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REVIEW PAPER

Polymer-Based Electrochemical Sensors for the Diagnosis of Neurodegenerative Diseases

Qitong Zhang[1] · Guangran Zhao[2] · Shilin Wang[2] · Yuxuan Song[1] · Yuanzheng Sun[2]

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Abstract

Acute and chronic neurodegenerative diseases (NDs), including multiple sclerosis (MS), Alzheimer's disease (AD), and Parkinson's disease (PD), are characterized by neurodegeneration, which is the gradual malfunction and damage of neurons and axons in the central nervous system. Improved clinical diagnostic workups and the development and tracking of successful disease-modifying treatments are made possible by detecting appropriate neurodegenerative disease (ND) biomarkers. Important biomarkers, such as Tau proteins, amyloid-β, and α-synucleins, are essential for precise identification but are often evaluated using time-consuming, expensive, and traditional techniques like polymerase chain reaction (PCR) and enzyme-linked immunosorbent assay (ELISA). Due to its exceptional selectivity and sensitivity, electrochemical biosensing has become a popular, low-cost substitute for more conventional diagnostic methods. Nanoparticles in biosensors are particularly noteworthy because they improve electron transport and aid in immobilizing biorecognition components. Conducting polymers have shown great potential in the field of electrochemical sensing. Conducting polymers have shown great potential in electrochemical sensing. Additionally, research has shown that polypyrrole, polyaniline, poly(3,4-ethylenedioxythiophene), and poly(thiophene) are often regarded as among the best conducting polymers for fabricating electrochemical sensors. Moreover, a hydrogel biosensor allows for the detection of many parameters simultaneously with real-time monitoring, allowing for more accurate and timely tracking of multiple indicators of a patient. Hydrogel nano(bio)composite sensors that use electrochemical transduction methods to detect analytes are also available. Hydrogel-based polymer sensors for early-stage neurodegenerative diagnosis are examined in this review in a novel way. Afterward, we reviewed electrochemical sensors developed for detecting biomarkers related to diseases, including multiple sclerosis, Alzheimer's, Parkinson's, and Huntington's. There have also been developments devised to enhance efficacy of electrochemical diagnostic tools to address their limitations. In this respect, we have also reviewed many polymers used in electrochemical diagnosis of neurological disorders. Finally, we have also evaluated the limits and prospects of clinical trials involving these electrochemical means of diagnoses.

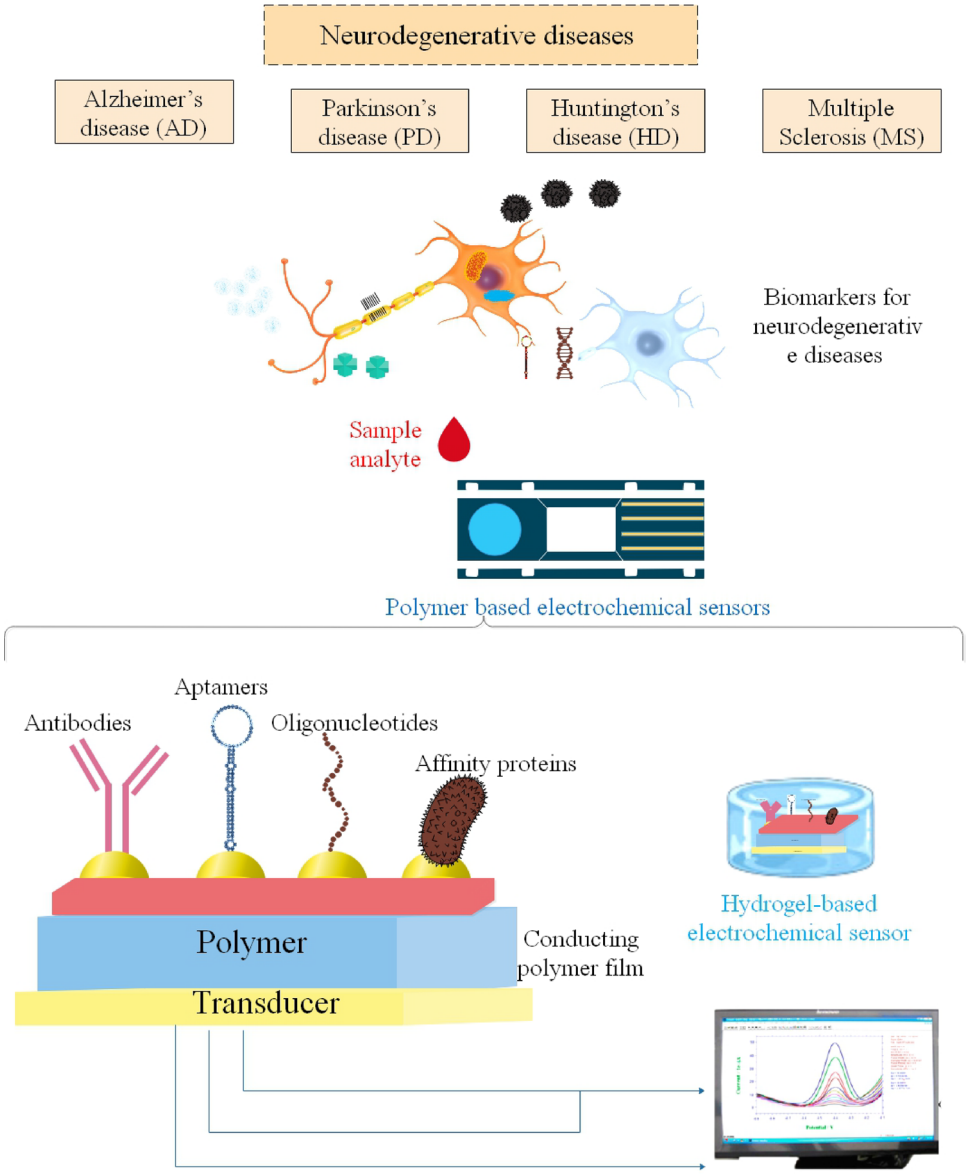
Qitong Zhang and Guangran Zhao are co-first authors.

✉ Yuanzheng Sun
yuanzhengsun24@gmail.com

[1] Heilongjiang University of Traditional Chinese Medicine, Harbin 150040, Heilongjiang, China

[2] The Second Department of Acupuncture and Moxibustion, The Second Affiliated Hospital of Heilongjiang University of Traditional Chinese Medicine, Harbin 150000, Heilongjiang, China

Graphical Abstract



Keywords Electrochemical sensors · Hydrogel nanocomposites · Conducting polymer sensors · Neurodegenerative diseases · Point-of-care diagnostics

Introduction

In neurodegenerative diseases, the nervous system transiently deteriorates. Several diseases fall within this category, including Alzheimer's disease, Parkinson's disease, and prion diseases. There is currently no known cure for these diseases. The only therapeutic option is symptomatic relief. Additionally, they are progressive and often involve fibril entanglement or abnormal protein aggregation, creating bigger protein aggregates called plaques. These proteins are first seen in healthy brains' central nervous system (CNS). Some play crucial roles in the biological system, such as regulating membrane integrity, transporting vesicles, and keeping cells running smoothly (Li and Kerman 2021). Diagnosing NDs is challenging due to the long diagnosis process and the fact that the first therapy always lowers treatment results (Gómez-Río et al. 2016; Domínguez-Fernández et al. 2023; Akram et al. 2024). Individual assessment procedures and signs often lack selectivity, which is commonly encountered in many diagnoses of NDs. Consequently, accurate results

are sometimes impossible without repeated diagnoses, which may increase the associated cost (Thakur et al. 2025).

Many techniques have been employed to detect biomarkers of neurological disorders. These include enzyme-linked immunosorbent assays (ELISA), in vivo positron emission tomography (PET), mass spectrometry, high-performance liquid chromatography (HPLC), surface plasmon resonance (SPR), field effect transistors (FET), and others. Applying these techniques requires the analysis of cerebrospinal fluid (CSF), an intrusive procedure, restricting its use in point-of-care (POC) biomarker analysis. In addition, these methods are also costly and complicated (Adampourezare et al. 2023). For example, contact lenses and other chip-based sensors may be POC devices for quick and affordable early detection at home. A neuroimaging or ocular examination in the hospital is the next step for the patient's subsequent diagnosis and treatment if the sensors identify changes in the concentrations of the proteins that act as biomarkers for NDs. The frequency of hospital visits and the turnaround time for diagnostics may be considerably decreased in this manner, in addition to the financial burdens that patients and society bear. More significantly, the combination of POC and neuroimaging diagnostics may increase the speed and affordability of diagnosing NDs (Song et al. 2020).

The subject of biosensors has recently seen the development of several novel components, including aptamers, molecularly imprinted polymers (MIPs), and nanomaterials. Since nanoparticles (NPs) have a high surface-to-volume ratio that aids in obtaining better sensitivity and efficiency, nanotechnology has greatly benefited the biosensor industry. Electrochemical detection, such as amperometric, voltammetric, and impedimetric detection, has been used in one form or another in the majority of biosensors created to date. Additionally, half of the biosensor manufacturing is covered by catalytic biosensors, which employ enzymes of some type, while the other half is represented by affinity biosensors, which use antibodies (Abs). Affinity biosensors are mostly utilized for DNA detection in processes (hybridization) and food product quality and safety monitoring. The reference, counter, and working electrodes make up the electrochemical biosensors. A signal that aids in the detection process is produced using the electrons produced or consumed during the catalysis of enzymes (Song et al. 2020).

One potential way to diagnose NDs is via nanobiosensors. Even at low concentrations, biomarkers may be detected using very sensitive nanobiosensors. Atto- (a, 10^{-18}), femto- (f, 10^{-15}), pico (p, 10^{-12}), and even zepto-(z, 10^{-21}) scales have all been attained via nanosensor detection. Additionally, electrochemiluminescence and fluorescence detection have achieved sensitivities down to picomolar (pM, 10^{-12} M) concentrations (Swierczewska et al. 2012). These capabilities significantly improve early diagnosis. Nanomaterials, including quantum dots (QDs), carbon nanotubes (CNTs), and metal NPs, were often incorporated in constructing nanobiosensors. Because of their high reactivity and quick electron transfer rates, nanomaterials may shorten the response time of electrochemical sensors. This fast reaction is essential for dynamic changes in biomarker levels and real-time physiological parameter monitoring (Dhahi et al. 2024; Jalalvand and Karami 2025). Advancements in data analytics and microfluidics have then facilitated the developments of portable, affordable, and accurate diagnostic instruments. Nonetheless, there are also challenges and limitations. For example, it is essential to precisely manipulate nanomaterial characteristics in developing nanobiosensors, in particular their biocompatibility. Additionally, many technologies may not be ready for commercialization until they overcome regulatory obstacles. Scientists are working hard to address these problems. Owing to advancements in engineering and materials science, researchers have demonstrated the developments of more reliable nanobiosensors (Dhahi et al. 2024). For instance, there have not been many technical developments up to this point that demonstrate the suitability of nano-level biosensors for identifying biomarkers for AD in sweat samples. Sweat dopamine levels are reported to be decreased in AD sufferers. Using cyclic voltammetry (CV) and electrochemical impedance spectroscopy (EIS) techniques, Lei et al. have developed a single-atom-doped molybdenum disulfide with manganese for the ultrasensitive detection of dopamine from an artificial sweat sample, demonstrating a limit of detection (LOD) of 0.05 nM. This might provide a fresh method for pathologically diagnosing AD via perspiration (Swierczewska et al. 2012; Lei et al. 2020).

