocompatibility, biostability, biodegradability, and safety of such materials.[29,32]

For further technical situations, there are adversities related to captured data, such as the correct positioning of devices so that neurons are preserved during implantation, ensuring a selective and specific process, aiming only at the target region of the neurological system.[23,25,26] Thus, there must be used flexible materials that accommodate the natural movement of the brain, maintaining the integrity of target and peripheral neuronal populations and the quality of the specific signal captured.[33,34] This is relevant because by tracking the activity of the same neuron over a long period, a better understanding of learning, memory, and plasticity can be achieved based on data from a population of neurons.[35] Therefore, by reducing the size and rigidity of electrodes, it may be possible to suppress the inflammatory and tissue response, promoting long-term stability and quality of recordings.[34] Hence, it is important to produce electrodes with materials that approximate the rigidity of brain tissue, evaluate the device's shape and size, and develop surgical implantation methods capable of maintaining brain integrity, such as using biodegradable materials that alter the device's rigidity before and during insertion.[34]

Intrinsic to this, there is concern about signal contamination, which complicates distinguishing the signal's origin and its interpretation. Causes of this problem include electrode encapsulation and scarring around it for invasive methods, and for the superficial ones, eye movement and other external impacts near external devices.[20,23] Thus, in the development of implantable devices, attention should be paid to electrode geometry parameters, materials, and invasiveness levels to decrease the encapsulation tendency.[24]

As these challenges are overcome, devices become more complex in terms of cost related to precision manufacturing and the density of real-time biological data collected. Hence, there is a need to maintain a reduced size, preferably wireless, with battery autonomy while avoiding device heating.[26] Simultaneously, another difficulty lies in inferring and modeling biological patterns for the development of algorithms capable of interpreting the meaning of electrical signals considering the complexity of the data.[30,36] Thus, to mitigate such obstacles, one possibility is to compress collected data without losing physiological information. Therefore, a coding method with high compression rates, along with another algorithm for further size reduction, can be chosen. For instance, applying Huffman encoding in combination with delta compression, as shown by Cuevas-López et al.[37,] enables the encoding of biological data in real-time by creating a dictionary from previous recordings, using fewer bits than the more uniform symbol distribution that raw signals possess.

Another aspect that poses a possible barrier is the ethical implications related to testing on animal and human models, as well as privacy, security, and ensuring autonomy of each individual. This difficulty is driven by the challenges of implanting human values into technologies.[5] Due to societal diversity, it is necessary to avoid cultural disagreements associated with the use of these devices, such as in the case of Deaf culture, where the languages and habits of the deaf community should be valued while preserving residual hearing, for example, in children.[23] Also, it is important for the technology beneficiary to make independent decisions and actions, express individuality, and for devices to be more attractive and discreet cosmetically. To achieve this, the effectiveness of devices should be combined with user usability.[5,23]

Moreover, another challenge associated with neuroengineering is finding which method suits each patient, respecting their specificities.[14,38] From this standpoint, the prosthesis should undergo calibration and training with the user to ensure optimized performance. In this scenario, one of the recurring problems of invasive brain-machine interfaces is the regular need for recalibration due to signal instabilities, limiting their applicability.[15,20] Another common obstacle is related to degrees of freedom (DoF), the number of basic ways and object can move through 3D space. For instance, commercially available upper limb prostheses have few DoFs.[39] For motor neuroprostheses, this parameter is relevant considering functionality and greater similarity to the limb and natural movement.[40]

Finally, similar to the approval process for new drugs and treatments by health regulatory agencies, each new device aiming to enter the market must undergo an extensive testing period in animal and human models to prove viability and reliability.[26] Additionally, techniques should be developed to enable commercial production on a large scale with quality assurance and facilitate device maintenance.[41] Thus, due to the recent development of the field and the technological and administrative barriers faced, expanding knowledge into other sciences becomes increasingly relevant to leverage the entry of more devices into the market. After all, it is in this multidisciplinary research that the success achieved so far is rooted.[20]

