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# Overview of Nanobiotechnology Towards Various Application

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## ABSTRACT
This review article delves into the synergistic realm of nanotechnology and neuroscience, exploring the transformative impact of nanomaterials and nanoparticles in the burgeoning field of nanoneuroscience. We comprehensively survey the latest advancements, methodologies, and applications where nanotechnology interfaces with neuroscience, focusing particularly on the role of nanoparticles. Our analysis encompasses various dimensions, including diagnostic and therapeutic interventions, imaging techniques, and targeted drug delivery systems. Through a critical synthesis of the existing literature, we highlight the multifaceted contributions of nanotechnology to unravel the complexities of the nervous system, from fundamental research to clinical applications. Additionally, we discuss the challenges and future prospects associated with the integration of nanomaterials in neuroscience, emphasizing the potential for revolutionary breakthroughs in understanding and treating neurological disorders. This review aims to provide a valuable resource for researchers, clinicians, and enthusiasts alike, fostering a deeper understanding of the intricate interplay between nanotechnology and neuroscience.

**Keywords:** Nanoparticles, Nanoneuroscience, Quantum dots, Magnetic nanomaterial

## I. INTRODUCTION

### 1.1 Historical Aspects

The understanding of the brain and how it is functioning started nearly around 500BC, right from the Ancient Greeks who believed the brain to be mere densely packed organ. It was Hippocrates (400BC) who told brain is the seat of intelligence whereas Aristotle assumed the heart to be the seat of consciousness and intelligence. The importance of the brain gradually grew and the major discussion was about mind and body problem which led to the concepts of dualism and monism by Rene Descrates. He is the one who said 'I think therefore I am'.

In depth, anatomical study of the human brain was first conducted by Greek anatomist Galen and later carried further and published by Thomas in his book *Cerebrianatome* (1664). This led to the beginning of neurobiology. In 1780, Luigi Galvani's work on role of electricity in nerve conduction and muscle activation, Helmholtz's work on neural activity is electrical in nature and Cajal's hippocampus diagram that showed the direction of flow of information fuelled the emerging of neuroscience. The function of the brain and its interpretation with other body organs was challenging to study. As brain has the most complex organisation, it was even more exciting to go deeper at the research level to know how brain has been made.

Phrenology is the outdated technique used to study what neurons do in the brain. Later advancements in the technology led to more techniques like positron emission tomography (PET), functional magnetic resonance imaging (fMRI), light microscopy to know which part of the brain is active and the site of injury (lesions).

### 1.2 Why Nanotechnology

Processing of brain at molecular level will reveal more interesting concepts to study which will be useful to find treatment for many neurodegenerative diseases. Nervous system has many parts and each part has to be analysed at a smaller scale level to bring out its irregular interactions and development that causes many diseases.Nanoparticles and its recent advancements can do wonders in this field irrespective of the very few disadvantages.

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Once the nervous system has suffered damage, its repair and regeneration are difficult. Neurodegenerative diseases (ND), traumatic events, and iatrogenic injuries (the result of diagnosis and therapy leads to certain problems) all would lead to lesions of the nervous system, including protein degeneration, inflammatory responses, neuronal death, and malformations of cellular structural elements [1] [2].

### 1.3 Nanoneuroscience

Nanotechnologies use engineered materials or devices with a functional organization on the nanometre scale (that is, one billionth of a metre) in at least one dimension, typically ranging from 1 to 100 nanometres. Nanotechnologies are therefore primarily defined by the functional properties that determine how they interact [3]. The major advantage of using nanodevices for neuroscience is that it has fewer side effects and can be manipulated by physical and chemical means. Nanomaterials have excellent physicochemical properties and good biological activities, such as a large surface-area-to-thickness ratio, high levels of adhesion, and adjustable flexibility. In addition, they can be designed to have superior biocompatibility and electrical or nano-carrier properties. [4]

### 1.4 Properties of Nanomaterials in Neuroscience

- Nanomaterials, when compared with traditional micrometer-scale devices, are capable of more precisely reflecting the surface features of organic tissues, such as energy and topography [5].
- Their adjustable size and the advances that have been made in the methods of synthesis, nanostructures have a wide variety of suitable characteristics. These characteristics include controlled release profiles, site specific targeting or delivery, a high ratio of surface area to volume, adaptability in facilitating surface modification, and multifunctionality [6] [7][8].
- The central nervous system (CNS) is a highly critical and protective part of the brain where the disease diagnosis and treatment is complicated. The blood brain barrier doesn't allow the larger molecules to penetrate the surface of the brain. Various researches has been undertaken to study the diminutive nanodevices that can penetrate into the brain with less side effects.
- Nanoparticles enhance the resolution and the sensitivity of the diagnostics.
- Nanomaterials can be used as vectors for drug delivery which is more concerned with the neuroprotection, changes in neuroregeneration and differentiation, as modalities for neuroimaging and as devices for neurosurgery [9] [10].