Researchers can now detect the chemical, cellular, electrical, and behavioral changes linked to neurodevelopmental disorders (NDDs) development using a variety of modern-age sensors, made possible by the fast advancement of sensor technology. Surprisingly, miniature sensors for detecting biomarkers associated with neurological diseases have been developed with the proliferation of nanomaterials, electroactive polymers, and the Internet of Things. Simply put, a sensor is any device or technology that can take in an input signal and convert it into a quantifiable and visible form. Any measurable amount of physical fluctuations could serve as the input signal. Biosensors are state-of-the-art detection methods that have recently arisen in several medical diagnostic applications, one of which is the real-time detection of human fluids (Falk et al. 2020; Nawrot et al. 2018; Gautam 2022). Global estimates placed the value of the biosensor market at USD 25.5 billion in 2021 (Paul 2024). The medical and health industry is expected to have the most substantial growth, with a predicted increase of 43% to 44% during the next 5 years (Gautam 2022).

Electrochemical biosensors have gained popularity over the years for several reasons, including their

biocompatibility, cost-effectiveness, simplicity, ease of handling, portability, high sensitivity, and capacity to analyze turbid samples (Valkova and Pohanka 2021). One kind of biosensor, an electrochemical biosensor, may transform biological data, such as the concentration of an analyte, into a current or voltage (Singh et al. 2021). An amperometric, potentiometric, conductometric, or impedimetric transducer generates the amperometric signal. Different electrochemical sensors are used depending on the measured parameter: amperometric transducers measure electrical current, potentiometric transducers measure generated potential, conductometric transducers measure medium conductance, and impedimetric transducers measure medium impedance (Valkova and Pohanka 2021).

In addition, biosensors often use CV, differential pulse voltammetry (DPV), EIS, and square wave voltammetry (SWV) as electrochemical methods for the early detection of NDDs (Silva et al. 2024). In terms of neurological and physiological processes in real time, electrochemical sensing of metabolites, neuromodulators, and neurotransmitters in vivo is crucial. The need to monitor neurotransmitters and neuromodulators in living organisms, from individual cells to brain slices or even the whole brain, has driven the development of cutting-edge electrochemical biosensors and technology. The miniaturization of electrodes may be explored by voltammetry, a universal tool for studying electrochemical processes in complicated matrices. Additionally, the rapid oxidation–reduction kinetics of neurochemicals make amperometry an ideal method due to its high temporal resolution. Potentiometry allows for quantitative analysis with less invasiveness and excellent compatibility by measuring the potential difference. In analytical chemistry, potentiometry is a tool for determining the solute concentration in a solution. In this technique, a high-impedance voltmeter detects the voltage between two electrodes (Zdrachek and Bakker 2020; Yang et al. 2025). As amplification methods, field effect transistor (FET) and organic electrochemical transistors (OECTs) outperform more conventional technologies regarding sensitivity (Yang et al. 2025).

Using molecular and atomic-level control, nanotechnology may develop new materials, tools, and systems. At the nanoscale, material dimensions significantly impact their characteristics because physical and chemical properties of individual atoms and molecules will vary from bulk materials, making particle size a critical factor in this technology. In general, nanomaterials have a dimensionality of less than 100 nm. Incorporating nanomaterials into the design of biosensors opens up new possibilities for diagnostic interactions. Nanomaterials are purposely used in biosensor architecture to enhance biorecognition element characteristics or activities, or augment the active surface area of a transducer. Nanomaterials improve diagnostic sensitivity and amplify output signals in electrochemical biosensors (Negahdary and Angnes 2022).

With the increasing popularity of employing biocompatible and less cytotoxic materials, novel biomaterials for biological and chemical sensing applications have become more prevalent in the diagnostic field. The swellable, nano-/microporous, and aqueous 3D structures of hydrogel-based electrochemical sensors have made them a potential candidate for implantable and wearable applications due to their ability to immobilize electroactive species, whole cells, and complex tissue models. In addition, bio-nanocomposite of hydrogel is also often considered for use in biocompatible, "smart," and sensitive POC health monitoring devices (Shafique et al. 2023).

One effective way to achieve high-quality sensor performance with improved signal stability, biocompatibility, LOD, and low-cost sensor design is to incorporate hydrogel NPs (HNPs). Biomaterial immobilization has extensively used HNPs with various compositions, pore sizes, and shapes, with applications spanning almost all biomaterials, including enzymes, proteins, antigens, and DNA. Because of their many valuable properties, HNPs have become well known as promising materials for biosensor production. Hydrogels have a wide range of potential applications due to their biocompatibility and chemical variety. These domains include temperature sensing, health monitoring, and drug detection. Hydrogels are also very reactive to environmental factors like temperature, light, electric fields, and solvents. Hydrogels are versatile and may be used as electrode materials and sensors (Hasanzadeh et al. 2014; Zhang and Wang 2022). Several examples of applications of HNPs, together with their benefits and limitations, are provided below to illustrate their future advances in this area. In addition, surface modifications using HNPs were explored to study the impact of polymeric characteristics on biosensor performance and to demonstrate the applications of HNPs to various transducers for analyte detection (Hasanzadeh et al. 2014). Researchers developed an Amyloid-β oligomer (AβO) biosensor by immobilizing a thiolated cellular prion protein (PrPC) peptide probe on gold (Au) NP-modified hydrogel electrode. Based on EIS, their work showed an enhanced electron transfer resistance of the redox marker by an AβO | PrPC probe-modified hydrogen electrode compared to AβO. Additionally, one possible pathological method of AD manifests as the misfolding and aggregation of amyloid-beta (Aβ). The CSF or blood circulation may receive AβO and fibrils formed from Aβ monomers. Compared to insoluble aggregates, AβO is considered the most neurotoxic type and is more strongly associated with AD severity. It may distinguish AβO from Aβ fibrils or monomers with at least 99% efficiency. At the same time, it could identify synthetic CSF or blood plasma with a sensitivity of as little as 0.1 pM

AβO. From 0.1 pM to 10 nM is the linear range for detecting AβO (Sun 2018).

The digestive system provides an easy place for the body to absorb α-lipoic acid, a powerful antioxidant that dissolves in water and fat. By doing this step, nerve tissue may be protected from damage. So, it is a medicine for managing and curing oxidative stress-related chronic diseases like diabetic neuropathy. Senses are altered by neuropathy. In addition, α-lipoic acid could mitigate dapsone's effects, including diminished activation of microglia and astrocytic cells, reduced levels of pro-inflammatory cytokines, increased brain-derived neurotrophic factor, enhanced antioxidant capacity, and diminished oxidative damage due to iron buildup. Thus, α-lipoic acid is seen as a potential and practical substitute for traditional medicine in treating disorders associated with neuroinflammation and oxidative stress (Lu et al. 2024; Gomes et al. 2025). The biocompatibility, specific receptor immobilization, and wide surface area of chitosan make it an attractive candidate for electrochemical sensing applications, where it may enhance the sensor's selectivity by increasing analyte adsorption. Also, chitosan is a good electron transfer facilitator, which may improve the sensitivity and reliability of α-lipoic acid detection (Bounegru and Bounegru 2023). Functionalized multi-walled CNTs may also be used as nanosensors for detecting α-lipoic acid. These nanotubes' unique electrical and mechanical characteristics allow them to be very selective and sensitive. The electrochemical performance of the sensor is enhanced by functionalizing multi-walled CNTs, which increases the analyte's dispersion, stability, and contact. To avoid activation of microglia inflammation in the nervous system, α-lipoic acid was electrochemically detected at a poly(vanillin-co-chitosan)-functionalised multi-walled carbon nanotube (CNT)-modified glassy carbon electrode (GCE) (Lu et al. 2024). In this study, a sensitivity of 0.047 μA/μM, a LOD of 0.012 μM, and a broad linear range between 0 and 3000 μM α-lipoic acid were achieved. These findings are comparable to a sensitivity of 0.04664 μA/μM, a LOD of 0.012 μM, and a broad linear range between 0 and 3000 μM α-lipoic acid using an ELISA kit (Lu et al. 2024).

There have been developments in multiplex paper-based electrodes using vacuum filtration (Gu et al. 2024). Among them, a five-electrode pattern was formed on a cellulose paper by progressively vacuum filtration single-walled CNTs and AuNPs (Gu et al. 2024). Jinyu Gu et al. (Gu et al. 2024) developed a nanocomposite of AuNPs-loaded dendritic mesoporous silica NPs ($dmSiO_2$-Au). Further, they deposited thionine (Thi) for signal amplification, and multiplex electrodes to create an immunosensor for AβO and Fetuin B at the same time. In addition, ferrocene was added to a separate working electrode to conduct ratiometric electrochemistry and improve precision. There was no clear evidence of cross-talking across the three functional electrodes, and the results showed excellent selectivity, sensitivity, and stability. Using this sensor effectively allowed us to measure Aβo and Fetuin B levels in the blood and brain of transgenic AD mice (Gu et al. 2024). In particular, the paper electrodes were created using a quick and easy vacuum filtration method that formed a conductive underlay and electrical connections by successively filtering AuNPs solutions and single-walled CNT dispersions through cellulose paper in a five-electrode pattern. The electrode included three Au working electrodes, an Ag pseudo-reference electrode, and an Au counter electrode. To improve detection performance, a nanocomposite of $dmSiO_2$-Au conjugated with Thi and antibody (Ab) of Aβo or Fetuin B ($dmSiO_2$–Au–Thi–Ab) was used as the signal transducer and amplification for the immuno-sensing. This was because $dmSiO_2$ NPs had a large specific surface area, which allowed them to load large amounts of AuNPs and effectively capture Abs. In conclusion, the offered electrochemical immunosensors for multiplex diagnostics have the potential to pave the way for the discovery of additional blood indicators associated with AD (Gu et al. 2024).

