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Review

Scope of Nanomaterials in Treating Neurological Disorders

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Special Issue: Natural Products and Their Bioactive Compounds for Treatment of Neurodegenerative Brain Disorder

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Abstract

In the last decade, development in nanotechnology has been used intensively. By studying nanotechnology and nanomaterials, we can generate excellent responses in healthcare related to neurological disorders. It also includes easy diagnosis of diseases in their early stages, delivery of genes, and many more. Neurological disorders are one of the most sensitive topics. Therefore, nanomaterials promise to treat neurological disorders as they are highly

efficient. Nanomaterials will significantly expand our knowledge of how the disease originates in the nervous system so that we can diagnose the disease in its early stages. This review will describe nanomaterials as an overview of neurological disorders. This paper will present the utilization of nanomaterials in neurological disorders with the help of recent data and current research. This paper will also focus on the significant importance of nanomaterials and their toxicology in neurology. This review paper will deal with many of the different applications of nanomaterials in neurological studies and their impact on developing new types of treatment for neurological disorders. Lastly, this paper will discuss all the challenges nanomaterials face and all the promises that will help their future development in this vast field.

Keywords
Neurological disorders; nanomaterials; drug delivery

1. Introduction

Neurological disorders are diseases that include impairment in the nervous system. The nervous system coordinates all the movements and functions done by the body. The nervous system is the body's command center, instructing all other body systems. The nervous system comprises the brain, spinal cord, nerves, and muscles [1]. There are some symptoms of a neurological disorder, many of which are common in almost all neurological disorders. Some symptoms are:

1. Tremoring
2. Facing trouble speaking
3. Numbness
4. Memory loss or difficulty in learning
5. Instant changes in mood and behavior [2].

Neurological diseases in humans are increasing year to year and affecting billions of people in the world without consideration of any specific sex or age. Many neurological disorders are posing severe pressure on human health. Some disorders include Alzheimer's (AD), Parkinson's (PD), Schizophrenia, and many more. Many drugs can help achieve therapeutic effects, but there is one barrier in the brain that does not allow easy entry of any pathogens or toxins in the brain, called The Blood-Brain Barrier. We must pass the drugs through it, which is possible through nanomedicines [1]. Nanotechnology is a field that focuses on particles whose size is in the range of 0.1-100 nm, which mainly includes single atoms or single molecules. It helps in building systems that are related to biotechnology and can help in the treatment of neurological disorders. It also helps in manufacturing nanoparticles, which include nanomedicines. Nanomedicines are used in disease diagnosis and also in the treatment of diseases. They have unique properties such as high specific surface area, transformable shape and size, and tunable chemical reactivity. They have a colossal adsorption capacity to load various molecules like drugs, proteins, genes, and metal ions for drug delivery, targeting ability, or disease interventions [3]. Neurological disorders, including Alzheimer's, Parkinson's, and stroke, affect billions of people worldwide. The blood-brain barrier (BBB) prevents most drugs from freely entering and leaving the brain, making it challenging to achieve therapeutic effects [1]. Due to their small size, nanomaterials can help bypass or cross this barrier without

destroying the BBB. In addition, nanomaterials also exert great potential through their high surface area, high affinity, and drug delivery functions, effectively inhibiting the inflammatory response after nervous system trauma and promoting the repair of nervous system damage [4].

Many nanomedicines have been tested for treating neurological disorders, including PEGylated IFN beta-1a and PEGylated factor VIII. PEGylated IFN beta-1a is a long-acting interferon beta-1a for treating Multiple Sclerosis (MS). It slows the progression of MS and reduces the frequency of relapses [3]. PEGylated factor VIII is a blood-clotting protein used to treat Hemophilia A. It's not directly used in treating neurological disorders. Still, it plays a crucial role in preventing and managing bleeding in the brain, which can occur in severe cases of Hemophilia A [5].

While nanomedicines have shown promise in treating neurological disorders, they also face several limitations. The primary challenge is the Blood-Brain Barrier (BBB), which prevents many medications from entering the brain at adequate concentrations [2]. Even though nanomedicines can cross the BBB due to their small size, not all nanomedicines succeed. Another limitation is the potential for unintended adverse effects resulting from drug release from the carrier before it reaches the brain [5]. Furthermore, the brain structure's complexity and the disorders' irregular pathophysiology add to the difficulty of developing effective nanomedicines. Lastly, the presence of overlapping clinical symptoms at early stages, the limited biocompatibility of drugs, and poor targeting of traditional therapies make the diagnosis and treatment of neurological diseases more difficult [6]. Despite these challenges, research in this field is ongoing, and advancements are being made to overcome these obstacles.

2. Treatments and Therapies

The diagnosis of disorders from which the patient suffers and can be treated according to that. Some problems that can cause a few types of neurological disorders are mentioned below:

1. Muscular dystrophy or Huntington's can occur because of a fault in genes.
2. Spina bifida is caused by problems in the development of the nervous system.
3. Infection of blood can result in diseases like strokes.
4. Spinal cord and brain injuries can result in neurological disorders [7].

There are some ways in which we can treat those who are suffering from different types of neurological disorders, which include management of pain, medications, changes in lifestyle, therapies, etc. [6].

Some treatments that are used for treating neurological disorders are:

2.1 Brain Mapping

Brain mapping is a technique used by scientists to map the brain to remove a tumor, and this technique can remove the brain tumor by reducing the effect that it will have on significant parts of the brain. It is done without permanently damaging the patient's brain [5].

2.2 Gamma Knife

Gamma Knife is a machine that can deliver a single dose to the intended target without harming any other surrounding tissues. This treatment is excellent for disorders with abnormalities less than 3 cm that need to be treated instantly.

2.3 Cyber-Knife

Cyber-Knife is a form of radiosurgery with little advance in nature. In this technique, high doses of radiation are targeted, which helps destroy tumors inside the body [4].

2.4 Deep Brain Stimulation

It is a technique that was initially created to treat Parkinson's disease. It is a type of brain surgery, but it is a little more advanced than it is. After that, it is used to treat many neurological diseases, such as dystonia. In this disease, people suffer from tremors as well as depression. This technique helps send electrical signals to parts of the brain linked to various disorders, and it helps cure disorders [7].

2.5 Lumbar Puncture

Lumbar Puncture is a technique that was initialized for testing spinal fluid. It is usually done when a problem in the nervous system causes the symptoms in your body. A small needle is inserted into the spine after desensitizing the body.