## II. UTILIZING NANOPARTICLES IN NEUROSCIENCE

### 2.1 Carbon-based Nanoparticles

The fundamental element for the effective creation of nanodevices is the ongoing refinement of the materials needed to create the instruments or apparatuses employed in nanotechnology-related domains. Carbon is one such substance. Graphene, fullerenes, carbon nanodiamonds, and carbon nanotubes are examples of synthetic allotropes, which are two or more physical forms in which an element exists [11].

Due to their unique characteristics over other metals, carbon nanostructures are the most favoured. In addition to their amazing strength, they are excellent heat and electrical conductors. The two most commonly employed forms of carbon nanomaterials among all others are graphene and carbon nanotubes.

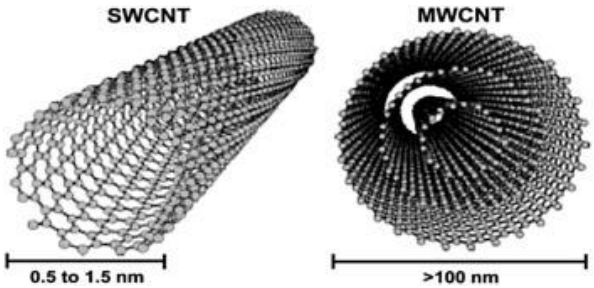


Fig.1 multi walled carbon nanotube, science direct.com [13]

**Carbon nanotubes in neuroscience:**

- In order to support the development of neurons, carbon nanotubes have been widely employed [14]. Coated carbon nanotubes are employed as substrates to observe the growth of the neuron when the conductance is varied [15].
- In organotypic spinal cord explants, there was an increase in axonal outgrowth over two-dimensional carbon nanotube environments [16].
- The ability to increase neuronal signals and boost synchronization in vitro was demonstrated by the development of three-dimensional scaffolds (temporary structures) using carbon nanotubes [18]. These scaffolds were proven to be more limited in scar formation when implanted in the rat visual cortex in vivo [17].

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Graphene is a single atomic layer of crystalline graphite characterized by a bi-dimensional structure. Graphene has a huge impact on science and technology with its outstanding physical and chemical properties. [18]

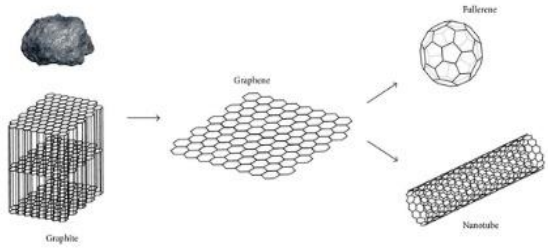


Fig.2 one material many possibilities [19]

**In Neuroscience, graphene:**

- Graphene-based nanomaterials are used as substrates for primary neuronal culture growth and have been shown to constitute a permissive interface on which the neurons retain their unaltered growth [20].
- In the interface with the hippocampal neurons, graphene seems to adjust to the extracellular ion distribution (hippocampus neurons are made up of many different types of neurons that signal each other by releasing chemicals). This enhanced ion-trapping ability occurred when graphene was applied in a single layer [21].
- In order to accelerate neural regeneration and brain damage recovery, graphene is emerging as a cutting-edge scaffold for neural tissue engineering [22].

**2.2. Gold Nanomaterials**

Long-term brain interconnections that are altered at the nanoscale level could result from the convergence of neuroscience and nanoscience. Gold nanoparticles have drawn a lot of interest in neuroscience because of their intrinsic physicochemical properties, particularly when used for combination therapeutic and diagnostic applications. The use of gold nanoparticles to activate and observe neurophysiological signals has been booming. Therefore, gold nanoparticles may offer a promising option for neuroprotective techniques, biocompatible implantable materials, and brain tissue regeneration and recovery.

**The Use of Gold Nanoparticles in Neuroscience:**

The last several years have seen a significant rise in the application of modified gold nanoparticles in the field of neuroscience. Just combine gold nanoparticles to target certain cells; inject them to mimic the size of subcellular components like ion channels and cell receptors[24]. In the context of stimulating and regulating neural activity, gold nanoparticles have already been effectively applied in a number of different contexts, such as improving neurite outgrowth [25], regulating intracellular calcium signaling [26], depolarizing neurons [27], and suppressing neural activity [28].