Using MIPs, a polymer receptor material with three-dimensional memory of the detected compounds and particular target molecular recognition sites may be quickly and effectively synthesized (Lu et al. 2023). Researchers used a peptide epitope from the protein to build electrochemical sensors for the protein α-synuclein (α-Syn), a marker for PD, using a molecularly imprinted polymer (MIP). The conductivity of MIPs was enhanced by electropolymerizing them with or without template molecules, depending on the concentration and species of transition metal dichalcogenides (TMDs). The rational design of conducting MIPs for biomarker identification in biological fluids may be aided by this link, which researchers discovered. Electrodes coated with TMDs-doped imprinted poly(Aniline (AN)-co-m-Aminobenzenesulfonic acid (MSAN)) had a sensing range of 0.001–100 pg/mL and a LOD of 0.5 fg/mL based on a signal-to-noise ratio of 3. An analysis of cell culture medium from midbrain organoids unique to Parkinsonian patients, generated from induced pluripotent stem cells, was conducted to demonstrate the possible use of the MIP electrochemical sensor. The organoids derived from these patients showed considerably lower levels of α-Syn when compared with those of age-matched controls. Recovery is between 95 and 115%, and the relative standard deviation is less than 5% (Lee et al. 2021).

This article thoroughly summarizes the history and importance of early diagnosis in NDs. We underline the need for trustworthy biomarkers and discuss the difficulties with current diagnostic methods. In addition, critical novel biomarkers of neurological illness are summarized below in this article. With a focus on their potential for diagnosing NDs such as multiple sclerosis, Alzheimer's disease, and Huntington's disease, this study thoroughly compares newly

published electrochemical biosensing technologies. In this respect, strategies were devised to address the efficacy of electrochemically based diagnostic tools. Consequently, we examine the many polymers used in electrochemical methods to diagnose neurological disorders. Hydrogel-based polymer sensors for early-stage neurodegenerative diagnosis are discussed in this review. Lastly, we will also present the limits and prospects of clinical trials. Additionally, polymer-based electrochemical sensors for diagnosing NDs are offered for the first time in this study. It is stated how important these platforms are for diagnosing diseases. In contrast, this review highlights significant uses of polymer-based electrochemical sensors for identifying neurological diseases, such as HD, AD, and MS. This strategy will raise awareness of the subject, inspire more researchers to work on clinically useful analytical devices, and promote cross-disciplinary and inter-disciplinary cooperation, such as when clinician scientists collaborate with device developers.

Electrochemical Sensor in Biomarker Identification of Neurodegenerative Diseases

Magnetic resonance imaging (MRI) and PET are the primary methods for diagnosing AD. Despite their value, these technologies are costly and only available to those with the means. In the early stages of AD, they also show reduced sensitivity. Although identifying biomarkers like phosphorylated tau (p-tau) and total tau (t-tau) in CSF is dependable, it necessitates invasive lumbar punctures, making it unfeasible for regular or large-scale screening. Blood-based biomarkers have become viable, low-invasive, and affordable options for early AD identification, especially p-tau subtypes as p-tau181 and p-tau217. However, there is a major analytical hurdle due to the low levels of tau in blood, which are about an order of magnitude lower than in CSF (Luo et al. 2025; Kim et al. 2016).

An ideal approach for tau detection is ELISA, which is accessible via commercially available kits and can detect such low concentration levels. Nevertheless, along with these benefits come certain downsides, such as the need to utilize optically tagged Abs, lengthy incubation and washing procedures, and the usage of many Abs. A second strategy based on PCR-related methods has effectively measured trace amounts of tau protein. In particular, a technique called nano-iPCR was employed to measure tau concentrations. This involved adding a tau-specific monoclonal Ab (HT7) and a single-stranded thiolated oligonucleotide to Au-NPs, which were then detected using real-time PCR (Carlin and Martic-Milne 2018). This method's efficacy produces an outstanding detection range at the pM level. The sensitivity of PCR amplification makes it a potential downside that any detecting components attached nonspecifically to the walls of the PCR wells would be substantially amplified, leading to an increase in the background signal. The fM detection of tau protein in plasma was recently accomplished using surface plasmon resonance (Kim et al. 2016; Carlin and Martic-Milne 2018). The current electrochemical ELISA-based biosensor testing may display up to 4857 signaling molecules per probe molecule binding event, in contrast to the five to ten signaling molecules shown in classic ELISA testing (Carlin and Martic-Milne 2018; Hosseini et al. 2025). Traditional, costly, and time-consuming techniques for measuring Tau CSF levels include ELISAs, mass spectrometry, and SPR. The development of biosensor-based detection assays that are quick, inexpensive, and very sensitive has been an area of intense research focus. For example, the researchers created a label-free electrochemical biosensor to detect Aβ oligomers. Although the threshold of detection is 0.2 μM, which is about five orders of magnitude greater than the CSF tau cut-off value (4.3 pM) that differentiates AD patients from controls, an electrochemical biosensor for tau was recently created (Luo et al. 2025).

For the very sensitive detection of analytes in bodily fluids, electrochemical biosensors use an electrical transducer and a recognition element. Crucially, they may provide quick readings and be incorporated into wearable, implantable, and portable devices for POC diagnostics. For instance, the personal glucose meter makes it possible to measure blood glucose levels at home, significantly improving diabetes treatment. In addition, to facilitate POC diagnostics and health monitoring, electrochemical biosensors—such as amperometric, voltammetric, potentiometric, organic electrochemical transistor, photoelectrochemical, and electrochemiluminescent sensors—can be incorporated into wearable, portable, and implantable devices. Enhancements in instability, sensitivity, repeatability, multiplexing, and digitalization—and, crucially, inexpensive materials and simple production techniques—will be necessary for commercializing and wide POC application of integrated electrochemical biosensors (Wu et al. 2023).

Amperometric biosensors provide precise quantitative analytical data by measuring the current generated when an electroactive biological element is oxidized or reduced at a constant voltage between a reference electrode and a working electrode. These biosensors are based on Clark's groundbreaking 1956 amperometric oxygen sensor, which measured oxygen content by measuring the current that flowed through a platinum electrode in response to an applied voltage. In contrast, for a voltammetric biosensor, a current may be generated between a working electrode and a counter electrode by scanning the applied voltage across a window between the working electrode and a reference electrode, within which the redox reaction of the analyte occurs. The peak current may then be quantitatively related to the

analyte concentration. One benefit of this technique is that it may provide qualitative and quantitative information based on the peak current intensity and its possible location (Ding and Qin 2020; Lakard 2020; Lakard et al. 2021).

In DPV, a sequence of voltage pulses is added to a linear potential sweep. Applying a voltage pulse to the electrode at a base value where the Faradaic reaction does not occur is the starting point of DPV. With each pulse, the base potential is raised by an equal amount. Before each potential pulse change, the current is measured, and the difference between the current and the potential is plotted against the potential. By measuring the current at the end of a pulse, the impact of the charging current will be minimized. While oxidation processes generate peaks in the DPV method, they cause waves to appear in the voltammogram in the linear sweep method. Compared to linear sweep voltammetry, DPV is more accurate because of the voltammogram's accuracy, making it easier to interpret. Because the peaks in the DPV method produce sharper waves associated with dopamine, ascorbic acid, or uric acid, as opposed to the vast waves created in a linear sweep voltammogram, this is especially helpful in the context of electrochemical biosensors. In addition, to yield a wave in a linear sweep voltammogram, the analyte solution must not be quiescent (e.g., using a magnetic stirrer, a flowing system, or a rotating electrode) (Lakard et al. 2021; Simões and Xavier 2017; Baranowska et al. 2008) (Fig. 1).

Electrochemical sensors based on nanomaterials such as graphene, CNTs, MIPs, metal–organic frameworks, and metal NPs demonstrate stability, selectivity, sensitivity, accuracy, and precision to measure neurochemicals. Even in the most complicated physiological settings, these sensors can measure target molecules reliably. In vivo measurements are now more reliable due to increased selectivity from subsequent developments in recognition units (such as enzymes, aptamers, and MIPs). Unfortunately, there are still obstacles that make long-term monitoring unstable and inaccurate. These include protein adsorption, contamination of the electrodes, and foreign body reactions from implanted electrodes. The visualization, real-time in situ measurement, and interference-free simultaneous detection of several neurochemicals may constitute future research priorities. The future of electrochemical neurotransmission analysis seems bright, with the development of more precise clinical neurotransmitter measurements promising to revolutionize the field of neuroscience (Xu et al. 2024a).

Important Novel Biomarker Identification of Neurodegenerative Diseases

Improved diagnostic developments in clinical and easier monitoring of effective disease-modifying treatments became possible owing to the availability of biomarkers for NDs. Clinical trial and observational study designs have been enhanced with the increased use of PET technologies to identify amyloid-β and tau pathology in AD (Hansson 2021). Recent developments of affordable and readily available blood-based biomarkers that may identify the same AD have the potential to completely alter the diagnosis process for AD on a worldwide scale (Thambisetty and Lovestone 2010; Hampel et al. 2018). Blood-based indicators of general neurodegeneration, glial activation, and relevant biomarkers for α-Syn pathology in PD (Hansson 2021).

Designing and preparing samples, separating proteins and peptides, identifying them, using bioinformatics, interpreting the results, and validating and confirming the biomarker are all crucial aspects of the discovery process. However, readily obtained fluids, such as plasma, show only a limited connection with illness. To make early detection of NDs possible, clinical sensitivity, selectivity, high-throughput quantitative proteomic technologies, system-driven molecular diagnostic approaches, and new biomarkers must be improved in this area of research (Sharma et al. 2024).

In general, acquiring reliable diagnostic tools to identify neural dysfunctions and NDs early, ideally before symptoms appear, is difficult. In addition, more accurate methods of tracking the development of these diseases are also being researched. The perfect biomarker would reflect the disease's development, be straightforward to assess, and have high sensitivity and selectivity. Exosomes (EXOs) and microRNAs (miRNAs) are examples of molecular biomarkers. They are detectable in CSF and blood, the two most critical extracellular fluids for NDs (Doroszkiewicz et al. 2022).