2.6 Tensilon Test

The Tensilon Test is a type of test in which a medicine called Tensilon is injected into the body. After observing the patient's muscle movement, the neurologist can diagnose whether the patient has myasthenia gravis or not [5].

2.7 Electromyography

Electromyography is a technique that helps measure the electrical activity between your brain or spinal cord and a peripheral nerve. The peripheral nerve is found mainly in limbs and helps control muscles during movement and tests. With the help of this technique, neurologists can diagnose whether the patient has spinal cord disease or not [6].

2.8 Electroencephalogram

An electroencephalogram is a test whose primary purpose is to help diagnose brain conditions such as tumors and inflammations. It is done by applying electrodes to the patient's scalp. This test is a rapid process as it takes only one hour and can be done while asleep [7].

Using all these techniques is helpful to a certain extent, as all methods have huge risks, and only a little mistake can lead to life-threatening outcomes. So, to reduce these risks, nanomaterials were introduced, which can have a huge impact on nanotechnology as they can treat neurological disorders better. In the coming future, they promise efficient ways of treating neurological disorders. They will provide a better understanding of neurological disorders. There is a need to understand the mechanism of nanomaterials for now, and this will lead to a significant change in the field of neuroscience [8].

3. Nanomaterial for Neurodegenerative Disorder

Neurodegenerative disorders are in which proper functioning is not happening, and these diseases affect more than 1 billion people around the world. These disorders include many disorders, for example, Parkinson's disease, Alzheimer's disease, etc.. These diseases have long-term effects, or in the biological term, we can say that they are chronic diseases. These diseases cause significant harm to the patient and even to their families [9].

The main focus given to nanomaterials is that they help in drug delivery and early diagnosis as they can overcome the blood-brain barrier, which was not possible using traditional methods. There is a considerable need to consider disorders related to the central nervous system, and it is one of the most ignored disorders in this developing world. The massive growth in nanotechnology, neuroscience, and nanomaterials is helping a lot in this field. Still, there are some consequences that we need to address so this field can help more in curing disorders related to the nervous system. Stanley Prusiner put forward one hypothesis, which said that a prion can duplicate and become misfolded, which is harmful to cells [8]. Figure 1 shows different transport mechanisms through which nanoparticles can be transported to brain through blood.

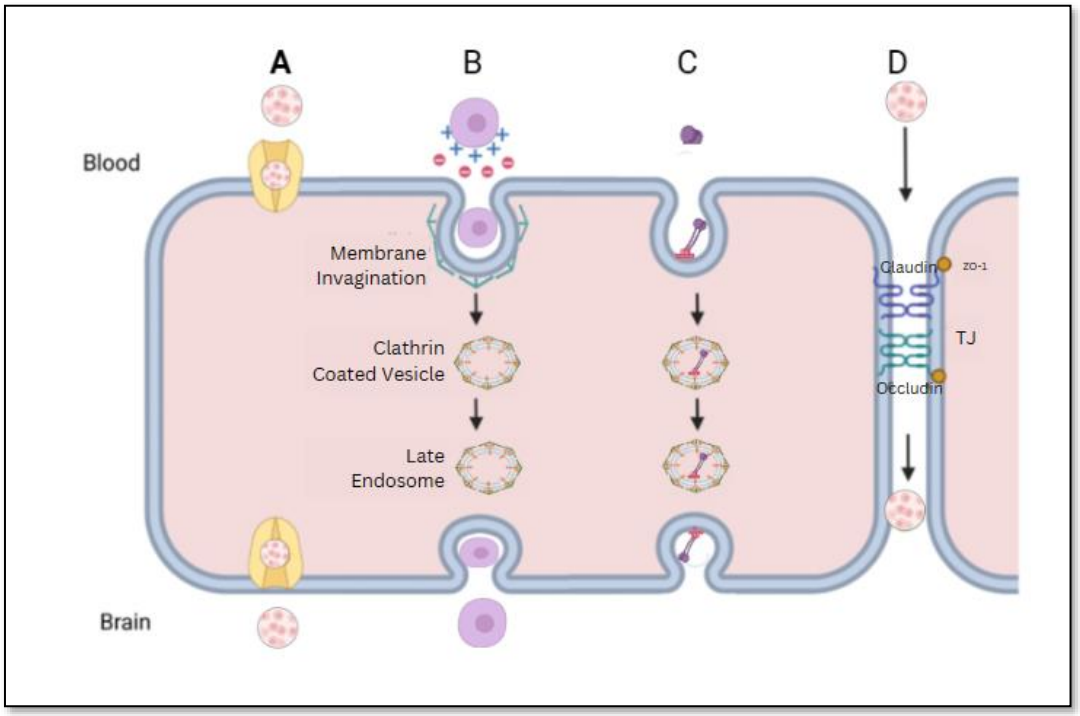

Figure 1 Representing different transport mechanisms of nanomedicine across the blood-brain barrier. (A) Carrier Mediated Transport (B) Adsorptive Mediated Transport (C) Receptor Mediated Transport (D) Paracellular Transport [7].

In the next section, the paper will describe some neurological disorders and discuss the use of nanotechnology in diseases such as Alzheimer's disease, Parkinson's disease, etc.. We will also discuss approaches used for their study.

3.1 Alzheimer's Disease

Alzheimer's disease predominantly affects the elderly population, manifesting in the later stages of life. It is characterized by memory deficits, often presenting as momentary forgetfulness, which can progress to dementia requiring lifelong management. It is noteworthy that the onset of Alzheimer's disease occurs several years before its diagnosis. Post-diagnosis, the average life expectancy ranges from 8 to 10 years [10].

In the last few decades, we have experienced a significant increase in patients with Alzheimer's disease, but with the advancement in technology, we have found its pathology. We also know that it is because of the misfolding of proteins because of the accumulation of amyloid-beta proteins in the patient's brain [11]. There are other concepts for Alzheimer's disease, like Neuroinflammation, in which brain nerves become reddened, swollen, and often painful, or we can say nerves of the brain get inflamed because of some injury or allergic reactions. Another concept is tauopathy, an accumulation of tau protein [12].

When the autopsy is done, we can see tangles of neurofibrillary and myriad amyloid plaques. These abrasions are the beginning of numerous genetic studies and various neurological disorders. The disentangling in the relationships between genotype and phenotype of Alzheimer's disease results in putting up one hypothesis that the accumulation of the amyloid-β protein in the cerebrum is one of the most common reasons for the development of this disease [13].

