



Next-Generation Neural Interfaces Enabled by Nano-Bioelectronics- Review

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Abstract: This review paper is dedicated to state-of-the-art in brain-machine interfaces (BMIs) based on nano-bioelectronics (NBE). The report elaborates how convergence in nanoscience, biotechnology, information technology and cognitive science (NBIC) has resulted in new set of neural interfaces that overcomes the size limitation of macro-scale neural interfaces. The paper will discuss certain properties of nanomaterials, in particular, carbon-based nanostructures, metals nano clustering structures and hybrids composite materials, that have the potential to enhance signal recording, stimulation of neurons and drug delivery. The technological revolution in the application of the technologies to the sphere of neural prosthetics, neurorehabilitation and targeted therapeutics are considered. In addition, critical appraisal of current technical and biological issues, such as foreign body reaction (FBR) and degradation of the signal, is undertaken and one that is explored here is self-healing materials, contactless energy delivery, and artificial intelligence interface. The article ends with the positive perspective to the future development of this cross disciplinary endeavour in that it would change the nature of how the brain has been known and operates in terms of neurologically.

Keywords: FBR, NBE, NBIC, Neurorehabilitation

1. Introduction : A New Paradigm for Neuro-Technology

1.1 Evolution of Brain-Machine Interfaces (BMIs)

One such paradigm shift is the technological advances of Brain-Machine Interfaces (BMIs) where both the neurological activity is controlled in a pro active manner and more importantly in two way communication. The history of the start of work in the field is related to the discovery of the electroencephalogram activity of the brain and the establishment of the electroencephalography (EEG) by Hans Berger in 1924, when he did not interfere with the human brain and recorded it without interfering with it non-stimulatingly. With the course of time, these primitive early devices that looked like silver wires inserted beneath the scalp gave way to more sophisticated equipment. Experiments by an American composer Alvin Lucier in the 1960s utilized EEG neurofeedback and analog signal processing to control

the audible output of percussion instruments- one of the first practical applications of a brain-machine interface [1], although the term itself had not yet come into use.

The advances of these primitive systems created the basis of the current BMIs, which are starting to be advanced to enable the user to perform a range of tasks far surpassing simple spelling (prosthetics control, or even the control of paralyzed muscles, again usually through one of several biomimetic schemes of translating the brain activity into commands directly to a secondary device in a more natural way). Above all, the evolution of crude signal detection to detailed bio-realistic control systems has transformed technology into an effective biomedical instrument of scientific analysis capable of investigating neuroscience fundamentals [2]. The qualities of providing direct access to target neurons or regions in the cortex makes MIs a good tool to answer some of the most fundamental questions concerning brain physiology; how the neurons act, how they can

learn and how oscillations can drive their behaviour. One of the examples is needed as the motor cortical neurons have been shown to have the potential of learning specific and arbitrary associations to guide a cursor [3], with the insight into the brain plasticity and ability to achieve new tasks learned.

1.2. The Limitations of Conventional BMIs

Although successful in restoring the sensory-motor functions, the use-value of conventional BMIs is hacked by several imperative issues in the long-term perspective. Conventionally, neural implants are made of stiff materials including silicon and platinum that share almost opposite structural and physiochemical characteristics with the soft, viscoelastic neural tissue that they interact with. This large mechanical mismatch is typified by the large difference between the Young modulus of polyimide [4].

As first expressed in Newtonian terms, 1680s and explicitly in terms of local deformation, 1890s D, the micromotion at the implant site as a result of tissue damage which causes local tissue technique damage is due to the shear stress level at the implant site (e.g., hard disk: 600 kPa, or bone: 2.5 GPa) and brain tissue (5.51 kPa).

Such physical incompatibility leads to a strong and long-lasting host immune reaction the foreign body reaction (FBR). The FBR is the persistence of a cascade of inflammation that results in the growth of fibrous scar tissue (gliosis) around the implant. This covering of the device separates it with the surrounding neural tissue, thus its functionality dramatically decreases [5]. In particular, the process of fibrotic deposits formation leads to the increase of electrical impedance of tissue-device interface, consequently, to the decrease in signal-to-noise ratio (SNR) of signals over time. These interdependent technical and biological challenges are a significant obstacle to the goal of chronic, long-term stability and performance of neural implants, such that recording performance typically deteriorates significantly within a month after implantation.