Future perspectives and solutions

Neuroengineering has emerged as a rapidly growing field, showing the potential to revolutionize human life quality, spotlighting various technologies developed to promote health.[36,38,42] Research in this area initially demonstrates the importance of cost reduction in materials and increased efficiency and ease in device manufacturing to provide broad access to the population benefiting from these therapeutic approaches.[5,14,15,21,43]

In this view, the investigated solutions can start with basic elements of the devices, such as the materials they are composed of. Therefore, departing from rigid arrangements produced with silicone, the advantages of carbon-based materials, such as graphene and graphene oxide, are explored, showing potential for technological and biochemical applications.[31] Particularly, graphene exhibits optical transparency and good electrical conductivity, fostering various studies in optogenetics. Its viability in chronic recordings for extended periods has been reported due to the good biocompatibility promoted by its mechanical conformity.[24]

Consequently, the manufacturing technique is another element that should be improved to meet targeted technological expectations. The complementary metal-oxide semiconductor (CMOS) is a technology that has already been used to develop high-density MEAs.[4] This method can reduce wire width so that the electrode probe contains all necessary wires for amplification, digitalization, and multiplexing, allowing a device with 960 recording sites. Additionally, its low cost enables mass production, thus aiding the broader distribution of devices to the population.[27]

Also, in the realm of new materials, the academic field has encountered more robust possibilities, such as the Neuralink device. This comprises 3072 electrodes arranged in flexible biocompatible polyamide fibers under a thin layer of gold, aiming to reduce immunological response and electrode array rigidity. It allows brain movement tracking and extends signal capture periods with high accuracy.[33] Consequently, device improvements in biocompatibility, degradability, and stability become feasible,[32] as seen in biohybrid microsystems. These systems combine biological components (cells, tissues, or organisms) with synthetic components (sensors, electrodes, etc.), promoting better integration of the device with nervous tissue.[20]

In the same aspect, three-dimensional micro-tissue engineered neural networks are being developed, creating "living biological electrodes." These electrodes are formed by a connection between neuron populations and axonal tracts, where the final portion remains on the brain surface, collecting information non-invasively, while the biological component penetrates the tissue for detection and response via dendritic signals and action potentials.[20]

Still, within the device context, structural alternatives are being developed to avoid associated complications. These are relevant as they prevent alterations in neurological and biological activity due to equipment heating, interruptions in tests for recharging, or battery replacement. One recently developed example is the resonant near-field magnetic coupling, transferring energy between nearby devices through magnetic fields. This technique can be used in fully implantable, battery-free, and wireless devices for intracranial parameter monitoring, optogenetic stimulation, and even pharmacological modulation. Moreover, it has the potential to reduce some long-term security risks.[43] Another possibility is the use of closed-loop devices. As device activation occurs only when there is feedback from the change in neurological activity, energy consumption is reduced compared to open-loop systems that continuously deliver signals.[18] Battery-free and wireless devices not only offer greater reliability due to their precision and effectiveness but also involve potential for new applications such as remote monitoring, photonic therapy, and microfluidic drug delivery.[43]

Another line of study being developed is neuroprostheses for patients with motor dysfunctions. Intelligent adaptations of beep brain stimulation are envisioned to adjust stimulation parameters based on electrophysiological data in motor tasks, applicable to movement disorders like Parkinson's.[14] This involves electrically stimulating muscles or nerves for the user to perform movement or suppress symptoms. Another possibility is integrating motor prostheses with the user's nervous system, like exoskeletons or robotic limbs. An example, the DEKA Arm, an upper limb prosthesis approved by the Food and Drug Administration (FDA), uses electrical signals captured by surface electromyography (EMG) sensors to promote multiple, coordinated, joint movements and possesses a feedback mechanism. These factors allow the prosthesis to perform a greater range of movements, more naturally and intuitively for the user.[44] Another technology utilizing EMG-provided feedback is myoelectric control for lower limb muscles. The intention is for the feedback to assist "walking" via exoskeletons or a combination of rehabilitation systems using functional electrical stimulation (FES) and robotic exoskeletons.[45]