Because of their high cost and invasiveness, the most sophisticated diagnostic methods for NDs, such as detecting proteins in CSF and several imaging techniques, are inappropriate for primary screening and monitoring. Cost-effective, minimally invasive ND biomarkers would be very beneficial for improving ND diagnosis and care. Finding these biomarkers is made more difficult by several circumstances. First, the mechanisms of ND initiation and development are poorly understood; second, NDs can develop for 10–20 years before showing any symptoms; and third, the differential diagnosis of NDs is complicated by common comorbidities and symptom overlap, including cognitive impairment (Sheinerman et al. 2017). To normalize the miRNA biomarkers, other brain-enriched miRNAs can be used to offset the effects of factors unrelated to a particular ND and to account for more minor changes in miRNA concentrations accompanying slowly developing pathologies (compared to those in acute diseases like stroke). The miR-132 and miR-134 families of miRNA biomarker pairs can distinguish moderate cognitive impairment (MCI) from age-matched controls with an accuracy of almost 0.90, thanks to this miRNA "pair" technique. As the illness worsens, the number of

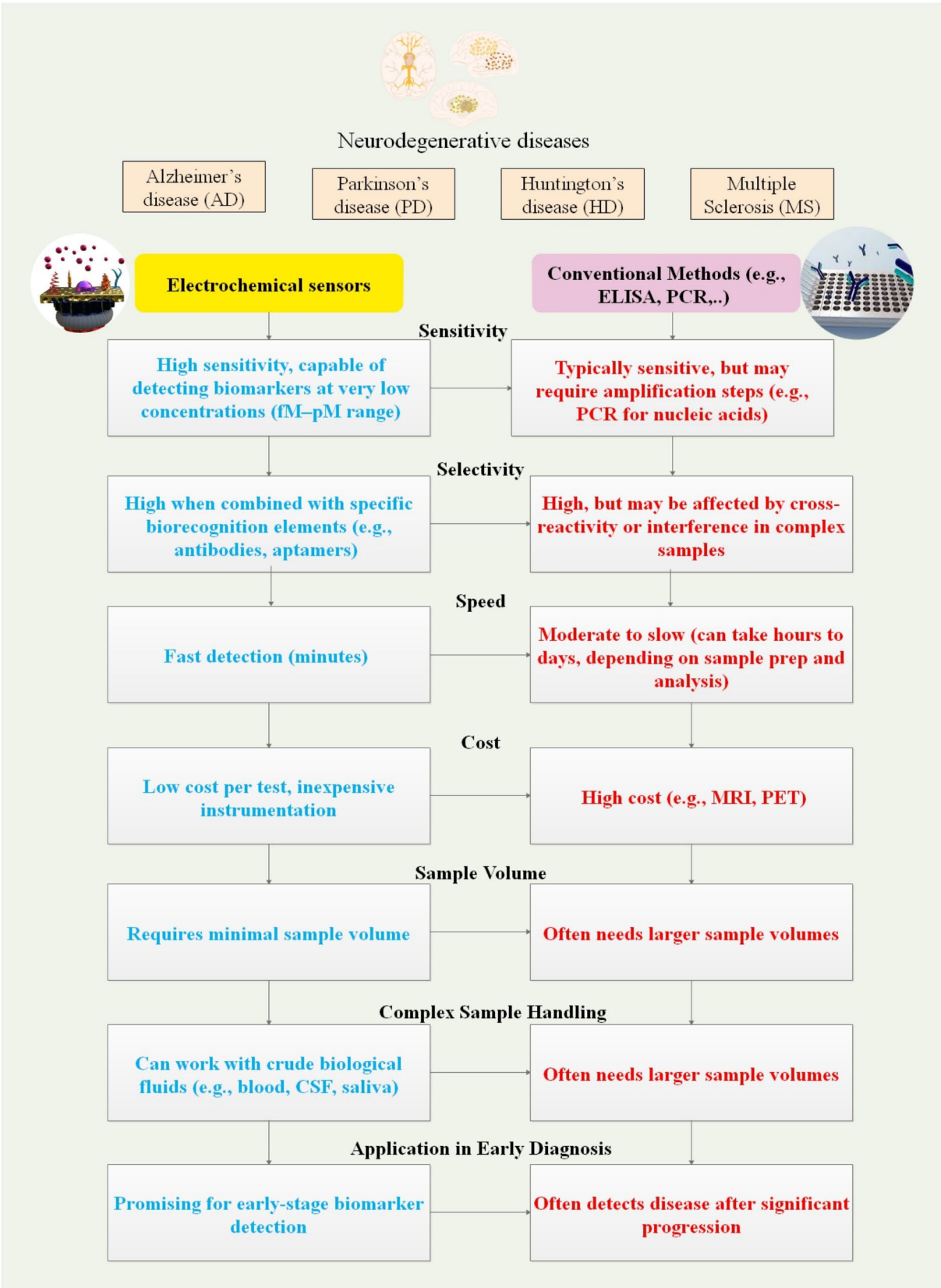


Fig. 1 Comparison of electrochemical sensors with conventional diagnostic methods. When it comes to neurodegenerative disorders, such as multiple sclerosis, Alzheimer's disease, and Huntington's disease, electrochemical sensors provide several benefits over traditional detection methods

hippocampal synaptic miRNAs in plasma may decrease due to the loss of synapses and death of neurons in the hippocampus, which may explain why these miRNA pairs were less successful as biomarkers for identifying the stages of AD dementia (Sheinerman et al. 2017; Sheinerman et al. 2012).

Since analyzing gene expression using plasma samples is non-invasive, owing to developments in microarray and high-throughput sequencing technologies, investigating biomarkers by miRNA expression has tremendous therapeutic promise. There has been a surge in interest in miRNAs in recent years due to their potential as early biomarkers and diagnostic tools for several disorders. Cell proliferation, differentiation, maturation, and death are just a few developmental events that they significantly regulate. There is promising evidence for diagnosing and treating several disorders linked to miRNA dysregulation, as shown in a large body of research (Selvam and Ayyavoo 2024; Jain et al. 2019; Hernández-García et al. 2025; Feng et al. 2025). Recently, miRNAs in serum and those produced from blood cells have been investigated as potential non-invasive diagnostic biomarkers for various disorders, including PD and glioblastoma (Selvam and Ayyavoo 2024). In Fig. 2, we show the types of biomarkers important for NDs.

The optimal biomarker for early diagnosis should be able to distinguish between the disease state and normal aging circumstances, and it should be sensitive and specific for early neurological abnormalities. According to this explanation, peripheral markers indicate cognitive and biological changes in the brain, provide non-invasive alternatives for diagnosing diseases, and are crucial in resolving diagnostic constraints. CSF is one of the most beneficial biological fluids, and it accurately depicts the biochemical reactions occurring in brain tissue. This matrix makes early preclinical diagnosis of a disease possible, perfect for presenting a biological fingerprint of the CNS. However, a less intrusive and more accessible solution, such as blood plasma or serum, is needed for monitoring NDs (Koníčková et al. 2022). Clinical trials often utilize prognostic biomarkers to determine higher-risk groups and establish study admission and exclusion criteria. The main problem is that the number of occurrences, not the sample size, determines a trial's statistical power. Event rates are raised when trials are enriched in this way; if the treatment is successful, the variations in results

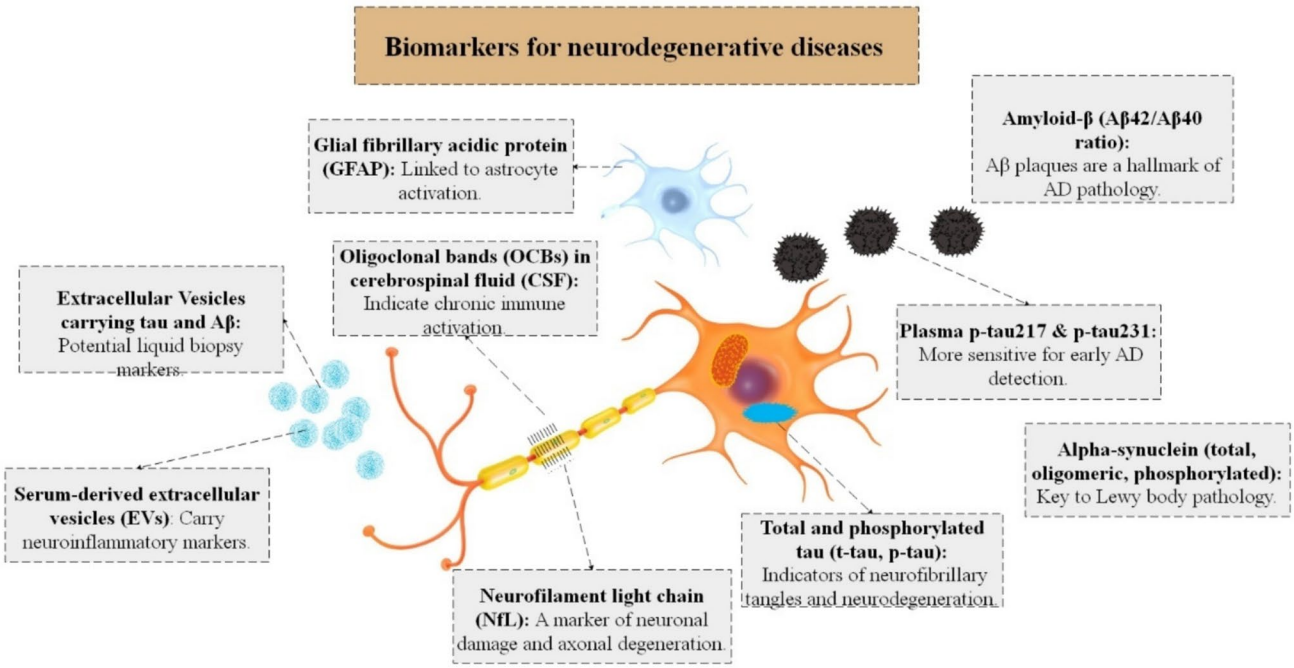


Fig. 2 Biomarkers for neurodegenerative diseases include multiple sclerosis, Alzheimer's disease, and Huntington's disease. Developing novel medicines, early diagnosis, and disease monitoring depend on identifying meaningful and distinctive biomarkers. Immunoassays for identifying tau phosphorylated at specific epitopes in CSF have recently been developed. According to 4 years of clinical study, p-tau in CSF fluid is significantly elevated in AD compared to healthy controls. This may help distinguish AD from its most pertinent differential diagnoses (Hampel and Teipel 2004). Promising biomarker candidates to determine the course of the illness from preclinical phases have been found in p-tau proteins, namely p-tau217 and p-tau231 (Jarek et al. 2024). The neurofilament light chain protein (NfL) is a promising biomarker. NfL has become a popular axonal damage marker since the advent of ultrasensitive assays, and it is relevant to the diagnosis, prognostication, follow-up, and treatment monitoring of a variety of neurological conditions, such as AD, MS, and amyotrophic lateral sclerosis (Arslan and Zetterberg 2023)

as a consequence of therapy are amplified numerically but not qualitatively. Additionally, prognostic biomarkers are crucial for forecasting an individual's likelihood of an incident or unfavorable result. Decisions about the duration of hospital and/or critical care unit stays depend heavily on this information. A healthcare organization can identify which patients would benefit from more intensive evaluation while allowing others to avoid additional diagnostic tests or medical interventions by stratifying the risk for adverse clinical and financial outcomes. This is just one of the many significant uses of prognostic biomarkers in population health resource allocation (Califf 2018).