1.3. The Rise of Nano-Bioelectronics

To overcome these inherent drawbacks, the scientific studies related to the notion of nano-bio electronics (NBE) have been developed into an exponentially growing interdisciplinary discipline. Nanomaterials offer valuable properties exploited by NBE technology to overcome the drawback of traditional bioelectronics. NBE has the potential to raise

both the sensitivity and biocompatibility of neural interfaces by miniaturizing electronic transducer components down to the nanoscale and approaching the properties of the biological tissues [6]. The novel strategy has the potential to not just explore advance clinical applications in medical care, however, it also promises a greater interpretation of underlying biology. The eventual aim is to go beyond simple contact and develop an interface that will enable the nonliving electronic and living biological systems to interpenetrate so that there is direct precise interaction with complex biological information processing systems, for example the brain.

1.4. Scope of the Review

This review takes an in-depth journey into NBE in BMIs, going through a wide range of material developments, groundbreaking applications, unresolved issues, and promising topics in the future. It explores the symbiotic relationship between nanotechnology and artificial intelligence with an aim towards understanding how convergence between the two is allowing a new generation of intelligent and adaptive neurotechnologies as shown in figure 1. This paper will explain the characteristics of some of the most important nanomaterials, provide an overview of the literature of relevant research, and a discussion of their applications to therapy and prosthetics, and finally, reflect upon the barriers that need to be addressed in order to be able to deal with the full promise of this interdisciplinary science.

2. Foundational Principles: The Convergence Driving Innovation

2.1. The NBIC Convergence Paradigm

The modern framework of nano-bioelectronics as applied to BMIs is a paradigm called NBIC convergence; the combination of Nanoscience, Biotechnology, Information Technology (IT), and Cognitive Science (CS). The marriage between these areas is making it possible to build more complicated systems that are able to interact with and respond to the environment in unprecedented fashion [2].

Nanoscience offers the advanced functional components and the assembly/manufacturing methods of designing the hardware of next-generation BMIs. Nanofabrication technologies, including 3D printing and lithography, are now giving the possibility to design implantable devices and biosensors with orders of magnitude finer precision than those of bio systems with increased signal resolution [7].

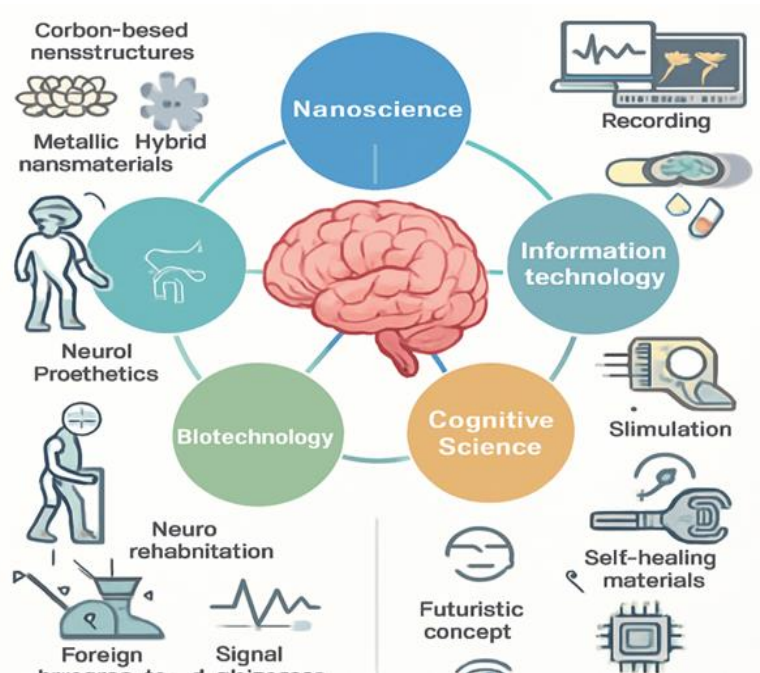


Figure 1. Overview of Nano-Bioelectronics

Biotechnology provides a profound knowledge of biological systems and an ability to engineer biological parts. These include the development of biological systems that can perform in an elaborate manner such as gene editing, and synthetic biology [8]. In the BMIs context, this enables the development of technologies capable of interfacing with and controlling living cells and tissues i.e. stimulating the maturation of brain organoids.

IT and Cognitive Science (IT, CS) equip nano-scale interfaces with the computational power, information processing and algorithmic structure to turn them into a functional interface. The large amount of data collected that high density interfaces generate requires robust algorithms to find useful patterns and convert those patterns into meaningful action.