**Why Gold Nanoparticles?**

The use of gold nanoparticles in neurobiology may lead to the discovery of novel treatments for illnesses that now lack one. Their special qualities—such as optical responsiveness, chemical and physical stability, low toxicity, and a broad range of potential surface functionalization—give birth to this outlook [29]. For instance, cellular and molecular specificity made possible by the use of particular ligands enables more controlled intercommunication with target cells and tissues. Voltage-gated sodium channels, which are significant channels that control the action potential of neurons, have been shown to bind to gold nanoparticles [30].

**Characteristics of gold nanoparticles:**

The numerous uses of gold nanoparticles in biology and medicine are associated with their special optical characteristics. The localized surface plasmon resonance is a resonant coherent oscillation that occurs when gold nanoparticles are disrupted by an external light field in the visible or near infrared range [31]. This occurs when the conduction electrons leave their equilibrium location. The visible to infrared light spectrum is where plasmon resonance wavelengths naturally occur, and the precise location depends on the interparticle distance, particle morphology, and refractive index of the surrounding medium [32]. The plasmon absorption peak is chosen for many biological applications so that it matches the 600–1200 nm transparency window of biological tissues; thus, the most appropriate morphologies include nanorods, nanoshells, nanostars, and nanocages [33].

In addition, gold nanoparticles are "high-precision" photothermal agents with a number of desirable properties for in vivo brain regulation. Compared to mammalian cells, gold nanoparticles are minuscule and only generate heat in their immediate surroundings. As long as the particles are positioned cardinally close to the target cell, this reduces the overall heat delivery. Additionally,

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it results in a shorter cooling diffusion route. Thus, sub-millisecond timescales are acted upon by gold NP photothermal modulation, which is essential for precisely timing the stimulation of neuronal activity.

Furthermore, off-target environmental heating can be reduced by precisely targeting NPs to the neurons and eliminating surplus particles through the circulation of interstitial fluids. These characteristics could be extremely crucial for preventing thermally sensitive tissues from being harmed and reducing toxicity from high foreign particle concentrations.

**Biosensors using gold nanoparticles:**

In recent times, effective gold nanoparticles have been utilized in biosensors to monitor and detect different nervous system functions [34, 35]. The purpose of several of these biosensors was to measure certain physiological characteristics of the vertebrate brain. Dopamine is a significant neurotransmitter that is impacted by a wide range of neurological and mental disorders. These sensors have shown to be extremely selective for dopamine.

Another indirect technique for measuring dopamine levels involves the use of streptavidin conjugates or ferrocene-capped gold nanoparticles [36]. The electrochemical biosensor of sandwich type underwent tests to evaluate its dynamic range, detection level, selectivity, interference, and reproducibility.

To measure the levels of glutamate, another neurotransmitter, a bimetallic combination of gold and platinum nanoparticle biosensors was created [37].

Numerous biosensors based on gold nanoparticles were developed especially to identify pathological alterations in brain tissue.

**Gold nanoparticles for drug delivery:**

To date, a range of neurological and psychiatric drugs, such as antipsychotics, antidepressants, antiepileptics, and chemotherapy for brain tumors, have been delivered by nanoparticles in vitro and in vivo in laboratory animals. Drugs for brain cancer have been the primary focus of gold nanoparticle research.

**2.3 Silver Nanomaterials**

Due to their ability to affect fibroblast, lung, and skin cytotoxicity, silver nanoparticles (NPs) have been widely used in a wide range of consumer products, including food packaging and antibacterial sprays [38]. This has led to worries about the potential negative effects of NPs on human health. [40][41][42]. Silver nanoparticles have been demonstrated to be able to penetrate the blood-brain barrier and accumulate in the brain, leading to ingestion and inhalation with regard to the central nervous system [43, 44].

Moreover, an increasing amount of data suggests that oral gastric or nasal delivery of silver nanoparticles might directly affect neuronal cytotoxicity in vitro and result in neurodegeneration in vivo [45]. As such, further investigation is warranted into how silver NPs affect other CNS cells and if they cause silver NP-induced neurotoxicity in them.

The immune cells called microglia exist in the brain and are in charge of coordinating defensive inflammatory responses to eliminate foreign invaders [46] as well as controlling brain growth, neuronal network upkeep, and injury healing. In addition, chronic neuronal death observed in neurodegenerative diseases like Parkinson's and Alzheimer's disease is linked to excessive microglial inflammation, which can cause collateral neuronal damage through the overproduction of pro-inflammatory factors like reactive oxygen species, nitric oxide, and the pro-apoptotic protein tumor necrosis factor (TNF)-α. [47] [48][49].