There are more concepts for Alzheimer's disease, but the most accepted one is amyloid cascade because this hypothesis has the most scientific results through experiments conducted in the lab.

When we reach the final stage of Alzheimer's disease, many of the cells in the cerebral hemispheres start burning, and by the end, the patients become completely unresponsive [14].

In Alzheimer's disorder, many accumulations occur due to molecular and cellular alteration, which results in increasing dysfunction of the neural system and can also lead to dementia. Because of this vague behavior, their pathology can't be adequately understood, as many processes co-occur [13].

There are lots of difficulties in moving from cellular advances to clinical therapies. With the development of technology, there are many hypotheses for genetic therapies. Still, many of them are under clinical practice. Now, there are no therapies that can change the effect of Alzheimer's disease till now [15]. Many treatments are available, but they cannot be delivered effectively. Some treatments are:

1. Clearance of aggregated Aβ
2. Devitalisation of neuroinflammatory activities
3. Modification of redox responses and oxidative stress
4. Stopping the formation of reactive oxygen species (ROS)
5. Cell-, tissue- and/or immune-based neuroregeneration
6. Prevention and modification of known biochemical responses [16].

Suppose we can improve drug delivery through the Blood-Brain Barrier and apply the therapies directly to injured areas. If we can diagnose the disease in the early stages, then the direct application of drugs can also work. To improve the delivery of drugs, in recent years, there has been significant growth in nanotechnology [15].

Amyloid self-aggregation is of small surface area and higher-order structure, making designing the drug very difficult as it is difficult to target. For the treatment of Alzheimer's disease, many nano-

based strategies are coming into play, such as liposomes, dendrimers, or other nano-carriers that are known for carrying drugs across the Blood-Brain Barrier [17].

One experiment showed that poly lactic-co-glycolic acid nanoparticles circulated by the process of PEGylation can apprehend oligomer Aβ in serum and solution. In the same way, SH SY5Y cells can be protected from amyloid toxicity when nanoparticles, like LVFFARK, can be functionalized with Aβ ligand [16].

It was suggested that the anionic lipids in the cell membranes could originate from nucleation sites for cardiolipin lipid nanoliposomes [17]. When they get developed, they mingle with oligomers and fibrils, which can be used to focus on Aβ. Later on, another experiment was conducted, and in that lipid ligand, nanoliposomes were compared to curcumin, which was assimilated into the nanoliposome, and it was shown that curcumins are more efficient in inhibiting the formation of the fibril [18].

During studying the data from hundreds of laboratories across the world, treatments that can help to inhibit or stop the progression of Alzheimer's disease during the early stage are:

1. β-secretase inhibitors
2. Notch-sparing y-secretase inhibitors or modulators
3. Aβ aggregation inhibitors
4. Tau-lowering agents
5. Anti-aggregation agents
6. Regulators of abnormal inflammatory mechanisms [19].

These treatments are complicated to achieve, and nanomaterials are used to cure them as they are the only ones that can go through the blood-brain barrier. A better drug delivery system is still on top for many researchers.

Presently, we are using five biomarkers to diagnose Alzheimer's disease. However, there is a need for more effective biomarkers as well as early detection of disease. If we can analyze it early, we can do early treatments for it and provide drug therapies to cure it at an early stage. Nanotechnology is the only one that can provide us with better machines that can detect Alzheimer's disease at the early stages [20].

The use of PET with anti-amyloid radiolabeled tracers is one of the most exciting types of research in imaging Alzheimer's disease. Patients with Alzheimer's disease get amyloid collected in the brain. This strategy of using amyloid as an imaging agent will increase the accuracy of the detection of diseases [21].

3.2 Parkinson's Disease

This disease is second after Alzheimer's disease in the number of people affected by it. According to statistics, after the age of 60, 1.5% of people get affected by Parkinson's disease. This disease is characterized by symptoms like difficulty maintaining body balance, stiffness, tremors, and ambulation [20].

Parkinson's disease causes complex and debilitating non-motor symptoms, and it also results in sleep disturbances as well as psychiatric disturbances. No test till now can diagnose Parkinson's disease. It entirely depends on understanding the pathology and clinical features of the disease. There is no exact explanation for the development of Parkinson's disease as there are many causes

for the disease, like misfolding of proteins, inflammation of neurons, production of ROS, exposure to toxins, and aging [18].

Pathologically, PD is defined by the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc), with subsequent loss of striatal dopaminergic projections to both the caudate and putamen. Symptoms arrive after a very long time from the start of the disease [16]. Dysfunctioning of the body can be an early symptom of it. Deterioration of motor neurons leads to neuronal damage, which can ultimately lead to the breakdown of the blood-brain barrier. Due to the breakdown of the Blood-Brain Barrier, leukocytes start entering the brain, further enhancing and perpetuating the neuroinflammatory cascade [19].

There is no specific cause for Parkinson's disorder as they are scattered. However, aging is one of the most recognized factors, typical for all neurodegenerative disorders. With the gradual progression of Parkinson's disease, there is an impairment in the mitochondrial coalition. Some cases of Parkinson's disease are hereditary, too, and in almost all, the patient's genetics and environmental factors lead to the development of Parkinson's disease [22].

Neuroinflammation is another factor that is considered an essential cause of this disease. In one study, it was put forward that only a few cases of Parkinson's disease are due to heredity. Advancements in neurobiology have given some essential data about this disorder [22].

Till now, we haven't discovered any specific cure for Parkinson's disease. We are just able to target its symptoms. One drug, Levodopa, can fill the lost dopamine in the brain by converting it to dopamine after crossing the Blood-Brain Barrier. These treatments can reduce its symptoms, but no drug can cure Parkinson's disease permanently till now [16].

In a few years, nanotechnology will do its best to find its cure and stop neurodegeneration. Nanomedicines will help a lot in this by assisting in drug delivery to the patient and can reduce many side effects of other drugs. The main aim of nanotechnology is to improve drug delivery, which can increase the success rate [22].

When nanotube arrays made up of titanium dioxide were assimilated with nanoparticles of gold, they were used to design an immunosensor for the spotting of α-SYN. This helps form efficacious antibody immobilization arrays and immobilized primary antibodies, which are highly stable. This study ensures an efficient way of detecting protein in diagnosing Parkinson's disease [23].