There is a strongly symbiotic relationship between these two fields which can provide a new generation of intelligent and adaptive BMIs. The high fidelity data stream is provided by Nanoscale hardware and the real-time processing and contextual learning to make the data actionable is provided by artificial intelligence (AI) and machine learning (ML) [9]. A conventional BMI is a hard coded controller, which can implement a predetermined neural code into a particular command. However, in comparison a nano-bioelectronic BMI that integrates an AI has the advantage of being able to utilize feedback and telemetry of the hardware in near real-time to learn and adjust to the physiological and environmental

changes as they occur, and in such context become personalized and context aware [10]. The combination of this nano-hardware/AI power is highly promising because the former allows high-fidelity data and the latter allows high-fidelity adaptation.

2.2. Principles of Nano-Bioelectronic Interfaces

The essence of any BMI is that it is used to record / stimulate the nervous system. Nano-bioelectronics leads to fundamental changes in both these processes.

During neural recording, one seeks to accurately localize the responses of firing neurons with a large sampling density in space and time and a small signal loss or tissue damage. The sensitivity of affinity-based biosensors to detect electrical signals and biomolecules in the most sensitive way can be improved appreciably by reducing the size of electronic transducers to nano scale dimensions using materials such as semiconductor nanostructures [11]. As an example, the addition of nanoelectronic components to three-dimension cell networks has only shown the potential future possibilities of revolutionary advances of cellular, and in vivo measurements.

Nanomaterials, in turn, serve as mediators and transform a primary stimulus that is remotely collected into the form of a secondary stimulus at the nanomaterial-neuron interface. The method is a

minimally invasive alternative to the electrical stimulation which produces intervening electric fields using electrodes [12]. The principal stimulus may be light, magnetic fields, or ultrasound and then converted by the nanomaterial to a different stimulus, e.g., localized electric field or heat. As an example, quantum dots may be used to electrically stimulate with the conversion of light into an electric field and gold nanomaterials may be used to thermally stimulate with conversions of light into heat. This allows very specific and local neuronal activation without direct, physical contact and high-intensity signals.

3. Advanced Nanomaterials for Neural Interfaces: A Literature Survey

Various types of nanomaterials are under investigations in regard to the possibility of their use in neural interface applications. With their special characteristics, these materials provide solutions to the issues of the conventional implantable devices, providing an increase in biocompatibility, mechanical compliance and electrical characteristics [13].

Table 1. Literature Survey of Nanomaterials for Neural Interfaces

Nanomaterial Class	Specific Material	Key Properties	Primary Applications in BMIs	Challenges/Notes	Source References
Carbon-based	Graphene	High conductivity, flexibility, optical transparency, biocompatibility, high mechanical strength, chemical stability	Neural probing, brain organoid maturation and control	Ultra-flexibility makes implantation difficult; low capacitance can lead to high impedance and noise	[14]
Carbon-based	Carbon Nanotubes (CNTs)	High electrical conductivity, high surface-to-volume ratio, low impedance, mechanical strength, biocompatibility	Electrode coatings to improve SNR, nerve cell adhesion, and durability	Functionalization is crucial to reduce toxicity and aggregation; electrical properties can diminish in assemblies	[15]
Metallic Nanoparticles	Gold (AuNPs)	High chemical stability, photothermal properties, surface plasmon resonance	Targeted drug delivery, opto-thermal neural stimulation, biosensing	Potential to affect neural cell proliferation and excitability, can aggravate seizure activity	[16]
Metallic Nanoparticles	Platinum Black (Pt black)	Porous, high surface area	Electrode coating to increase electrical contact area and catalytic reaction area	Coating adherence can be an issue	[17]
Other Classes	Quantum Dots (QDs)	Semiconducting, opto-electric transduction	Opto-electric neural stimulation		[18]
Other Classes	Piezoelectric Nanomaterials	Piezoelectric properties	Acousto-electric stimulation		[19]
Other Classes	Magneto-electric Nanoparticles	Magneto-electric transduction	Magneto-electric stimulation		[20]

But what is less apparent is that the statement of biocompatibility has been more complex and situation specific as it might sound in terms of a label.

The table below entails the literature survey on the properties, application and the challenges of the most significant nanomaterials.