Considering all the solutions being developed, it is crucial to safely test the equipment and obtain reliable results for human application. Rodents have become the dominant mammalian model in neuroengineering research, but they struggle to record large neuronal populations due to their small size. Therefore, particularly in the initial stages of a study, a model with increasing popularity for experiments with human tissues is 3D brain organoids.[28]

An example of a device recently approved for clinical use by the FDA is the NeuroPace®, a responsive neurostimulation system, functioning as an adjuvant DBS therapy for drug-resistant epileptic patients.[46] Another FDA-approved therapeutic for patients not responding to traditional approaches is TES for depression treatment. This non-invasive technique relies on inducing magnetic fields to activate or inhibit specific brain areas.[26]

Beyond overcoming the difficulties perceived in the field of study, new approaches are emerging in disease treatment that go beyond conventional neuroprostheses. Hence, early-stage research is exploring neuroprostheses based on neuromorphic elements aiming to restore bidirectional communication between neuronal populations, leveraging the plasticity window after a stroke or traumatic brain injury, for instance.[4] This closed-loop system inherently allows energy-efficient real-time data processing. Due to the neuromorphology of the elements, neurobiological computation can be mimicked for better synergy and plasticity between technological and biological elements.[4]

Furthermore, as the contributions that neuroengineering can make in numerous scenarios are being investigated, research has expanded into the field of optogenetics. This technique relies on optical stimulation, lighting restricted to cells that have incorporated opsins, generating a change in membrane potential that can be either inhibitory or excitatory for cells.[20,26] It involves genetically modifying a cell to respond to light, allowing monitoring and control of neural cells and circuits. Applying optogenetics to neurons in the context of brain-machine interfaces enables new approaches and enhancements to existing technologies, extending DBS devices to selectively target neural circuits using light or for auditory nerve and retinal stimulation, as well as aiding stroke recovery.[20] Additionally, optogenetics can be applied in closed-loop systems, as shown in a study in rodents with induced epilepsy, where the onset of seizures was detected, analyzing neuronal activity. Subsequently, epileptic activity was interrupted by selective optogenetic silencing of involved neurons.[47] However, challenges exist, such as chronic functionality due to probe stiffness, the need for a completely implantable laser system, light in a wavelength that significantly penetrates tissue, and nanoparticles capable of absorbing it to emit light activating receptors.[20] Ethical implications associated with testing this methodology are also more significant due to involving viral transfection.[26]

Given the variety of existing equipment, especially in the academic field, it is noticed the amount of research seeking in-depth understanding of the electrophysiology of the nervous system and development of materials, circuits, microelectrodes and software. This fact, elucidated by the literature review, points to significant advances in neuroengineering, despite the struggle with the lack of financial incentives to enter the market and overcoming barriers related to legislation, biosafety and ethical parameters. Thus, it was possible to delineate the content related to the electricity of the nervous system, in addition to establishing an overview of neurodegenerative diseases and their respective correlations with neuroengineering technologies. In this regard, several technologies and strands were exposed that explore the nervous conditions of different neurological dysfunctions to obtain solutions from the hardware of the equipment to software and algorithms applicable to biological data on a large scale. In addition, some challenges faced by these technologies and areas with growth potential were described. It is concluded, therefore, that despite the eminent growth of neuroengineering, there are still obstacles to be overcome so that the full potential of this area can be achieved. However, it is precisely in the face of these challenges that the interest of the academia has been driven, resulting in a significant increase in devices and methods emerging in the scientific scenario. Thus, overcoming these obstacles, promising perspectives emerge for neuroengineering in order to contribute to therapeutic development and quality of life.

CONCLUSION

The complexity and breadth of possibilities encompassing neuroengineering when applied to human health care become evident. Therefore, researchers in the field believe in the promising future that can be achieved in this therapeutic interface through overcoming the numerous challenges raised.