A variety of neurological disorders, including Parkinson's disease, are attributed to neuronal inflammation. Research indicates that modulating this neuronal inflammation could reduce mortality associated with neurodegenerative disorders. Specific phospholipids, such as phosphatidylglycerol, have been found to alleviate neuroinflammation significantly. VP025, a phospholipid derived from phosphatidylglycerol, interacts with antigen cells and manages inflammation by controlling cytokine production. This has proven to be highly effective in treating Parkinson's disease [15].

The administration of proteins with beneficial functions is a crucial approach in Parkinson's disease treatment, as it can address the affected cells within the Central Nervous System (CNS). In addition to the Blood-Brain Barrier, neuronal cell membranes present another obstacle within the CNS. However, both barriers can be traversed with the aid of nanoparticles. Polybutylcyanoacrylate is a nanoparticle that facilitates the simultaneous transport of multiple proteins [13].

3.3 Prion Disease

The most important thing that makes prion disease different from all is its transmissible nature, and it is a neurodegenerative disorder as well. It is a rare disease compared to others, as there are only around 1.2 million cases of prion disease yearly. Their unique nature has resulted in their best understanding at the molecular level of all neurodegenerative disorders. Prion's disease progresses very rapidly, and it is the most fatal one of all of them. Some leading causes of prion disease are an aggregation of PrPSc, spongiform degeneration of neurons, astrocytosis, and neuronal loss [24].

Transmissible spongiform encephalopathies (TSE) can occur in humans in three different forms: sporadic, familial, and acquired forms [25]. The sporadic form is the primary form among them as it causes about 85% of the total cases worldwide, and why it is the primary cause is still unknown. Genetic mutations can result in familial cases, and they cause around 10-15% of the total cases. The left cases happen because of exposure to surgical instruments or prion-contaminated brains [26].

One research conducted by Sousa et al. studied the polyelectrolyte multilayer-coated AuNPs and their in vivo distribution. The coating of these particles was developed with functional moieties that can be ensured as a potential nano-drug therapy for prion disease [27].

Researchers are doing their best to find a cure for the prion's disease, but its transmissible nature makes it challenging to find its treatment. As a result, there is no cure yet to be known. Recently, a new variant of prion disease has come up because of blood-contaminated products [28]. Scientists have constantly used nanomaterials and nanotechnology to find a cure as it is the most fatal neurodegenerative disorder, so we have to find its treatment as soon as possible. Nanomaterials are successfully passed through the blood-brain and stored in the brain [25].

Early detection of these diseases is critical to controlling their progression as they spread quickly. In the early stages, when they are applied, there are no symptoms until they spread to specific parts of the body and start degenerating neurons. The experiments should treat this disease before high damage to the central nervous system [29].

3.4 Lysosomal Storage Disorders

Lysosomal storage disorders (LSDs) are a group of inherited metabolic disorders that result from defects in lysosomal function. Lysosomes are sacs of enzymes within cells that digest large molecules and pass the fragments on to other parts of the cell for recycling. If one of these enzymes is defective due to a mutation, the large molecules accumulate within the cell, eventually killing it. Neurological symptoms or signs, including developmental delay, seizures, acroparesthesia, motor weakness, and extrapyramidal signs, manifest in most LSDs. The aberrant metabolic processes often lead to the cellular accumulation of incompletely metabolized macromolecules or their metabolic byproducts [29]. Most of the patients affected by LSD can experience a variety of neurological presentations, including, but not limited to, psychiatric complications, seizures, and/or developmental delays. The onset of symptoms can range from birth to adulthood, and disease severity can vary. Since there is significant overlap in the symptomatology of LSDs, diagnosis is typically confirmed through biochemical and molecular assays. There are currently no approved cures for any LSDs; however, in most cases, treatment of symptoms can lead to better outcomes and improvements in quality of life [30].

Nanotechnology has opened up many gates for new treatments for various neurobiological disorders. Many scientists have shown multiple treatments for different types of brain diseases,

such as brain tumor therapy and altered chemotherapy agents, and have modified existing tumor therapy using nanomaterials. The modified chimeric lysosomal enzymes (LysoEnz), small molecules, gene therapy exploring specific AAV serotypes, and nanoparticle-based therapies (Exo-LysoEnzy) are designed to overcome the BBB and tackle the neuropathogenesis processes prevalent in many LSDs [31].

In recent years, several approaches have been explored to find effective and successful therapies, including enzyme replacement therapy, substrate reduction therapy, pharmacological chaperones, hematopoietic stem cell transplantation, and gene therapy. In the case of gene therapy, genome editing technologies have opened new horizons to accelerate the development of novel treatment alternatives for LSD patients [30]. This narrative will provide an overview of current therapeutic strategies under development to permeate the BBB and address an unmet need to treat the progressive neurological manifestations prevalent in these inherited lysosomal disorders. For example, no treatments are currently approved for nearly two-thirds of all lysosomal diseases, and the existing drugs have a limited impact on the central nervous system. Furthermore, the costs of these therapies are incredibly high. Therefore, ongoing research is crucial to develop more effective and accessible treatments for LSDs [31].

3.5 Mental Health Disorder

Several mental health disorders, such as schizophrenia, bipolar disorders, Attention Deficit-Hyperactive Disorder (ADHD), depression, and anxiety disorders, are recognized. However, the precise pathology of these disorders remains elusive, and they are primarily identified through clinical symptoms. The absence of available biomarkers for these disorders contributes to the lack of definitive cures [16].

Brain imaging studies since the 1990s have helped in developing MRI that showed that there are structural and functional differences in different mental health disorders, but the exact pathology is not known [17]. The susceptibility to these mental disorders within a family is heightened due to genetic factors. We can devise more effective treatments for these disorders by pinpointing specific genetic sequences. Such therapies would surpass the efficacy of current drugs that merely address symptoms [13].

Some disease requires psychotropic treatments, and some require psychological therapies. Some diseases require long-term treatments, and others require short-term treatments. Drugs that are used to treat these orders have a vast amount of side effects and can affect our hearts, lungs, and kidneys. On the other hand, these drugs are beneficial for treating mental health disorders, so we need nanomedicines to treat disorders with fewer side effects. Nanomedicines can be targeted directly to the exact site where there is a problem in functionality [28].

For optimal management of these disorders, initiating treatment at the earliest is recommended. Early intervention can lead to short-term resolution of the disease. However, delayed treatment can result in the disorder becoming chronic, necessitating prolonged medication. Gradual alterations in brain functionality may occur over time, and these dysfunctions can cause significant bodily harm if left unchecked [18].