Although it is often reported that nanomaterials are more biocompatible, the trend is not absolutely encouraging. As an example, the current application of gold nanoparticles (AuNPs) is hailed due to their stability on a chemical level and the broad usage in clinical practice with regard to drug delivery. Indeed, other studies also proved the ability of AuNPs to interfere with human embryonic neural precursor cell development and even enhance the neuron excitability and exacerbate seizure in mouse brains when proceeded intracellularly [21]. This simply means that the impact of a nanomaterial on the biological systems is extremely parameter-specific, including the size of the nanoparticles, the amount of it, and its location in the tissue. It highlights an essential feature of the field that is bioeffect of a nanomaterial is an idiosyncratic and at times even contradictory phenomenon that demands particular attention beyond a simple characterization as being biocompatible.

4. Key Applications in Brain-Machine Interfaces

4.1. Neural Prosthetics and Assistive Devices

The use of nanomaterials offers viability of neural prosthetics by enabling the replication of actual behavioral dynamics of natural limbs and transmission according to intentions of the user.

One such example is development of e-skin, which is a touch sensor consisting of nanocomposite with enhanced characteristics. e-skin constructed with silver nanowire, carbon nanotube, or polydimethylsiloxane (PDMS) are well-flexible and sensitive, with multimodal sensing ability to measure the force and temperature of the surroundings. As another example, a skin-like sensor consisting of polyurethane scaffolds coated with silver nanowire arrays using layered carbon fabrics is able to transmit physical feelings into a visual or auditory representation, making a synthetic limb feel and perform better [12]. Carbon materials as a conductive nanofiller in a polymeric compound are especially

promising, because it will provide a cheap, flexible, and stretchable solution to human motion detection and soft robotics.

In addition to sensation, nanomaterials are permitting a new generation of neuro- biohybrid control systems. A UC San Diego study was foundational in showing that human brain organoids of graphene stimulation could make telekinetic control of a simple robot a reality in real-time. The graphene-mediated optical stimulation (GraMOS) slowed the process by taking advantage of the optoelectronic characteristics of graphene to convert light to mild electrical signals that stimulated neurons to grow together and develop more quickly [22]. When placed in a closed-loop test, recording their neural activity managed to redirect the robot once it collided with an obstacle to complete the loop in less than 50 milliseconds. This exceptional work is proving the future of neuro-biohybrid systems where living the brain is connected and can communicate with robotics to propel smart prosthetics or adjustable interfaces.

4.2. Targeted Therapeutics and Neurorehabilitation

Nano-bioelectronic usage is allowing a paradigm shift in extending BMI functionality beyond a simple communication channel and into diagnostics and therapy. This is of great importance in the treatment of the neurodegenerative disorders.

Possibly the biggest application is nano particle mediated delivery of drugs. The blood-brain barrier (BBB) is a formidable obstacle in arriving at treatment delivery to the central nervous system. Nanoparticles have the advantage of being small, non-toxic, and being able to surface-engineer delivery properties, making them capable of BBB crossing and delivering valuable payloads to specific molecules and cells with high specificity and safety compared with current medications [23]. As an example, nanomelatonin has been demonstrated to be protective against toxicity initiated by rotenone in models of Parkinson disease on loading with human serum albumin nanoparticles (HSANPs). Functionalization of nanocarriers with biomolecules to increase bioavailability and stimulate receptor-mediated endocytosis also provides a route to target delivery of therapeutic and disease-related biomarkers.

The uses of this technology in creating closed-loop therapeutic BMIs are that they are able to record

and stimulate the neural tissue in an adaptive fashion. These bilateral interfaces employ machine learning on-board to identify certain neurological symptoms, i.e. tremors in Parkinson's disease or seizures, and stimulate in real-time to prevent them. This is a paradigm shift, in which passive control has been changed to active and adaptive therapy [24]. One such future device might include a nano-sized sensing array that detects the signal of an approaching seizure, processes that information with an on-board AI, and then either activates specific electrical stimulus via a nano-electrode or releases well-timed drugs through a nanocarrier at the target site. This is not only a high-tech breakthrough but a new paradigm of affordable healthcare, individualized medicine.

5. Technical and Biological Challenges for Chronic Implantation

At best, only a complex and interconnected cascade of technical and biological difficulties are considered to limit the eventual usage of neural implants on a wide and lasting scale.

5.1. The Foreign Body Reaction (FBR)

Foreign body reaction (FBR) has been termed as the main biological deterrent to long-term implantation. The FBR is a persistent immune reaction caused by physiological incongruence between the hard and the soft, pliant neural tissue and the implant. This physical incompatibility coupled with the introduction of a foreign material triggers the host immune system and subsequently results in sequelae of unfavourable biological and technical effects [25].