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REFERENCES

1. Thakor NV. Translating the Brain-Machine Interface. Science Translational Medicine. 2013;5(210):210ps17–7. Doi: 10.1126/scitranslmed.
2. Andersen RA, Musallam S, Pesaran B. Selecting the signals for a brain–machine interface. Current Opinion in Neurobiology. 2004;14(6):720–6. Doi: 10.1016/j.conb.2004.10.005
3. Hochberg LR, Bacher D, Jarosiewicz B, Masse NY, Simeral JD, Vogel J, et al. Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. Nature. 2012; 485:372–5. Doi: 10.1038/nature11076
4. Chiappalone M, Cota VR, Carè M, Di Florio M, Beaubois R, Buccelli S, et al. Neuromorphic-Based Neuroprostheses for Brain Rewiring: State-of-the-Art and Perspectives in Neuroengineering. Brain Sciences. 2022;12(11):1578. Doi: 10.3390/brainsci12111578
5. Ienca M, Kressig RW, Jotterand F, Elger B. Proactive Ethical Design for Neuroengineering, Assistive and Rehabilitation Technologies: the Cybathlon Lesson. Journal of NeuroEngineering and Rehabilitation. 2017;14(1):115. Doi: 10.1186/s12984-017-0325-z
6. Lebedev MA, Tate AJ, Hanson TL, Li Z, O'Doherty JE, Winans JA, et al. Future developments in brain-machine interface research. Clinics. 2011;66(Suppl 1):25-32. Doi: 10.1590/S1807-59322011001300004
7. Patil PG, Turner DA. The development of brain-machine interface neuroprosthetic devices. Neurotherapeutics. 2008;5(1):137-46. Doi: 10.1016/j.nurt.2007.11.002
8. Barha CK, Nagamatsu LS, Liu-Ambrose T. Basics of neuroanatomy and neurophysiology. Handbook of clinical neurology. 2016;138:53-68. Doi: 10.1016/B978-0-12-802973-2.00004-5
9. Warwick K. Neuroengineering and neuroprosthetics. Brain and Neuroscience Advances. 2018;2: 2398212818817499. Doi: 10.1177/2398212818817499
10. Potter SM, El Hady A, Fetz EE. Closed-loop neuroscience and neuroengineering. Frontiers in Neural Circuits. 2014;8:115. Doi: 10.3389/fncir.2014.00115
11. Cheng G, Ehrlich SK, Lebedev M, Nicolelis MAL. Neuroengineering challenges of fusing robotics and neuroscience. Science Robotics. 2020;5(49). Doi: 10.1126/scirobotics.abd1911
12. Thakor NV. In the Spotlight: Neuroengineering. IEEE Reviews in Biomedical Engineering. 2009; 2:18-20. Doi: 10.1109/RBME.2008.2008231
13. Dorsey ER, Sherer T, Okun MS, Bloem BR. The Emerging Evidence of the Parkinson Pandemic. Journal of Parkinson's Disease. 2018;8(s1):S3–8. Doi: 10.3233/JPD-181474
14. Neumann WJ, Turner RS, Blankertz B, Mitchell T, Kühn AA, Richardson RM. Toward Electrophysiology-Based Intelligent Adaptive Deep Brain Stimulation for Movement Disorders. Neurotherapeutics. 2019;16(1):105–18. Doi: 10.1007/s13311-018-00705-0
15. Seppich N, Tacca N, Chao KY, Akim M, Hidalgo-Carvajal D, Pozo Fortunić E, et al. CyberLimb: a novel robotic prosthesis concept with shared and intuitive control. Journal of NeuroEngineering and Rehabilitation. 2022;19(1):41. Doi: 10.1186/s12984-022-01016-4
16. Neumann WJ, Köhler RM, Kühn AA. A practical guide to invasive neurophysiology in patients with deep brain stimulation. Clinical Neurophysiology. 2022;140:171–80. Doi: 10.1016/j.clinph.2022.05.004
17. Cota VR, Moraes MFD. Editorial: Engineered neuromodulation approaches to treat neurological disorders. Frontiers in Neuroscience. 2022;16. Doi: 10.3389/fnins.2022.1038215