4. Types of Nanoscale Materials

The properties of nanomaterials give hope to researchers with a promising future in healthcare as they can cure a wide variety of diseases. The main reason for using nanomaterials is that they are efficient and cost-effective [22].

The size range of nanoparticles is 10-1000 nm. It can be constructed from various materials, such as lipids, polymers, metals, etc. They are helpful for many applications in nanotechnology as they can provide numerous advantages, such as chemotherapeutics [24].

Now, we will study some of the explanations of different nanoscale materials so the reader can better understand their properties, characteristics, overcoming, and advantages [30].

4.1 Liposomes

They are one of the most widely used nanoparticles used in nanotechnology. Liposomes are spherical, and their size ranges between 0.025 and 2.5 micrometers. They are created from cholesterol and phospholipids [16].

Liposomes excel in drug delivery due to their ability to easily permeate lipid bilayers and cell membranes. The transit of liposomes through these bilayers is contingent upon their size and lipid composition [31]. Liposomes are very useful in reducing the toxicity of drugs [22].

Liposomes pack hydrophilic drugs in an aqueous compartment and lipophilic drugs in liposome membrane for rapid delivery and efficiency. Liposomes are coated with biomaterial layers like cholesterol and polyvinylpyrrolidone polyacrylamide lipids to overcome macrophage attacks. This coating helps increase the time the drug acts by enhancing its circulation time and protecting it from an attack on the immune system [7]. It helps reduce the harmful effects on normal cells and increases the delivery of the drugs to the target point; as a result, it increases the drug efficacy level. These methods have not reached clinical trials till now. They are still in the research phase as they are found to be biocompatible. They have the excellent property of easily carrying therapeutic agents across the Blood-Brain Barrier [9].

Liposomes conjugated with cardiolipin-carrying curcumin and Nerve Growth Factor get evaluated for therapeutic aspects in the presence of β-amyloid peptide in Wister rats. The surface of the conjugated liposome was covered with agglutinin. This showed decreased phosphorylated expression [4].

In their experiments, Kuo and colleagues synthesized liposomes composed of cardiolipin and phosphatidic acid. These liposomes are designed to target the hyperphosphorylated state of the tau protein. The transport of these liposomes across the Blood-Brain Barrier is enabled by the Trans-activator of transcription peptide [13]. The liposome was packed with nerve growth factor, rosmarinic acid, curcumin, quercetin, and phospholipids. Hence, liposomes are an efficient delivery agent across the Blood-Brain Barrier, and they will protect nerve cells against amyloid plaques once they pass clinical trials [11].

4.2 Micelles

Micelles are particles that are present in colloidal dimensions. Micelles are dynamic structures that can break and form again in no time (milliseconds to seconds). Their size ranges from 1 to 1000

nanometers. Their formation and decomposition depend on various factors such as temperature and the composition of Micelle [14].

Micelles are similar in structure to liposomes as micelles protect substances from degradation by preventing them from getting exposed to harmful physiological conditions. They are usually composed of two parts: the inner part is hydrophobic, and the outer part is hydrophilic. The hydrophilic is the most important, which helps the micelles to go through the Blood-Brain Barrier [12].

Micelle formation is initiated by the amphiphilic universe, which usually blocks copolymers with hydrophobic and hydrophilic groups [18]. Amphiphilic universes are aggregated at critical micelle concentrations and form micelles with hydrophilic corona and hydrophobic core. Hydrophobic blocks can be modified to form a better alternative in various ways for drug molecule formulations with high drug-carrying capacity and excellent compatibility [22].

Polymeric micelles can increase the bioavailability of drug molecules by protecting the loaded drug, prolonging the residence time of the carried drug, releasing the drug at the targeted sites, increasing the residence time of the drug, and hindering the efflux pump. These advantages of polymeric micelles can be helpful in Central Nervous System drug delivery [32].

The studies conducted by Kabanov and his colleagues showed that delivery of haloperidol to the brain was enhanced with the help of polymeric micelle formulations formed by Pluronic copolymers with conjugations of antibodies against insulation.

Lu et al. formulated a polymeric micelle with resveratrol, promising protection from Aβ peptide toxicity. The resveratrol's protecting feature was acquired without long-term toxicity [26].

4.3 Carbon Nanotubes

They are cylinder-shaped nanoparticles that are made of graphene sheets. They are developing as the platform for applications in biology because of their thermal, structural, and electronic properties. They are exciting due to their mechanical, intrinsic, and physiochemical properties. They have high flexibility with all these properties, which is incredible. They have a size range from 1 to numerous nanometers and can reach a size of one millimeter [32].

Carbon Nanotubes are classified as single-walled carbon nanotubes and multi-walled carbon nanotubes. This classification is dependent on inner layers viewed as rolled-up graphene sheets. The biological applications of carbon nanotubes are restricted because of their hydrophobic surface, which is vulnerable to harmful depositions upon subjection to aqueous solutions [33]. That is why functionalizations are urgently required for Carbon Nanotubes to address this problem in biomedical applications. Chemical functionalization is an excellent approach to increasing dispersibility and reducing toxicity, for it has fewer side effects than any other approach [15].

After modification of the surface of Carbon Nanotubes with the molecules of drug and target molecules, the acquired modified Carbon Nanotubes are significantly less toxic and immunogenic. They are capable of high drug payload, and they are perfect for targeting drugs to a specific position. Carbon Nanotubes can be used in various scientific fields like biosensing, bioimaging, nanoelectronics, and drug delivery [18].

Carbon nanotubes have a meager weight and a large surface area. They can be developed from drug carriers, targeting moieties, and contrast agents. They have arrived as a promising option for tracking neurological disease therapies [21]. The application of carbon nanotubes is studied

worldwide, and there is significant progress in this research on their therapeutic and diagnostic applications. Scientists have achieved considerable progress to date [34]. Carbon nanotubes can significantly regulate the behavior of the nervous system, and they have made significant contributions to the field of neuropathological disorders.

4.4 Gold Nanoparticles

They are growing widely as they are expected to be a source of good treatment and can be used as a helpful carrier for drugs for mental health disorders. Gold nanoparticles are unstable, so stabilizing ligands are used to improve their aqueous colloidal stability [25].

This nature of gold nanoparticles can allow them to be coated with various surface ligands. Due to the presence of the plasmon band, gold nanoparticles are red. On the other hand, if we add gold nanoparticles, the solution turns blue to aggregate scattering and surface plasmons [35].