Electrochemical Sensor for Detection of Novel Biomarker in Alzheimer's Disease

The development of senile plaques and neurofibrillary tangles, two prominent histological features of AD, is impacted by impaired phosphorylation events. Phospho-biomarker candidates may be found in blood-derived extracellular particles associated with diseases. In a pilot study, researchers used a high-density microarray with a focused phosphoproteomics method, including at least 913 phosphosite-specific Abs and 1145 pan-specific Abs, to examine the blood-derived extracellular particles of control and AD patients. This method was used in a novel way to identify 150 proteins that showed changed expression levels and/or phosphorylation patterns among AD patients. Gene Ontology (GO) enrichment and Reactome pathway analysis uncovered important biological targets and disease-associated pathways. Important targets were then highlighted by constructing protein–protein interaction networks. The discriminating value of the whole proteome and the phosphoproteome was assessed using multivariate and univariate techniques. Researchers found that blood-derived extracellular particles had abundant phosphor targets linked to AD, suggesting that they might be helpful as peripheral biomarkers for detecting the illness (Bigi et al. 2024).

These days, biomarkers like Aβ, p-tau, and t-tau are generally accepted as indicators of AD. On the other hand, acetylcholine (Ach) and α-Syn are not the subjects of many ongoing investigations. According to previous longitudinal and cross-sectional studies, aβ1-42, p-tau, and t-tau begin to alter after around 10–15 years before the onset of AD symptoms. Neurodegeneration, the underlying cause of AD, is signaled by an elevated blood concentration of p-tau. The more incredible formation velocity of aggregation makes A1-42 more hazardous than A1-40. Determining the Aβ1-42 level may help identify the onset of AD, and the ratio of Aβ1-42 to Aβ1-40 offers further insight into the present stage of AD development. In AD, p-tau181 and brain Aβ-plaque deposition are linked to changes in α-Syn levels. Deficits in synthesizing Ach, a neurotransmitter, accelerate the onset of AD. Electrochemistry, fluorescence, and colorimetry are the more recent approaches to identifying these AD biomarkers. Traditional approaches include PET, MRI, and near-infrared fluorescence (NIRF) (Le et al. 2023).

Possible indicators of neuronal injury might include other chemicals or cellular structures. Among promising biomarkers are neurofilaments, especially neurofilament light chain (NfL). Leakage of NfL into CSF and subsequent rise to measurable levels occur after axonal and/or neuronal injury. While not AD-specific, NfL is strongly tied to ND and becomes an even more effective predictor of ND when combined with other biomarkers. However, the strong association between NfL levels in CSF and blood is one advantage of NfL relative to different biomarkers. Increased levels of NfL may be found in the early stages of autosomal dominant AD, even before the first symptoms appear, much like Aβ. In addition, the correlation between clinical scales and NfL, a Tau-independent axonal degradation measure, was more significant than that of t-tau in a recent 18-month experiment with mild AD patients. So, NfL has the potential to be a diagnostic biomarker since it can identify alterations before they show up in the body (Cano et al. 2021; Raket et al. 2020; Weston et al. 2019).

One potential biomarker for several illnesses is glycosylation, a post-translational change that is cell-type specific. Researchers looked for glycan-biomarkers on transferrin (Tf) to identify AD in CSF (Hoshi et al. 2021). N-glycans, which are cell-type specific and reveal the molecule's biological origin, post-translationally modify Tf. Researchers have discovered three glycan-isoforms to be present in cerebrospinal fluid (CSF): Tf carrying mannose-terminated glycans (Man-Tf), Tf carrying N-acetylglucosamine (GlcNAc)-terminated glycans (GlcNAc-Tf), and Tf carrying sialylα2,6 galactose-terminated glycans (Sia-Tf). The fact that Sia-Tf has the same glycan as blood Tf indicates that it comes from the same source. However, as Man-Tf and GlcNAc-Tf were not found in individuals with congenital hydranencephaly, whose cerebrum was mostly deficient, these isoforms are produced from the cerebrum (Abe et al. 2022).

Researchers used mass spectrometry and HPLC to examine the Glycan bonds of CSF Tf. One Tf isoform in CSF carries a specific mannosylated glycocan, which researchers call Man-Tf. It has been suggested that Man-Tf in CSF originates partially from the cerebral cortex, as this isoform was found in the cortex. Researchers examined Man-Tf levels in CSF from people with neurological disorders. Man-Tf concentrations were strongly linked with p-tau, a typical AD marker. They were much higher in AD and MCI compared to other neurological illnesses. The idea that a combined p-tau and Man-Tf measure may serve as a biomarker for AD was prompted by the fact that p-tau and Tf were co-expressed in hippocampal neurons of AD. P-tau x Man-Tf

levels demonstrated excellent diagnostic accuracy for AD and mild cognitive impairment, with sensitivity levels of 84% and specificities of 90% for MCI and 94% and 89%, respectively, for AD, thereby, Man-Tf may represent a novel AD biomarker (Hoshi et al. 2021).

One intriguing path for improving AD care and diagnostics is using blood-based biomarkers. The diagnosis and treatment of AD may be redefined by these biomarkers' promise for less intrusive and more widely available diagnostic instruments. Strong validation studies that demonstrate these blood-based markers' accuracy, repeatability, and dependability in various clinical contexts should be the main emphasis of future research. Additionally, it is essential to investigate new blood-based biomarkers with improved specificity and sensitivity and to broaden the scope of current ones. According to Abukuri et al.'s study, plasma and CSF NfL levels may predict cognitive loss, while other studies show that CSF NfL may have a stronger correlation with cognitive decline. However, the association between NfL levels and cognitive deterioration may change depending on age and other variables. The potential of plasma and CSF NfL as indicators of cognitive decline requires further investigation. Additionally, plasma NfL is a generic neurodegenerative marker that may show elevated levels in various NDs. Therefore, further investigation is necessary to ascertain these biomarkers' specificity for AD and their capacity to distinguish it from other illnesses (Abukuri 2024).

A biosensor for AD called an ultrasensitive photoelectrochemical biosensor for Aβ40 was developed by combining g-C3N4 with AuNPs to form Au-C3N4 (Li et al. 2025). This was then mixed with TiO_2 to form a firmly bound TiO_2/Au-C3N4 heterojunction, which resulted in a very sensitive photocatalytic process. In addition to increasing photocurrent production, adding noble metal AuNPs firmly immobilizes the aptamer via Au–S bonds, which provides more surface binding sites. As a result, the sensor's capture efficiency is greatly enhanced. According to the researchers, the sensor demonstrated outstanding performance with a linear detection range of $10-15$ to $10-11$ g/mL and an impressive LOD of 0.33 fg/mL (Li et al. 2025). Clinical validation also showed effective detection in actual CSF and plasma samples taken from AD patients and healthy controls. Based on researchers' findings, photoelectrochemical biosensors are a viable tool for early AD screening in high-risk groups, as they are both inexpensive and susceptible to detecting ultra-trace chemicals in human bodily fluids (Li et al. 2025).

Researchers made a multi-fulcrum mediated amplified rolling nanomachine (MFN) for Tau detection using the internal drive inspired by the wind-driven windmill rolling to provide electrical energy. The backbone of the MFN is a DNA nanowindmill (DNM) that has self-assembled from DNA; it is originally inefficient but becomes an effective DNM after interacting with Tau and then being separated magnetically. Once reaching the electrode interface, the DNM keeps rolling with the help of the multi-fulcrum and signal probe to boost the signal. The modular design and DNM rolling exacerbate the spatial obstruction during protein detection, which impedes signal transduction and amplification. The flip side is that it has excellent sensitivity and a lightning-fast reaction time. With a low LOD 127 fg/mL, the suggested MFN electrochemical biosensor can effectively detect Tau concentrations ranging from 10 pg/mL to 2 µg/mL. This concentration is much lower than the pathological state concentration of Tau, which is around 400 pg/mL. Researchers' results also showed that MFN can accurately distinguish between healthy people and those with AD when applied to clinical samples (Cheng et al. 2025).

The quality of life for older people is profoundly affected by AD on a global scale. Glycosylated Aβ proteins are vital indicators for AD, but their very low levels challenge reliable identification. The sensor exhibits great sensitivity with a LOD for Aβ in human serum as low as 100 pg/ml (Arslan and Zetterberg 2023). To address these problems, a boronic acid-based novel covalent organic framework was used to construct a robust and adaptable sensing platform. Once formed on the material by simple interfacial disruption, this carbon cloth (CC)-based covalent organic framework substrate can potentially be used as an electrochemical platform for detecting glycosylated-Aβ16 via molecular interactions. Substrate characteristics include high electrical conductivity, a specific surface area, and many molecular recognition sites. Specifically, boronic acid-based COFs with rich pore architectures, linear shape, and particular functional groups efficiently enrich glycopeptides, increasing the response signal and the biosensor's capacity for detection. In addition, poly(thymine)-templated copper (Cu) NPs, attached to the glycosylated-Aβ16 aptamer, were used by researchers as electrochemical probes to enhance the signal. With an ultralow detection LOD of 0.32 pg/mL, high stability, the suggested assay for glycosylated-Aβ16 proteins showed a broad detection range of 5–1800 pg/mL; for the sensitive and specific detection of glycosylated-Aβ16 protein, a CC-based electrochemical sensor was built using the COF–$B(OH)_2$ with boronic acid functionalization and porosity. The subject of new research was the use of state-of-the-art covalent organic frameworks based on boronic acid materials to develop electrochemical biosensors for analyzing glycosylated proteins (Lv et al. 2025).