18. Fiorin FS, e Silva MA, Rodrigues AC. Electrical stimulation in animal models of epilepsy: A review on cellular and electrophysiological aspects. Life Sciences. 2021;285:119972. Doi: 10.1016/j.lfs.2021.119972
19. Chen S, Wu J, Cai A, Gonzalez N, Yin R. Towards minimally invasive deep brain stimulation and imaging: A near-infrared upconversion approach. Neuroscience Research. 2020;152:59–65. Doi: 10.1016/j.neures.2020.01.005
20. Moxon KA, Foffani G. Brain-machine interfaces beyond neuroprosthetics. Neuron. 2015;86(1):55–67. Doi: 10.1016/j.neuron.2015.03.036
21. Adewole DO, Serruya MD, Harris JP, Burrell JC, Petrov D, Chen HI, et al. The Evolution of Neuroprosthetic Interfaces. Critical reviews in biomedical engineering. 2016;44(1-2):123–52. Doi: 10.1615/CritRevBiomedEng.2016017198
22. Cavanagh JF. Electrophysiology as a theoretical and methodological hub for the neural sciences. Psychophysiology. 2019;56(2). Doi: 10.1111/psyp.13314
23. Coscia M, Wessel MJ, Chaudary U, Millán J del R, Micera S, Guggisberg A, et al. Neurotechnology-aided interventions for upper limb motor rehabilitation in severe chronic stroke. Brain. 2019;142(8):2182–97. Doi: 10.1093/brain/awz181
24. Shokoueinejad M, Park DW, Jung YH, Brodnick SK, Novello J, Dingle A, et al. Progress in the Field of Micro-Electrocorticography. Micromachines. 2019;10(1):62. Doi: 10.3390/mi10010062
25. Formica D, Schena E. Smart Sensors for Healthcare and Medical Applications. Sensors. 2021;21(2):543. Doi: 10.3390/s21020543
26. Johson MD, Lim HH, Netoff TI, Conolly AT, Johnson N, Abhrajeet R, et al. Neuromodulation for Brain Disorders: Challenges and Opportunities. IEEE Transactions on Biomedical Engineering. 2013;60(3):610-24. Doi: 10.1109/TBME.2013.2244890
27. Steinmetz NA, Koch C, Harris KD, Carandini M. Challenges and opportunities for large-scale electrophysiology with Neuropixels probes. Current Opinion in Neurobiology. 2018; 50:92-100. Doi: 10.1016/j.conb.2018.01.009
28. Voitiuk K, Geng J, Keefe MG, Parks DF, Sanso SE, Hawthorne N, et al. Light-weight electrophysiology hardware and software platform for cloud-based neural recording experiments. Journal of Neural Engineering. 2021;12;18(6). Doi: 10.1088/1741-2552/ac310a
29. Opris I, Lebedev MA, Pulgar VM, Vidu R, Enachescu M, Casanova MF. Editorial: Nanotechnologies in Neuroscience and Neuroengineering. Frontiers in Neuroscience. 2020;14:33. Doi: 10.3389/fnins.2020.00033
30. Brunton BW, Beyeler M. Data-driven models in human neuroscience and neuroengineering. Current Opinion in Neurobiology. 2019; 58:21-9. Doi: 10.1016/j.conb.2019.06.008
31. Ghezzi D. Retinal prostheses: progress toward the next generation implants. Frontiers in Neuroscience. 2015; 9:290. Doi: 10.3389/fnins.2015.00290
32. Monaco AM, Giugliano M. Carbon-based smart nanomaterials in biomedicine and neuroengineering. Beilstein Journal of Nanotechnology. 2014;5:1849-63. Doi: 10.3762/bjnano.5.196
33. Fiani B, Reardon T, Ayres B, Cline D, Sitto SR. An Examination of Prospective Uses and Future Directions of Neuralink: The Brain-Machine Interface. Cureus. 2021;13(3). Doi: 10.7759/cureus.14192
34. He F, Lycke R, Ganji M, Xie C, Luan L. Ultraflexible Neural Electrodes for Long-Lasting Intracortical Recording. iScience. 2020;23(8). Doi: 10.1016/j.isci.2020.101387