Similarly, it has been demonstrated that nanomaterials can cause alterations linked to neurodegenerative illnesses as well as inflammation in the brain. Thus, in order to comprehend silver NP-induced neurodegeneration and whether or not microglia exposed to silver NPs exacerbate this process, it is crucial to investigate the impact of silver NPs on microglial cell survival and inflammation.

Phagocytosing foreign material is one of the other roles played by microglia [50]. Microglia have been demonstrated to be capable of internalizing and breaking down nanoscale compounds [51]. They are therefore anticipated to be the primary cell type in charge of processing silver nanoparticles that penetrate the brain. The bioreactivity and biopersistence of silver NPs can therefore be more accurately anticipated by knowing how microglia absorb them and the processes by which they are processed.

The main cause of silver nanoparticle toxicity is interaction between released Ag+ ions and DNA, thiol protein groups, and cell membranes [52]. According to earlier research, sequestering released Ag+ ions through sulfiding processes may

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be able to reduce the toxicity of silver nanowires to some extent [53].

### 2.4 Quantum Dots

Small, nanoscale particles known as quantum dots have peculiar physical characteristics that give them the ability to shine in a variety of vivid hues. By chemically attaching themselves to other molecules and proteins on their surfaces, quantum dots can selectively interact with various cells. The application of quantum dots allows for the visualization and monitoring of molecular events within brain and other nervous system neurons.

**Why quantum dots?**

Quantum dots absorb light of specific wavelengths, and in return, they emit light and glow at different colors. The color that is glowing is not dependent on the material in which the quantum dots are designed but rather on the size and diameter of the quantum dot. Another point to be noted here is that they also photobleach (the intensity of their colors fades slowly over time). This property is of great advantage to 'track' how molecules are moving inside a cell over time, since the quantum dot tag continues to glow over longer periods.

**Quantum dots in neuroscience:**

Interestingly, long-duration chemical activities in the brain, ranging from seconds to minutes, may be visualized and tracked using quantum dots. Quantum dots are intended for use in studies and measurements conducted within the human brain, given our extensive understanding of the intricate and dense structure of the brain. As an illustration, the synaptic cleft—the area where two neurons connect—is minuscule and molecularly denser than the surrounding tissue. Here, quantum dots are employed.

Quantum dots are essential to the cell biology and labelling of brain cells. Chemical application is an option for the exterior coating on occasion. A few teams are looking at the application of quantum dots as objective measurements that reflect cellular activity as biomarkers for conditions such as Parkinson's disease. Developing novel diagnostics capable of early molecular alteration detection—before symptoms and neurological abnormalities manifest—is the primary goal. The ailment can now be detected more easily and the mechanism causing the issue can be stopped thanks to this breakthrough.

This important technology is also applied in human healthcare settings. The most recent research utilizing carbon quantum dots examined how they might be used to treat neurodegenerative conditions like Huntington's, Parkinson's, and Alzheimer's by disrupting the tangles of amyloid proteins, which are abnormal fibrous, extracellular, proteinaceous deposits found in organs and tissues and are linked to the advancement of these diseases.

Another development regarding quantum dots is that researchers are exploring the use of quantum dots for brain imaging.

The chemical makeup of quantum dots presents one of the main obstacles to their therapeutic application in humans. More specifically, there may be toxicity due to the heavy metal core included in quantum dots. The need to completely comprehend the extent to which quantum dots are eliminated from the body and brain as well as any potential modifications to internal cell signalling pathways brought on by the absorption of quantum dots are additional factors to take into account. However, quantum dots present a volatile chance to further the understanding of the brain by researchers.

## III. MAGNETIC NANOMATERIALS

### 3.1 Drug delivery to the brain by magnetic nanoparticles

The blood-brain barrier must be understood in order to comprehend how medications enter the brain.

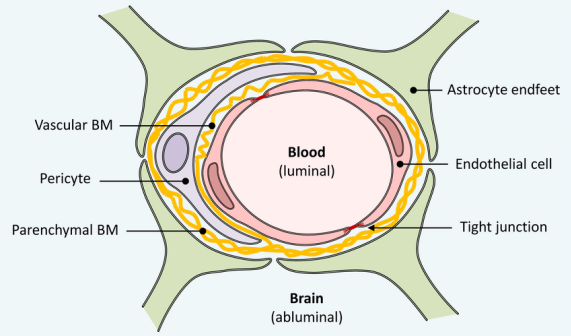


Fig. 3: outline of the blood brain barrier [54].

**What is a blood brain barrier?**

These blood arteries are what give the central nervous system (CNS) its vascularization. They have certain characteristics that enable them to precisely control the flow of ions, chemicals, and

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cells between the blood and the brain. Despite being made up of just one layer of endothelial cells connected by tight junctions, it is impervious to solutes found in blood plasma.