This inflammatory process entails mobilisation of immune cells (macrophages) towards the implant location. These cells produce inflammatory cytokines, which perpetuates the immune system that in turn leads to the generation of a fibrous scar (gliosis) that surrounds the implant. This biologic entrapment is not a benign process and it has drastic functional implications. The fibrous tissue elevates the electrical load at the tissue-device junction, and directly causes the absolute decline in the recording ability of the device and deteriorates signal-to-noise ratio with time [26]. This rational, sequential domino-effect shows that a technological, piecemeal solution, which includes a more powerful amplifier, is not enough. The remedy should take care of the cause of the biological cascade by the use of materials that will not be harmful to the neural environment.

5.2. Engineering Hurdles

Besides biological obstacles, there are serious engineering barriers to chronic BMIs.

Mechanical Mismatch: As indicated above, there will be a huge discrepancy between the stiffness of the implanted material and that of the physical tissue, which involves micromisplacements and chronic tissue damage. This has been a driving force to look into developing flexible electronics and materials which have mechanical properties more similar to brain tissue [26].

Energy and Signal: Fully implantable systems will necessitate innovative methods of wireless energy and data transmission because the infection risks that transdermal wires pose are mitigated against. The trend is the development of compact and low energy consuming systems with wirelessly rechargeable batteries and data transmission via inductive RF or Bluetooth in order to improve safety and living quality of the patient [27].

Signal Processing and Data Management: This process is generating large volumes of data that need to be manipulated and compressed real time since there are thousands of neural signals to record at a time [28]. To make a BMI work in the real-time, it is crucial to host the on-site processing and to downsample the data before wireless relay so that the BMI can benefit a closed-loop connection with minimum external requirements.

6. Future Perspectives and Emerging Trends

Bio-integration, wireless functionalities, and adaptive intelligence are the three converging pillars defining the future of nano-bioelectronics to BMI. These are not individual trends but elements of one vision of a new generation of devices.

6.1. Bio-Integrated and Self-Healing Interfaces

The most promising in terms of mitigating the FBR is the generation of biohybrid and biologically-inspired interfaces that actively facilitate host-implant biologic integration. This is done by utilizing materials with similar mechanical properties to that of the neural tissue, e.g. flexible electronics and hydrogels [29]. Scientists are also developing novel material that can self-heal applying some energy such that they can heal

small defects just the way humans can through the human skin.

Also, a new approach concerns coating a living electrode, such as biomaterial or introducing extraneous cells to an implanted location [30]. These immigrant cells are expected to make a physiological connection with the host nervous system, thus leading to smooth integration at a cellular level and minimizing the fibrotic encapsulation that hamper long-term performance.

6.2. Smart and Adaptive Systems

Artificial intelligence and machine learning integration is making possible a new type of adaptive BMIs that can modify and respond to the needs of the user over a lifetime. These state-of-the-art neural Algorithms are being used to facilitate superior hybrid neural decoding, whereby intricate neural signals can be interpreted in real-time with an above average level of effectiveness and quick responsiveness. Long term, the plan is to move processing to the device itself, eliminating overhead associated with communicating with a computer and allowing closed-loop operation in the real-time sense [31]. It is envisioned that this on-board processing will be able to extract the critical features of interest, detect the presence of disease neuro-markers, and lead to low-latency neural decoding hence the development of self-sufficient platforms that can work in a wide variety of environments.

6.3. Wireless and Minimally Invasive Paradigms

The trend is toward the development of fully implantable, miniaturized, systems with wireless power and communications to enable improved safety and patient quality of life. The systems will remove the risk of infection ported by transdermal wires and enable the patients to have more freedom of movements [32].

At the same time researchers are investigating methods of brain stimulation which are less invasive and do not require surgery to accomplish. This involves (1) using nanomaterials as carriers to translate signals remotely transmitted, eg light, ultrasound, into an effect at the nanomaterial-neurone interface. The methods can be used to provide low-level, high-resolution stimulation without the use of implanted leads.

7. Discussion

In this review, we draw some of the striking developments in brain-machine interfaced (BMIs) enabled by NBIC convergence nano-bioelectronics (NBE). The scale shift readily applied to neural engineering, where the scale-down approach in nanoscale neural interfaces has brought forward a new hope to neural engineering such as higher propinquity and minimal invasiveness in manipulating neural tissue through interfaces. Carbon nanotube-based structures, metal nanoparticles and hybrids have become the most important enabling structures, each with unique properties to increase electrical conductivity, biocompatibility and multifunction to allow dependable signal recording, neural stimulation and drug release [33].