Lactoferrin (Lf) is an essential biomarker for many illnesses. For Lf, a label-free electrochemical immunosensor based on an AgNP/Nafion-modified GCE was developed. A potential novel biomarker for AD that is both non-invasive and inexpensive is salivary Lf, which might indicate the presence of amyloid pathology. EIS, CV, scanning electron microscopy (SEM), and X-ray photoelectron spectroscopy (XPS) were used to characterize the construction of the

immunosensor; the results of which showed that the electron transfer rate changed significantly at each integration step. Every stage of the immunosensor manufacture was monitored by measuring the electrochemical signal, and the surface characteristics of the electrodes were improved considerably by depositing AgNPs and Nafion. The immunosensor displayed a linear dynamic range of 0.005–100 µg/mL based on DPV, with a 0.025 µg/mL LOD. It showed good reproducibility and selectivity toward potential interfering substances. Researchers showed recovery rates ranging from 101 to 103% when testing with Lf-spiked human saliva samples. In evaluating AD, this immunosensor based on AgNPs and Nafion offers a potential platform for the sensitive and quick detection of Lf (Rabbani et al. 2024).

This bottleneck might be addressed by developing liquid biopsy technology based on biosensors. An easy-to-use, inexpensive, and sensitive electrochemical aptasensor was developed for p-tau protein threonine 231, one of the first and most effective abnormally increased indicators of AD. AuNP-modified GCEs are excellent conductors that will enhance the electrochemical signal. To precisely trap the p-tau231 protein, a nucleic acid aptamer was engineered to facilitate an aptamer–antigen interaction. The suggested biosensor showed a 2.31 pg/mL LOD and a broad linear detection range (10 to 10^7 pg/mL) for p-tau 231. The biosensor proved helpful in complicated practical samples, with recoveries ranging from 97.59 to 103.26% in human serum (Kong et al. 2024).

New advances in electrochemical sensing technologies have made blood p-tau detection more precise. Because they convert biological interactions into electrical signals, electrochemical-based immunosensors allow for sensitive and inexpensive detection. Issues such as Abs' poor conductivity, the use of nanomaterials in sensor manufacture, and the impact of environmental factors challenge stability and repeatability. The platforms need enhancements to make them more practical and resilient in the face of the significant obstacles associated with analyzing complicated biological samples and performing real-time measurements (Chen et al. 2023; Wen et al. 2017; Wang et al. 2025). With their low manufacturing costs, structural flexibility, and excellent specificity, aptamer-based electrochemical sensors provide a viable alternative to Ab systems. However, issues such as improved sensitivity, reduced nonspecific binding, and stability of aptamers in complex matrices must be considered. Future research should focus on overcoming these challenges and incorporating aptamers into scalable systems. Tau detection has used several electrochemical methods, each with advantages and disadvantages, including CV, DPV, SWV, and EIS. Due to their sensitivity, quick reaction, and low detection limits, voltammetry techniques—specifically CV, DPV, and SWV—are extensively used. Problems with throughput and false positives caused by physisorption prevent further clinical usage. There must be an improvement in the capacity to scale and handle many samples. The charge transfer characterization of EIS-based sensors might be improved with a better grasp of AC electrical circuits, although these sensors already have a high sensitivity for tau detection. Multiplexed EIS sensors may be used to provide more thorough and earlier-stage AD diagnostics. The FET-based sensor can detect biomarkers at femtomolar or pM concentrations, giving it exceptional sensitivity. Nevertheless, significant problems remain, such as reliable signal modulation, the requirement to reduce background noise, and discrepancies in equipment performance caused by material flaws (Le et al. 2023; Wang et al. 2025; Brett 2022).

For the quick detection of BACE1 antigen in the diagnosis of AD, researchers have developed a one-step manufactured reduced graphene oxide (rGO), activated using carbodiimide chemistry, coupled with BACE1 Ab, and mounted on fluorine-doped tin oxide (FTO) electrodes. The synthesis and manufacturing processes were described using various voltammetric, microscopic, X-ray analytic, and spectroscopic approaches. Several parameters were standardized for maximal current production utilizing the redesigned electrode, including temperature, pH, response time, nanomaterial/Ab concentration, and scan rate. With a LOD 0.64 fM in buffer samples and 1 fM in spiking serum samples, as well as little cross-reactivity with neurofilament antigen in buffer, spiked serum, and spiked artificial CSF, the final validation was carried out by detecting BACE1 antigen at concentrations ranging from 1 fM to 1 µM. The suggested immunosensor is a potential option for the sensitive, specific, and early detection of AD since it produced a result in 30 s, had acceptable repeatability, and had good storage stability for a month. Therefore, compared to current sensors, the electrochemical biosensor for BACE-1 detection that was created enhances detection performance and lowers detection time and cost, indicating its potential for early AD diagnosis in clinical samples (Dey et al. 2022) (Fig. 3).

Electrochemical Sensor for Detection of Novel Biomarker in Multiple Sclerosis (MS)

The McDonald criteria are now used to diagnose MS. These criteria rely on clinical evidence and paraclinical tests, such as MRI, to detect characteristic lesions and identify IgG's oligoclonal band (s) in CSF. Finding a clinically isolated condition (CIS) or radiologically isolated syndrome (RIS) is the first step in diagnosing MS (McDonald et al. 2001; Jafari et al. 2021). Clinical or biomarkers that show both spatial (involving several areas of the CNS) and temporal (showing a persistent illness, such as two relapses) spread are essential for diagnosing MS. Early identification and treatment

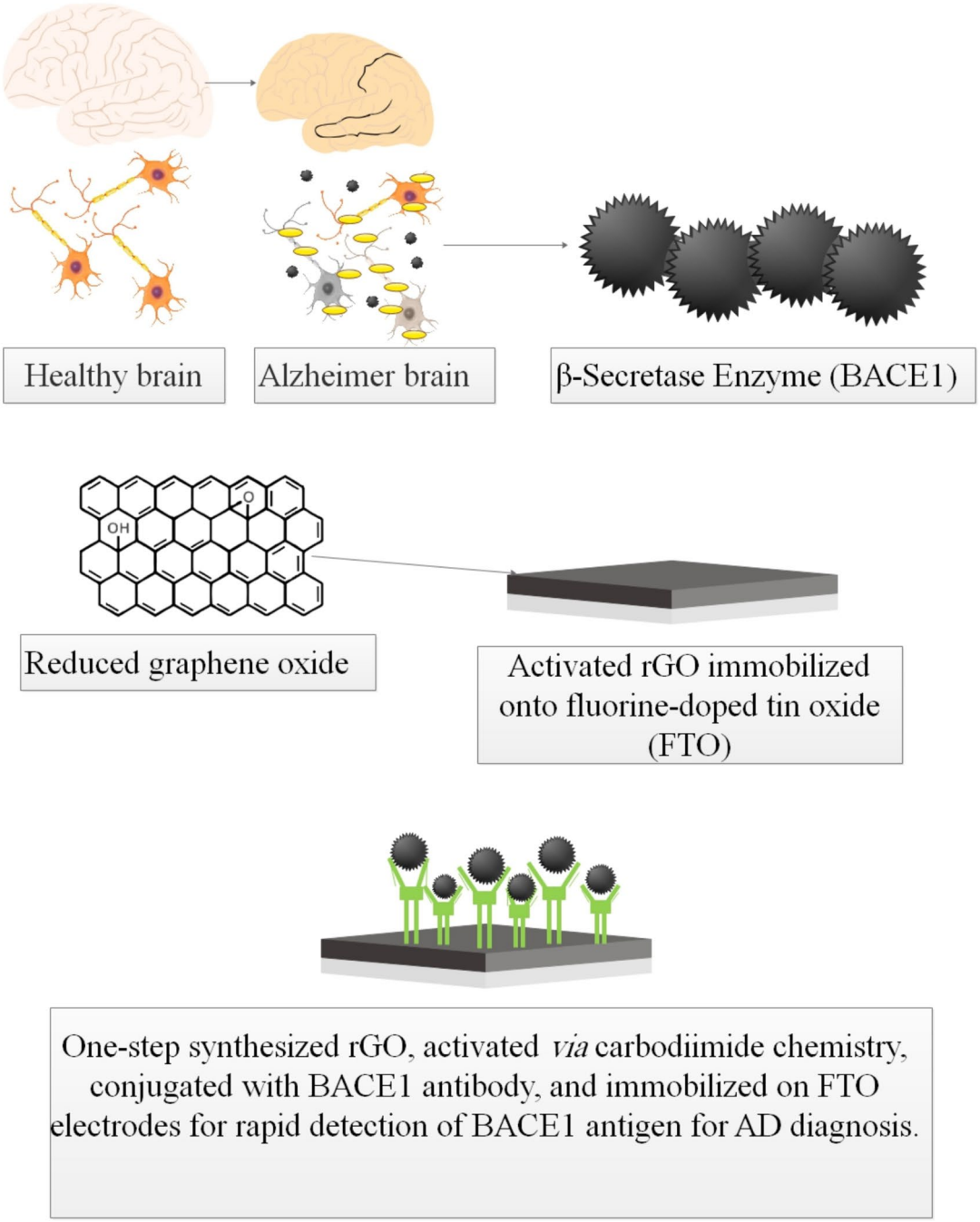


Fig. 3 Schematic of the fabrication and working of the developed electrode. For the quick detection of BACE1 antigen in the diagnosis of AD, researchers have developed a one-step manufactured rGO, activated using carbodiimide chemistry, coupled with BACE1 Ab, and mounted on fluorine-doped tin oxide (FTO) electrodes. The suggested immunosensor is a potential option for the sensitive, specific, and early detection of AD since it produced a result in 30 s, had acceptable repeatability, and had good monthly storage stability (Dey et al. 2022)

of MS patients via the use of clinical testing aims to modify the disease course and instances of progressive impairment. Biomarkers for MS have advanced in response to the need to enhance diagnostic methods and effectively track patient responses to treatment. Biomarkers are observable traits that may be used to assess the severity of biological or pathogenic processes and therapeutic responses. They are readings of compounds in a patient's bodily fluids or some indicator of their health, such as blood pressure or brain activity (Arneth and Kraus 2022).

Exciting developments have been made using NfL in the hunt for biomarkers that have more predictive value in diagnosing relapse and progression of MS. Clinical evaluations of individual patients, particularly those involving the monitoring of relapse or disease progression, may be challenging when NfL levels are included. In addition to the many confounding factors, including age, BMI, and blood volume, NfL signals damage to neurons. It is hence not unique to MS. Not only that, elevated NfL cannot differentiate between MS and other neurological disorders, infections, comorbidities (such as diabetes), or mild head injuries. A rapid increase in NfL levels in individuals indicates inflammation and active lesions. Therefore, elevated NfL levels may point to neuroinflammation rather than neurodegeneration in MS. Like NfL, other inflammatory biomarkers for axonal injury, neuronal damage, glial dysfunction, demyelination, and other conditions have limitations and contradictory study findings. To create usable diagnostic tools to predict actual relapse and disease progression for MS patients, a combination of different biomarkers (e.g., protein, immune cells, transcriptomics, extracellular vesicles (EVs), metabolites, microbiome, etc.) and state-of-the-art bioinformatics is required. New technologies like scRNAseq, proteomics, and metabolomics may considerably assist novel biomarkers and therapeutic targets for disease development in MS (Yang et al. 2022).