Gold Nanoparticles have some antioxidant and anti-inflammatory properties that can be used to treat neurological disorders. The toxicity of gold nanoparticles is the primary concern, as it is difficult to study both the toxic and therapeutic nature of nanoparticles together. Studies showed that daily use of gold nanoparticles for 7 days continuously can cause liver damage [31].

Muller et al. continuously conducted experiments on gold nanoparticles every 24 or 48 hours for 21 days and checked for any damage to the liver. Still, the experiments showed there was no toxicity in 48 hours. Therefore, it emerged as a safe and efficient treatment for neurological disorders with gold nanoparticles [24]. Some reports also show different reports on the toxic nature of gold nanoparticles that can impact the uptake of nanoparticles, which mainly include the size of particles, surface charge, the permeability of blood vessels, and phagocytosis with the help of the mononuclear phagocytic system [20].

The size of particles plays a very significant role in nanoparticle distribution. The liver can take up nanoparticles at a very rapid speed in the liver, bone marrow, and spleen. The particles of tiny size are released by renal excretion, and the particles with sizes ranging from 150-300 nm are mainly constituted in the spleen and liver. The particles between 30-150 nm sizes are present in the heart, stomach, bone marrow, and kidney [36]. The enhanced uptake in the spleen, liver, and bone marrow is done by mononuclear phagocytic system cells present in the tissues. They are accountable for clearing particulates and macromolecules circulating in the blood. The general relation between elimination and biodistribution and the size can vary, depending on the surface characteristics of nanoparticles [28].

4.5 Carbon Quantum Dots

Carbon dots are carbon-based fluorescent nanomaterials smaller than 10 nm and can be classified into carbonized polymer dots, carbon nitride dots, carbon quantum dots, and graphene quantum dots [33].

Quantum dots, nanocrystals ranging in size from 2 to 10 nm, consist of a metallic core enveloped by an outer shell. Their unique attribute is their ability to emit various colors, which is determined by the size of the crystals. They exhibit diverse electronic properties due to their distinct electronic band structures [37]. They are of great importance in infrared imaging and X-rays. There is a lot of stress because of their compatibility with biomedical applications. The significant risk posed by them

is their formation and disposal. One way of reducing their toxic nature is by coating them, which will make them biocompatible [33].

The surface of Carbon Quantum Dots has been functionalized with carboxyl groups and amine to adjoin the various types of CNS drugs to act as carriers of drugs for their delivery at target positions. Kuang and his colleagues conducted one experiment in which they fabricated a nanocomposite of CURFe_3O_4@CDs [38]. The drug delivery system of curcumin showed kinship towards inhibited extracellular Aβ fibrillation and Aβ. The nanocarriers inhibited the neurotoxicity in PC12 cells. Therefore, it restores the damaged nerve and can be one of the most efficient treatments for Alzheimer's [27].

4.6 Dendrimers

They are an upcoming type of nanomaterial and were formed in 1980. They are 3-dimensional structures, comprise many branches like a tree, and are symmetrical around their ABn core. They have a handy ability to carry many different materials, which allows them to perform other functions simultaneously [32].

There is a vast use of dendrimers in vitro as a transfection agent with a high-efficiency rate, i.e., up to 75% success rate, and has very few side effects. The most important thing to note about dendrimers is that they are less toxic. They also gave some successful results in treating brain injury. Dendrimers are better drug delivery agents than many other nanomaterials as they can easily cross through the blood-brain barrier [33].

Dendrimers are nanosized macromolecules characterized by hyper-branched globular structures and widely used for drug delivery. Dendrimers have well-defined chemical structures [32]. The specific dendrimer structures provide flexibility to carry therapeutic drugs by covalent conjugation or electrostatic adsorption. Dendrimers comprise a central core, and they have building units attached to the core repeatedly, and on the surface, functional groups are attached. Therefore, core, functional groups, and building blocks are the three components of dendrimers on which we can determine the physicochemical and biological characteristics of dendrimers [25]. Two synthetic methods can be used to prepare dendrimers: convergent and divergent. In the concurrent approach, compounds can be constructed to the core from the periphery, and in the divergent approach, dendrimers are built to the core from the shell [39].

There may be positive, negative, and neutral charges on surface groups, essential in examining suitable dendrimers as drug delivery carriers [37]. Destabilizing anionic cell membranes and even cell lysis when dendrimers are terminated with positively charged functional groups can lead to low biocompatibility. On the other hand, neutral or anionic-charged dendrimers exhibit comparatively less hemolysis [40].

5. Use of Nanomaterials in Neuroscience

Now that we have studied nanotechnology and neuroscience let's merge what we have learned till now. Nanotechnology can be used in imaging techniques, as drug delivery agents, and many more. Nanotechnology ensures massive development in the field of neuroscience. They offer potential benefits in passing through biological barriers [38]. This technique can also help detect the movement of tiny particles within the body and the various pathological processes that occur in the central nervous system. So, let's discuss the technologies that have helped us to a great extent [41].

5.1 Imaging

It is tough to find new treatments for the CNS as it is one of the most sensitive parts of the brain, and even the slightest of side effects can affect the body. But with recent advances in nanotechnology, it has become easy for us to see both the normal functioning and dysfunctioning of the brain [42]. The most significant advancement with this is that we can see how the brain responds to different drugs to prepare the medications in the way best suited to the brain [14].

MRI (Magnetic Resonance Imaging) is mainly used for the early detection of diseases using various agents such as small molecule paramagnetic contrast agents, ferromagnetic particles, superparamagnetic iron oxide nanoparticles (SPION), and different nanostructures. Other agents are widely used for MRI, too. They are perfluorocarbon, magnetic iron oxides (MIOs), cerium oxide, platinum nanoparticles, and QDs [41]. These agents detect many diseases, such as Alzheimer's disease, cerebral malaria, brain cancer, etc. [42].

Superparamagnetic reduces the magnetic resonance intensity of the signal of the place where they are delivered. Hence, those regions become darker in the image. Usually, these agents are used in the biomedical industry, such as targeting molecules of AD amyloid plaques [32].

Some other nano compounds are Quantum dots that have fewer limitations in imaging. They are fantastic nano vectors as they quickly go through the blood-brain barrier and deliver drugs within the brain. They are among the best particles for brain imaging in Alzheimer's disease [28].