Nevertheless, a number of technical and biological issues remain as obstacles to wide adoption in clinical applications of nano-bioelectronic BMIs. Foreign body reaction (FBR) is still a major challenge, which in many applications can lead to inflammation and fibrotic encapsulation that erodes signal quality and performance of the devices over time. Self-healing materials and better surface engineering cargo-preconditioning strategies have been proposed to overcome these responses but, need to be further validated in vivo and over time. The other formidable challenge is a decline in signal integrity as a result of biological reactivity and materials degradation. Here, advances to minimize invasive wiring (and related breakdowns) have been made, including contactless energy delivery, which may increase device life and patient comfort.

Additionally, coupling with artificial intelligence (AI) in real-time may be a potentially transformative strategy because AI can facilitate adaptive neural decoding [34], closed-loop feedback, and predictive modulation, all of which could also be used to personalize and optimize the therapeutic experience. This research epitomizes the multidisciplinary need of the project where nanotechnology and biotechnology, cognitive science and information technology come together in their collaborative research efforts. With the development upon the field, there is an increasing need to streamline the process of the evaluation and the regulatory frameworks that take into consideration the complications of these developing technologies [35].

To conclude, though numerous challenges are still to be solved, current advancements of BMIs in nanomaterials, self-healing mechanisms, energy, and



AI integration represent a bright future of BMIs [36]. The ongoing integration of NBIC areas of expertise promises to bring about smarter and even more biofriendly and highly functional neural interfaces that will not only drive neuro-prosthetics and neurorehabilitation [37], but in the process, further expand our knowledge and insights on brain functioning and how it interacts with machine systems.

8. Conclusion

The fast developing nexus of nanoscience, biotechnology, information technology, and cognitive science (NBIC) has markedly changed the panorama of brain-machine interfaces (BMIs), and is leading to radical strategies to access and perceive the brain in a nano-bioelectronic (NBE) future. To overcome the weaknesses inherent in macro-scale strategies, new forms of advanced nanomaterials have emerged that include carbon-based architecture, metallic nanoclusters, and hybrid composites, and that are changing the potentials of signal fidelity, neural stimulation and targeted drug delivery. Such innovations have already started transforming clinical areas including neural prosthetics, neurorehabilitation and precision therapeutics with direct benefits to patient care and curative functionality. Such emerging problems continue to include foreign body reaction, chronic biocompatibility, and decay in transmission, thus adding further significance to next-generation developments like self-mending materials, without-contact power transfer technologies, and the neural interface guidelines distilled by artificial intelligence. Such developments not only have the potential to increase device lifespan and integration but should also make it possible to have seamless, adaptive interactions between biological and electronic systems. The future implications of NBIC disciplines as applied to BMI research are a transformative technology in neuroscience: Interfaces that can incorporate a dynamic repair, intelligent reconfiguration, and a more overt operation potentially causing a technological transformation in the manner the brain interacts with technology. As these disciplines begin to synergize, we can more clearly imagine how neural processes could be deciphered and ultimately boosted by nano-bioelectronic interfaces, a development that will ultimately transform both our understandings of higher conscious experience and how it is treated with potential breakthroughs that can one day revolutionize our concept of all of the above.

This review has elucidated that nano-bioelectronics is a fundamental facilitator to address the foremost constrain of classical BMIs. The unusual characteristics of nanomaterials, such as the electrical conductivity of carbon nanotubes and graphene and their ability to deliver therapeutic functions of gold nanoparticles, are fuelling recent advances in neural recording, stimulation, and therapy. Although there have been great advancements, there have been challenges that are yet to be overcome; these include the foreign body reaction and the engineering challenges which are the major bottlenecks towards realising non-controversial long-term, functional and safe BMIs. The best solutions will not be one-off solutions but it will be a new breed of bio integrated flexible and wireless devices with adaptive intelligence embedded. The future of BMIs is such an appealing vision that unifies all the cited trends, an inevitable step of overcoming all the identified limitations at the same time. Such symbiotic relationship between nano-hardware and AI will mark the future of this study field, which is likely to change the way we rehabilitate the neurosphere as well as to change the way we understand human brain. The interdisciplinary practice has the potential to erase the distinction between living and non-living systems to produce devices that are not only integrated within the body but a part of it, which opens up a new horizon in personalized medicine and human enhancement.

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Conflict of interest

The Author's declares that there is no conflict of interest anywhere.



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Yes

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