Numerous indicators have shown encouraging results in group-level investigations, especially those linked to microglia and astrocyte activation. It has yet to be determined how significant they are individually. The only Abs that are now widely tested in many nations for MS diagnosis and prognosis are oligoclonal immunoglobulin G (IgG) bands in human CSF. Even though there have been notable advancements in identifying possible biomarkers, difficulties still exist. One difficulty is the need for uniformity and harmonization across labs and clinical settings. The lack of widely recognized cut-off values and different technologies that result in different absolute concentrations for certain biomarkers, including NfL, makes interpretation more difficult and prevents consistent clinical decision-making. To guarantee the accuracy and comparability of measurements, it is essential to standardize procedures and create strong reference standards. The incorporation of these indicators into standard clinical practice is another crucial element. Several of them are now mostly restricted to specialist facilities. Developing assays that are easy to use and thorough training programs for medical personnel are essential to closing this gap. The goal is to increase the accessibility of these biomarkers, irrespective of institutional resources or geographic location. Real-time monitoring capabilities and convenience are provided by fully automated analytical tools that enable advancements in blood-based measures (Filippo et al. 2024).

Biosensor devices provide a practical method for point-of-care testing (POCT). One small analytical tool that may detect the target analyte is a biosensor, which employs a bioreceptor such as an enzyme, Ab, or oligonucleotide. The main role played by a transducer is to detect the analyte–bioreceptor interaction and convert it into an appropriate signal. Using a biosensor to detect the target biomolecule has several benefits, such as its rapid response, easy, accurate, cheap, and not requiring highly trained individuals to conduct the task. These benefits, together with advancements in biosensor technology, have sparked a surge of interest in developing MS biosensor devices (Demirdöğen 2021).

Despite a rise in MS cases, a definitive diagnosis is still challenging, expensive, and requires a battery of tests. Of the myelin in the CNS, as much as 30% is myelin basic protein (MBP). One notable MS bioindicator is the release of MBP into the CSF. In this study, two identical nano-sensors, one was MBP Ab-modified and the other one was myelin-specific DNA aptamer-modified, were used for MBP recognition. In constructing the MBP biosensors, a bioactive layer consisting of GO NPs and each of the two bioreceptor molecules was immobilized on pencil graphite electrodes. EIS was the technique used for detection. Using EIS, the charge transfer resistance of a redox indicator at the electrode is measured (Serin and Kara 2025). Aptamers that particularly attach to myelin proteins and were created to eliminate them from the body have been discovered in the literature on this topic. These aptamers were previously generated in mouse models for potential therapeutic uses. The 40-nucleotide DNA oligonucleotide LJM-3064 was created by Nastasijevic et al. 2012 and bonded particularly to myelin. Crucially, the myelin-specific aptamer LJM-3064 demonstrated an exceptional ability to attach to myelin proteins characterized as MBP isoforms and had molecular weights of 17 kDa and 21.5 kDa. The G-quadruple structure on the 5′-end of the LJM-3064 is a noteworthy and significant characteristic. It has been shown that adding GQ to a nucleic acid aptamer improves its stability, specificity, and flexibility; as a result, bioanalysis often uses it (Serin and Kara 2025; Kolesnikova and Curtis 2019; Nastasijevic et al. 2012). This novel aptamer was named LJM-5708. Additionally, it was shown that the LJM-5708 aptamer binds to human oligodendroglial cells, or cells that exhibit myelin and MBP, despite being primarily designed for mouse proteins. The aptasensor based on LJM-5708 demonstrated an LOD of 0.65 ng/mL in artificial CSF, similar to the immunosensor's LOD of 0.36 ng/mL. The aptasensor was demonstrated to be useful within the 1–128 ng/mL clinical concentration range (Serin and Kara 2025).

Research and development of novel therapies for MS often use autoimmune encephalomyelitis, a mouse model of the disease. Researchers used a bioreceptor for MBP identification created for potential therapeutic uses in a mouse model: an MBP-specific aptamer. By incorporating GO NPs onto screen-printed carbon electrodes (SPCE) and

immobilizing an aptamer to form a bioactive layer on the sensor surface, a nanobiosensor was created to detect and monitor MBP. The artificial CSF containing MBP and MSA was the setting for the validation trials. In the concentration range of 0.01 … 64 ng/mL, the aptasensor demonstrated its usefulness, and its LOD in artificial CSF was 0.01 ng/mL (Serin and Kara 2024).

Researchers want to know how medications interact with double-stranded DNA to make better, more efficient medicines. Heat denaturation, ultraviolet, fluorescence, electrochemistry, and viscosity tests were among the analytical tools used to study cladribine's binding behavior with double-stranded DNA. At 298 K, researchers used the Benesi-Hildebrand plot to determine cladribine's binding constant (Kb) with double-stranded DNA as $2.41 \times 10^4 \pm 2.20$. Molecular docking simulations investigated the molecular-level interactions between double-stranded DNA and cladribine. For 50 ns, molecular dynamics simulations tracked the stability of drug-bound DNA. The simulations showed that cladribine forms hydrogen bonds primarily with the bases of Guanine in the minor groove region of DNA, which is how it attaches to double-stranded DNA. Researchers could track the DNA and cladribine complex stability using the post-MD analysis. In addition, researchers devised two approaches for low-level cladribine evaluation utilizing DPV based on electrochemical methodology. The first technique uses cladribine oxidation in a pH 2 phosphate buffer. In contrast, the second employs deoxyguanosine oxidation signals in a pH 4.80 acetate buffer, which are products of cladribine and double-stranded DNA binding. The two techniques' analytical effectiveness was confirmed by using cladribine concentrations varying from 2 to 25 µM, with a LOD of 0.30 µM and 0.92 µM, respectively. In addition, utilizing both standard procedures, the researchers tested the percentage of recovery using pharmacological injection (Şenel et al. 2025).

Electrochemical Sensor for Detection of Novel Biomarker in Huntington's Disease

An autosomal-dominant mutation in the huntingtin (HTT) gene causes HD, a rare and progressive ND characterized by severe physical, cognitive, and mental symptoms and neuronal loss in the brain. Because HD has a complicated etiology, biomarkers are crucial for early diagnosis, tracking disease progression, and determining how well treatments work. The various underlying biological mechanisms, the HD's diverse presentation, and the protracted premanifest HD period make it tough to develop consistent HD biomarkers. A bibliometric analysis of a decade's HD biomarker research shows key research trends and gaps. Researchers needed improved HD patient classification, well-designed longitudinal trials to verify HD biomarkers, and a thorough literature assessment of new HD biomarkers. Researchers focused on the prospective use of many wet HD biomarkers, such as NfL, miRNAs, the mutant HTT protein, and particular indicators of inflammation and metabolism in the premanifest stage of HD. In addition, imaging (e.g., MRI, PET, and diffusion tensor imaging) and neurophysiological (e.g., motor tapping, speech, EEG, and event-related potentials) indicators representing structural brain abnormalities and motor or behavioral impairments are also assessed. According to the results, improved patient classification and well-designed longitudinal studies are urgently needed to uncover and validate viable HD biomarkers. To optimize HD clinical management techniques, enable tailored treatment approaches, and advance clinical trials of HD-modifying medicines, reliable biomarkers, especially in the premanifest HD stage, are necessary (Aqel et al. 2025).

As a neurological illness that spreads throughout the body, HD has a devastating impact on people's standard of living. The pathophysiology and diagnostic literature around it have grown substantially in the last several years. Early supportive and symptomatic treatment may be established by using magnetic resonance spectroscopy (MRS) data to distinguish between healthy control (HC) patients and premanifest Huntington's disease (Pre-HD). To better understand MRS's potential as a biomarker, researchers conducted a systematic study to assess metabolic alterations utilizing the technique. There was a significant drop in N-acetyl Aspartate (NAA) in 77.9% of cases and a decrease in total NAA (tNAA) in 72.4% of cases in the putamen. In addition, all patients had lower levels of tNAA and NAA when compared with those with pre-HD in the putamen. While 50% of HD subjects had a significant drop in tNAA, 100% of HD patients demonstrated a substantial reduction in NAA and creatine in the caudate nucleus compared to pre-HD participants. Potential objective biomarkers exist for the beginning and pathogenesis of HD. MRS reveals variations between controls, pre-HD, and HD patients, suggesting that it might be a valuable technique for the early identification of HD. The reporting and technique of MRS should be standardized in future investigations (Martínez Lozada et al. 2024).

Despite progress, finding trustworthy biomarkers for HD is still very difficult because of the disorder's varied presentation, which includes a wide range of physical, cognitive, and mental symptoms. Through imaging methods and clinical examinations, longitudinal observational studies have shown significant neurological, behavioral, motor, and cognitive changes, offering essential insights into the course of the illness. Nevertheless, these initiatives have not yet produced reliable and consistent HD biomarkers. The discovery of biomarkers is complicated by the involvement of Huntington proteins in many biological processes, such as protein aggregation, neuroinflammation, and mitochondrial

failure. Additionally, discovering trustworthy biomarkers is made more difficult by variables other than the basic HTT gene mutations, such as genetic modifiers and environmental impacts, which increase heterogeneity in the onset, development, and presentation of the illness. Consequently, HD has a complex pathophysiology, highlighting the difficulty in identifying a single biomarker that precisely captures the illness process and requiring a panel of HD biomarkers (Aqel et al. 2025).

Another commonality among ND produced by proteins with a propensity to aggregate, such as AD or HD, is the disturbance of the normal balance of vital metal ions, such as Cu. Additionally, Cu^{2+} may be reduced to Cu^{+}, necessary for the Fenton-like reaction ($Cu^{+} + H_2O_2 \rightarrow Cu^{2+} + OH^{\bullet} + OH^{-}$) that produces reactive oxygen species (ROS), contributing to oxidative stress, which is crucial for HD. These compounds' pharmacological characteristics can be improved by their coordination on the Cu core, making it easier to pass across the blood–brain barrier (BBB). Thus, an extract from *Bacopa monnieri* L. was used to create a novel approach for screening anti-neurodegenerative drugs utilizing spectroscopic and electrochemical methods, considering the metal chelating properties of various natural compounds (Nastasijevic et al. 2012; Brinvillier et al. 2022; Bono-Yagüe et al. 2020). Within this framework, researchers investigated several organic compounds (trehalose, ethylenediaminetetraacetic acid, salicylate, metformin, phenylenediamine, and ethylenediaminetetraacetic acid) as well as organic extracts derived from *Bacopa monnieri* L., a plant with a long history of use in Ayurvedic medicine and a wide array of biological effects. Since Cu-based complexes can present enhanced pharmacological properties compared to the organic-free ligand, the chelation effect may play an essential role in NDs. Researchers used electrochemical measurements and Ultraviolet–Visible spectroscopy to achieve this goal. Another step toward a better understanding ND was using *Caenorhabditis elegans* models of polyQ toxicity in biological experiments (Brinvillier et al. 2022).