5.2 Diagnosis

Nanomaterials are better targeting agents than traditional methods of targeting the affected site. Nanomaterials can detect disease more sensitively and can simultaneously detect many diseases [41]. Some prominent applications of nanomaterials are:

1. Detect tumours at early stages
2. Demyelinating conditions
3. Help search for specific molecules that are present in trace amounts.
4. Nanoparticles help in the treatment of neurodegenerative disorders at the early stages [20].

Kim and the collaborator of this experiment developed a chitosan-conjugated pluronic-based nano-carrier and focused on peptides. The results were excellent as they showed that Pluronic-based nano-carriers were associated with peptides and chitosans, and it is one of the most efficient ways of accumulation in brain tissue [18].

Some scientists have proved this by doing various experiments. For example, Mourtas et al. formulated nanoliposomes of two types and functionalized them with derivatives of curcumin. Nanoliposomes are very useful to target Alzheimer's disease pathogenic markers and are even used for detection and treatment purposes [19].

5.3 Drug Delivery Systems

This is one of the most challenging steps in neurology, as any slight mistake in drug delivery can cause considerable side effects. We need to formulate the best drug delivery as we are delivering it to the most sensitive part of the human body. We should avoid the healthy organs and only work on the affected sites [43]. Nanotechnology is the best way to advance in neuroscience as it can

revolutionize how we treat neurodegenerative disorders by interacting with the affected organs and delivering the drugs to treat them by decreasing the side effects [30].

The nanomaterials' structure should be designed so that they get delivered directly to the site, so they need a lower dose and ultimately have fewer side effects [44].

Drug distribution depends mainly on the size of the particles, which poses a severe problem to researchers, i.e., size selection as we need a high degree of precision and a little bit of mistake can lead to not delivering drugs at a specific location because of the presence of the Blood-Brain Barrier [34]. It protects the brain from toxic substances and does not allow nanoparticles if they do not have the exact amount required to pass through the Blood-Brain Barrier, making the treatment of disorders difficult [41].

Many treatments have been applied and tried to cross the BBB, but no attempt was booming compared to nanotechnology's success rate. Scientists have tried to inject the drugs directly and chemotherapy, but all of these methods failed. Nanotechnology shows a promising future in the delivery of drugs and diagnosis [45].

One prominent advantage of using polymeric nanoparticles is that they have a high success rate when used as drug carriers, as they can cross through The Blood-Brain Barrier and control the release of biomolecules across it. Some research took place that was:

Mathew and his colleague targeted nanoparticles, which enhanced the uptake by the neuronal cells, and this helped treat Alzheimer’s disease [17].

Songjiang and Lixiang researched whether nano-carriers loaded with amyloid-beta could penetrate the blood-brain barrier. This was very helpful in developing drug-delivery particles [15].

The most recent research done by Fornaguera and his colleagues reported that poly lactic-co-glycolic acid (PLGA) nanoparticles can go through the Blood-Brain Barrier, which is very helpful in delivering drugs directly to the CNS [24].

Dakwar and his co-workers tested bolaamphiphilic cationic vesicles. They tried their ability to pass through the Blood-Brain Barrier by conjugating protein-bovine serum with fluorescein isothiocyanate. These systems were capable of delivering across it [46].

5.4 Therapy

Advancements in science have unfolded many new possibilities for scientific discovery. In short, nanotechnology has helped neurologists target specific organs to treat diseases. Many ways have been found to treat brain-related diseases, such as brain tumors, chemotherapy, etc. [47]. The way to treat these diseases has been improved over the years with the progress in the nanotechnology sector. For example, lipid nanocapsules can treat cancer, Alzheimer’s, and neurological disorders [48].

Different neurological diseases can be treated with more efficacy with nanoscale carriers, by targeting therapeutic agents at specific locations, therefore reducing harmful effects on healthy organs [33]. Nanotechnology has paved the way for innovative treatments for various neurobiological disorders. Numerous researchers have demonstrated diverse treatment methods for various brain diseases, including brain tumor therapy and modified chemotherapy agents. Existing tumor therapies have also been enhanced through nanomaterials [49].

Abdel-Hamid and Nasr explained some examples of one of these methods by using nanocapsules made up of lipids, as they are highly stable compared to other nano-vectors, which will increase the

efficiency of transporting therapeutic molecules to be delivered [50]. These capsules can be used to treat cancer, Alzheimer's disease, and various dermatological conditions. The therapies that need development are those that boost endogenous repair and those for cell replacement [51].

Wasiak and his colleagues synthesized two generations of cationic phosphorus-containing dendrimers and used them to assess the amyloid fibril formation. Liao and his co-workers evaluated the performance of AuNPs to hinder the fibrilization of amyloid-beta and mitigate neurotoxicity and fibril dissociation [36]. Agulla and his colleagues found that the HSP72 protein is a suitable biomarker for the peri-infarct region [52]. They produced anti-HSP72 vectorized stealth immunoliposomes that contain imaging probes to make them traceable by fluorescence and MRI. This was used to summarize a therapeutic agent for cerebral ischemia treatment. Cerebral ischemia in an animal model was found to have 80% of vectorized liposomes situated on the ischemic region's periphery, and animals treated with citicoline encapsulated onto these liposomes presented lesion volumes up to 30% smaller than animals treated with non-encapsulated drugs [53].

One of the most common types of brain tumors is glioma, which accounts for almost 33% of the total cases of tumors. Typically, gliomas originate in glial cells, oligodendrocytes, and astrocytes. Yi and co-workers constructed a brain model of rats by injecting C6 glioma cells into it at the right caudate nuclei of rats [54]. Magnetic nano-iron was injected into the tumors of tumour-bearing rats with fixed doses. A total of 80 rats underwent C6 glioma cell implantation, and 70 of them showed decreased appetite and mobility [55]. There was no significant difference in the survival time of different dose groups of tumor-bearing rats. Still, tumour size showed a significant decrease with magnetic nano-iron hyperthermia therapy at the two effective doses, 2.5 and 5 mg [56]. Figure 2 shows various possible applications or advantages of nanomaterials in the case of neurological disorders