35. Steinmetz NA, Aydin C, Lebedeva A, Okun M, Pachitariu M, Bauza M, et al. Neuropixels 2.0: A miniaturized high-density probe for stable, long-term brain recordings. Science. 2021;372(6539). Doi: 10.1126/science.abf4588

36. Bassett DS, Khambhati AN, Grafton ST. Emerging Frontiers of Neuroengineering: A Network Science of Brain Connectivity. Anual Review of biomedical engineering. 2017;19:327–52. Doi: 10.1146/annurev-bioeng-071516-044511

37. Cuevas-López A, Pérez-Montoyo E, López-Madrona VJ, Canals S, Moratal D. Low-Power Lossless Data Compression for Wireless Brain Electrophysiology. Sensors. 2022;22(10):3676. Doi: 10.3390/s22103676

38. Santaniello S, Gale JT, Sarma SV. Systems approaches to optimizing deep brain stimulation therapies in Parkinson's disease. Wiley Interdisciplinary Reviews: Systems Biology and Medicine. 2018;10(5):e1421. Doi: 10.1002/wsbm.1421

39. Bandara DSV, Gopura RARC, Hemapala KTMU, Kiguchi K. Development of a multi-DoF transhumeral robotic arm prosthesis. Medical Engineering & Physics. 2017; 48:131-41. Doi: 10.1016/j.medengphy.2017.06.034

40. Lum PS, Godfrey SB, Brokaw EB, Holley RJ, Nichols D. Robotic Approaches for Rehabilitation of Hand Function After Stroke. American Journal of Physical Medicine & Rehabilitation. 2012;91(11 suppl 3):S242–54. Doi: 10.1097/PHM.0b013e31826bcedb

41. Jeong JW, Shin G, Park SI, Yu KJ, Xu L, Rogers JA. Soft Materials in Neuroengineering for Hard Problems in Neuroscience. Neuron. 2015;86(1):175–86. Doi: 10.1016/j.neuron.2014.12.035

42. Raspopovic S, Valle G, Petrini FM. Sensory feedback for limb prostheses in amputees. Nature Materials. 2021;20:925–39. Doi: 10.1038/s41563-021-00966-9

43. Won SM, Cai L, Gutruf P, Rogers JA. Wireless and battery-free technologies for neuroengineering. Nature Biomedical Engineering. 2021;7:405-23. Doi: 10.1038/s41551-021-00683-3

44. Eapen BC, Murphy DP, Cifu DX. Neuroprosthetics in amputee and brain injury rehabilitation. Experimental Neurology. 2017;287:479–85. Doi: 10.1016/j.expneurol.2016.08.004

45. Ivanenko Y, Ferris DP, Lee K, Sakurai Y, Beloozerova IN, Lebedev M. Editorial: Neural Prostheses for Locomotion. Frontiers in Neuroscience. 2021;15. Doi: 10.3389/fnins.2021.788021

46. Panuccio G, Semprini M, Natale L, Buccelli S, Colombi I, Chiappalone M. Progress in Neuroengineering for brain repair: New challenges and open issues. Brain and Neuroscience Advances. 2018;2:2398212818776475. Doi: 10.1177/2398212818776475

47. Kim CK, Adhikari A, Deisseroth K. Integration of optogenetics with complementary methodologies in systems neuroscience. Nature Reviews Neuroscience. 2017;18(4):222–35. Doi: 10.1038/nrn.2017.15