Drug delivery is difficult because only substances with molecular weights of 400–600 Da can pass across the blood–brain barrier, unless they are extremely hydrophobic [55]. Further issues develop as a result of the blood-brain barrier's brain endothelial cells' high expression of multidrug resistance proteins, which block the entry of several lipophilic substances in a size-independent way [57] [58]. As a result, the majority of medications that are currently used to treat brain disorders are either tiny and hydrophilic molecules that enter the brain through facilitated transport or highly lipophilic compounds, such as hypnotics or anaesthetics, which easily cross the blood-brain barrier through diffusion. As an illustration, selective reuptake inhibitors of noradrenalin and serotonin [57].

Exploration of the blood-brain barrier impermeability is critical to be solved.

Using large, hydrophilic molecule-encapsulated nanoparticles is one unique way to facilitate drug delivery into the brain. The targeted distribution of nanoparticles at the blood-brain barrier may be facilitated by specific antibodies that target the transferrin receptor [59], a carrier protein for transferrin that is essential for the import of iron into cells. Unless the particular antibodies are designed in a way to reduce their binding affinity for the transferrin receptor, there will be a limit to how far the nanoparticles can penetrate the brain endothelial cells before they cannot pass any further. Novel approaches are desperately needed to allow nanoparticles to cross the brain's endothelial cells and enter the brain. Applying an external magnetic field is a fantastic method to enable magnetic nanoparticles to pass through the blood-brain barrier [60] [61].

The iron oxide core of the magnetic nanoparticles is often made of ferrite ($Fe_2O_3$) or magnetite ($Fe_3O_4$). The primary feature that allows for motion in a magnetic field is this iron oxide core. Nowadays, magnetic nanoparticles are being used for many different purposes, such as MRI contrast agents [62], treating hyperthermia [63], cell labelling and separation [64], magnetoception (a transfection technique that concentrates particles containing vectors to target cells in the body), and magnetic targeting drug delivery. The magnetic nanoparticles can be polymer coated for these uses, or they can be enclosed in liposomes to create magneto liposomes [65].Magnetic nanoparticles are employed to apply external magnetic force for targeted uptake and transport via the blood-brain barrier. The primary importance is related to the structure and permeability constraints of the blood-brain barrier and its immediate environment, known as the neurovascular unit. This unit is made up of astrocytes that divide the basement membrane from the outer layer of pericytes, which are covered in a membrane.

There are two steps by which the drug molecules can be transported to the brain. They are:

First, the blood must be transported to the brain endothelium. Antibodies targeting molecules produced by brain endothelial cells, such as the transferrin receptor, are conjugated to the exterior surface of drug carriers enclosed in magnetic nanoparticles and drug molecules to effectively target the blood-brain barrier.

The second step involves the delivery of endothelium to the brain. When the medication builds up in the brain endothelium, an external magnetic force is applied to the cranial surface. This causes the magnetic nanoparticle to be subsequently drawn through the brain's endothelial cells and transported to the neurovascular unit, which includes the basal membrane. As a result, a drug carrier forms inside the brain, from which the drug molecules can be liberated to facilitate neuronal targeting [66].

## IV. CONCLUSION

In conclusion, the intersection of nanotechnology and neuroscience represents a paradigm shift in our approach to understanding and addressing complex neurological challenges. Throughout this review, we have witnessed the diverse applications of nanoparticles in neuroscience, ranging from enhanced imaging techniques that provide unprecedented insights into brain function to targeted drug delivery systems that hold promise for more effective and less invasive treatments of neurological disorders. This comprehensive review has delved into the transformative role of various nanoparticles, including carbon nanotubes, gold nanoparticles, graphene, quantum dots, and magnetic nanoparticles, in the dynamic landscape of nanoneuroscience. The amalgamation of interdisciplinary efforts has led to the creation of innovative nanotechnological solutions, creating a bridge between the physical and biological realms.

Looking forward, the future of nanoneuroscience holds tremendous potential for

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groundbreaking discoveries and therapeutic interventions. The dynamic interplay between nanotechnology and neuroscience is poised to revolutionize our understanding of the nervous system and redefine the landscape of neurological treatments. As we stand on the precipice of a new era in science and medicine, the amalgamation of nanotechnology and neuroscience offers a beacon of hope for improving the lives of individuals affected by neurological disorders. Through continued research, innovation, and collaboration, we can harness the power of the nanoscale to unlock the mysteries of the brain and pave the way for unprecedented advancements in neurological healthcare.

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