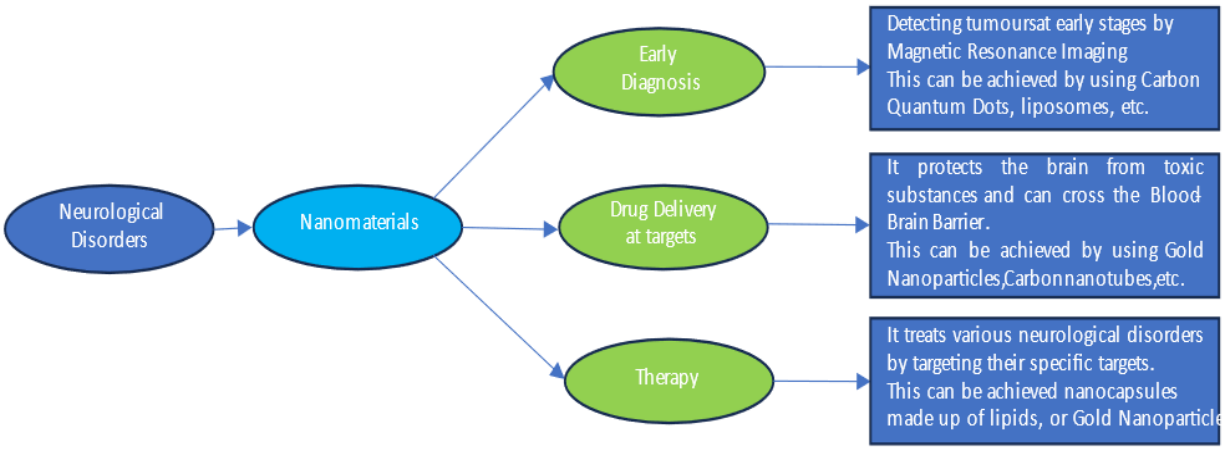

Figure 2 Representing advantages of nanomaterials in neurological disorders.

Lammers and his colleagues experimented with poly (butyl cyanoacrylate) - based microbubbles, which carry ultrasmall superparamagnetic iron oxide nanoparticles within their shell and can be used to monitor the Blood-Brain Barrier permeation [57]. Such theranostic methods are handy for monitoring drug delivery across the Blood-Brain Barrier and enabling efficient treatment of Central Nervous System disorders [58].

6. Toxicity

It is essential to focus on the effects of nanomaterials on animals, as they are very dangerous to use. They can affect various organs in the animal's body if there is some mistake in targeting them to the specific organ. Research shows that many are safe to use but have a toxic nature, so we have to understand the toxicology of different materials before using them. As we apply nanomaterials to one of the most scientific areas of the human body, i.e., the nervous system, we cannot apply them without checking them properly in the laboratories [59-62].

Skalska and colleagues studied the effects of citrate-stabilized silver nanoparticles on rats when they were exposed to it for a long time on synapse ultrastructure and specific proteins [63]. Their experiment showed that exposure of adult rats to both forms of silver leads to changes in the synapse. Silver nanoparticles cause more synaptic degeneration. In these studies, we can observe the impairment of the nerves' functioning; in the hippocampus case, we can expect a cognitive process [64-67]. Liu and his colleagues recently showed that nanoparticles of silver, which are used in consumer products for their well-known antibacterial activity, induce toxicity in neurons and rat embryonic stem cells, indicating that long-term exposure can cause a risk of neurotoxic effects [68].

The experiments conducted by Wang and co-workers [69] researched neurotoxicity and various side effects of the low-dose intranasal exposure of nano and submicron-sized Fe_2O_3 particles [70] in mice. Their experiments showed that oxidative stress was induced by the two different sizes of particles [71]. These Fe_2O_3 particles induce higher alterations and offer a more significant dose-effect response. This shows intranasal exposure to nanoparticles of Fe_2O_3 can cause highly severe oxidative stress and more nerve cell damage than the larger particles [72].

7. Challenges

Biological systems, particularly the nervous system, are inherently complex and require advanced technologies for their treatment. These systems are engineered to target distinct cell types with high precision, thereby providing more suitable solutions. However, due to their intricate nature, their applications are currently limited and require further development for efficient utilization [73, 74].

Nanotechnology has the potential to contribute to the field of neuroscience as it is a novel approach to treating neurodegenerative disorders, which has not been clinically possible till now [75]. The physiology of the brain is very complex. It has restricted anatomical access because the brain is a sensitive area, and any mistake can lead to paralysis or even death, so we cannot use nanomaterials until and unless we make them fit for use [76].

When delivered or injected into the bloodstream, the drug has to reach the Blood-Brain Barrier, which is a protective barrier and does not allow all the materials to go through the brain [77]. On the way, the drug has to produce minimal side effects, and when it reaches the Blood-Brain Barrier, it has to go through it with almost minimal damage to it. After passing through it, it has to target its specific cells [78]. This complete process has to be followed for the nano-drug to function in the body. If, in some cases, the drug doesn't reach the intended cell or not in the required quantity or without causing negligible damage, then this can result in a waste of all the efforts, and doing all these, a single drug is not enough [79].

8. Conclusion

As discussed in this review, nanoparticles can be considered one of the significant drugs for treating neurological disorders, with better implementation and diagnosis of the diseases. It can help prevent various diseases by early diagnosis of diseases. Nanotechnology can change the health sector completely with the impact on therapeutic knowledge. This technology guarantees new treatments for diseases and can help determine therapies for those diseases that don't have any treatments for now. They are a very controlled drug-delivery system, and with a few improvements, they can be considered one of the best treatments for almost all diseases.

Nanotechnology is the only way to diagnose neurodegenerative disorders at the earliest, so it is better to focus on improving nanotechnology. This technology helps regenerate neurons, provides protection to neurons, and helps deliver drugs to targeted cells.

The future is here: With advancements in nanomaterials, nanoscience, neurology, and nanotechnology, we can treat diseases most efficiently. We should use this technology to the fullest for the betterment of humanity. Only these materials can pass through the Blood-Brain Barrier, so we should understand the toxicity of these materials. The most challenging task for using nanotechnology will be their design and progress, as they are tiny in size, so it is not easy to work on them, and even minor mistakes can make considerable changes in the human body. For example, if we target toxic drugs to treat Alzheimer's disease. The generality of nanotechnology in neurobiology has been so impactful in recent years, resulting in organized research efforts. This is no longer a novelty; it is a critically implied component. The Bain Research Through Advancing Innovative Neurotechnology (BRAIN) initiative was launched at the Whitehouse in 2013, aimed at how scientists will study the interface of the brain. Neurotechnology has emerged from this initiative with various approaches to nanoengineering methods.

Author Contributions

AR planned the overall content of the paper. AG performed all the literature surveys for this work. AR, AG, KK, SR, SM, SP wrote the manuscript. All the authors approved the final version.

Competing Interests

The authors have declared that no competing interests exist.

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