Using voltammetry of microparticles, it is possible to conduct spectroscopic and electrochemical screenings in aqueous media at the biological pH of compounds and plant extracts that exhibit neuroprotective effects via the Cu-binding mechanism. Before submerging in Cu^{2+} solutions, electrodes were treated with microparticulate sheets containing the evaluated chemicals. In every instance, chemicals that interact strongly with Cu cause a noticeable peak splitting in the voltammetric signals of Cu^{2+} (Brinvillier et al. 2022; Boer et al. 2023). A Hess cycle procedure using surface-confined complexes may be used to analyze peak splitting seen in voltammetric peaks for electrodes treated with chemicals exhibiting neuroprotective action. The described solid-state electrochemistry screening achieves high sensitivity with chemical quantities to be examined in the microgram-nanogram range. This fascinating approach paves the way for nanoscopic-level investigation of cooper–ligand interactions in an aqueous environment at physiological pH, eliminating the requirement for prior incubation. Bacopa extracts showed a strong capacity to chelate Cu ions when tested using this method. This and the Bacopa and ND literature indicated that the extracts would help lower HD traits in animal models. As predicted by the researchers, *C. elegans* worms overexpressing these harmful chemicals in muscle cells showed less aggregation of polyQ-containing proteins. Restoring function does not always occur in tandem with reducing aggregation. Therefore, researchers used a worm model to assess the effects of these extracts on neuronal toxicity. Curiously, worms whose mechanosensory neurons are damaged by polyQs may have their neural function restored by these extracts. Some NDs, such as HD and spinocerebellar ataxias, have no known therapy because their proteins include aberrant CAG expansions and encode lengthy sequences of polyQs. Researchers established Bacopa as a potential new weapon in the battle against ND produced by proteins prone to aggregation (Brinvillier et al. 2022).

A new electrochemical detection approach based on enzymes has been developed for the chemical toxicant ethanolamine (EA). Researchers used monoamine oxidase A (MAO-A) to oxidize EA. By using the MAO-A enzyme, it was possible to achieve a direct electron transfer from the electrode to EA, eliminating the need for a mediator. This finding lends credence to the idea that this technology might be used to create a third-generation biosensor for EA detection, which would be able to detect levels of EA far below the IDLH value of 30 ppm. In addition, the number of electrons involved and the heterogeneous rate constant were determined for EA in the PBS buffer. With a LOD 4.1 ppm, the calibration plot demonstrated a linear relationship between 2.02×10^{-4} M and 10.10×10^{-4} M of EA in PBS buffer. Using Raman and EIS methods, the altered electrodes are described. Scientists have shown that this technique can detect EA in the environment and convert it to other chemicals without a mediator or signal (Sikarwar et al. 2016).

Due to their wealth of terminal functional groups, many active sites, and remarkable electrical characteristics, two-dimensional transition metal carbides/nitrides (MXenes) have a lot of promise as volatile organic compound (VOC) sensors. Pure MXene $Ti_3C_2T_x$, on the other hand, degrades quickly in natural environments due to oxidative stress, and there are still significant issues with its reaction time and stability. This results in a $Ti_3C_2T_x/SnO_2$ sensor that is highly selective for volatile organic compounds (VOCs), has excellent long-term stability, and was made possible by intentionally adding metal oxide semiconductors to multilayer $Ti_3C_2T_x$. Findings demonstrate that the $Ti_3C_2T_x/SnO_2$

hybrid sensor effectively detects hydrogen-bonded gases, with EA exhibiting exceptionally high efficiency. In addition to having excellent selectivity to more than twelve distinct VOCs, the hybrid sensor's sensitivity to EA is more than ten times higher than that of pure $Ti_3C_2T_x$. The functional terminal groups, the mesoporous-rich hierarchical structure, the enormous specific surface area of 45.186 m^2/g, and the synergistic effects of n–n nano heterojunctions allow for the facilitated EA-sensitive characteristics. Further enhancement in sensor sensitivity is achieved by the novel $Ti_3C_2T_x/SnO_2$ preparation that uses terpinol, which helps bring the $Ti_3C_2T_x/SnO_2$ into close contact with the ceramic tubes (Xu et al. 2024b).

Electrochemical Sensor for Detection of Novel Biomarker in Parkinson's Disease

The term "α-synucleinopathies" refers to a collection of NDs that include multiple system atrophy, dementia with Lewy bodies, PD (with or without dementia, e.g., PD with dementia), and α-Syn and later Lewy bodies. α-Syn inclusions are primarily seen in cell bodies and axonal processes of neurons at various stages in PD, dementia, and dementia with Lewy bodies (Atik et al. 2016). PD Lewy bodies are believed to be mainly composed of α-Syn aggregates, which are present in both the cytoplasm and intercellular space. Neuroinflammation and neuronal dysfunction may both be facilitated by abnormal α-Syn accumulation. As the brain's resident immune cells, microglia carefully monitor changes in the microenvironment and preserve their homeostasis. Experiments have shown that microglia may encircle α-Syn aggregates and that extracellular α-Syn aggregates can activate microglia, which results in elevated extracellular superoxide, inflammatory cytokines, and the selective death of dopaminergic neurons (Du et al. 2021). Skin α-Syn tests show great promise as PD diagnostic tools, especially seed amplification assays and phosphorylated α-Syn immunological approaches; seed amplification assays were more sensitive than immunology methods. It is still difficult to differentiate PD from other α-synucleinopathies, and methodological variations underscore the need for standardization. To improve diagnosis accuracy, further study should concentrate on combining skin α-Syn detection with additional biomarkers (Zhao et al. 2025).

Motor and non-motor impairments, as well as a lack of dopamine, are symptoms of PD, a complicated neurological illness that develops with age. Poor early diagnostic accuracy, difficulties tracking disease development, and a lack of therapy alternatives all contribute to the challenge of creating practical therapeutic approaches for PD. In three investigations, the three most prevalent and vital metabolites were acetyl phenylalanine (a subtype of phenylalanine), tyrosine, and kynurenine; a total of forty metabolites were shown to be associated with the early and mid-stage pathophysiology of the illness. In addition to disrupting mitochondrial function and brain energy metabolism, these metabolites impede dopamine production, all of which are thought to contribute to ND. In addition to three dihydrocortisol investigations, two others discovered that hydroxyprogesterone, phenylacetylglutamine, furoglycine, glycine, tiglyglycine, aminobutyric acid, and hydroxyphenylacetic acid were often dysregulated (Dhiman, et al. 2025).

Future studies should include genetic, biochemical, and neuroimaging markers to establish a comprehensive biomarker profile of PD. Because this multimodal approach captures the multifaceted nature of the illness, it may improve diagnostic accuracy and aid in early detection. People who are at risk of developing PD or who are in the early stages of the condition need longitudinal studies that look at biomarker changes over time. Examining gene–environment interactions may provide important information on the genesis of PD. Even with these developments, future research focuses on creating a complete biomarker panel tailored to PD. In addition, using a neurology 4-plex-A biomarker panel in conjunction with plasma α-Syn has shown promise in distinguishing PD patients from healthy people and forecasting the course of the illness. Blood biomarkers such as serum neurofilament light (NfL) and genetic status (GBA and APOE) are useful in PD prognostic modeling when paired with clinical variables, providing a more robust prediction of unfavorable outcomes. Moreover, PD patients' extracellular vesicles have shown potential as a source of new biomarkers for prognosis, diagnosis, and treatment monitoring (Abukuri 2024).

PD is a progressive ND marked by α-Syn buildup and dopaminergic neuron loss. Patients with PD have markedly reduced levels of glutathione (GSH), a vital antioxidant. Researchers demonstrated a dual-mode detection approach for GSH selection using a single probe. Resorufin (Re) was used as the reporting unit in a series of "turn-on" electrochemical and fluorescent probes with particular GSH recognition sites. The 7-(3,5-dinitrophenoxy)-3H-phenoxazin-3-one (Re-DNP) probe was chosen from among them because of its strong selectivity as an electrochemical and fluorescence probe. Compared to hydrogen sulfide (H_2S) and cysteine (Cys), it responded better to GSH. GSH has a linear range of 25–500 μM and a LOD 5 μM for electrochemical detection SPCE/CNT-modified electrodes. With a LOD 2 μM and a significant linear association between fluorescence intensity and GSH content in the 10–700 μM range, the probe increased emission at 630 nm by 78 times when GSH was present. When applied to actual clinical blood samples, the probe showed considerably reduced GSH levels in PD animals and human patients compared to healthy controls. With prospective uses in comprehending GSH's

function in PD and associated ND, this dual-mode detection technique offers a sensitive and accurate instrument for GSH detection (Dong 2025a).

Detecting the relevant biomarkers correctly is crucial for accurate PD diagnosis and efficient therapy. A key component of PD pathophysiology is cellular oxidative stress caused by accumulating ROS, including H_2O_2. Using a simple one-step process, scientists created two compounds: Re–B and Re–OB. When Re–B reacts with H_2O_2, the phenol group is restored by the selective cleavage of the borate ester group. The result is a "turn-on" fluorescence effect and an electrochemical response that uses dual-signal ratiometry. When interacting with H_2O_2 on an SPCE modified with single-walled CNTs (SPCE/SWCNTs), the Re-B probe shows a distinct "turn-on" electrochemical current response at − 311.1 mV, followed by a "turn-off" response at − 257.6 mV. At the same time, a peak at 586 nm in the fluorescence spectra indicates a "turn-on" reaction. The researchers demonstrated a remarkable selectivity and sensitivity for H_2O_2, with electrochemical detection limits as low as 0.5 µM and fluorescence detection limits as low as 0.1 µM. This method of measuring H_2O_2 levels in serum is reliable since the findings from electrochemical and fluorescence measurements are consistent. This method shows great promise as a POC diagnostic tool for early PD detection, yielding important data for prompt diagnosis and therapy (Dong, et al. 2025b) (Table 1).

Challenging and Limitations of the Electrochemical Sensors in Neurodegenerative Diseases

Many POC biosensors are simple, low-cost options. Potentially improved patient care could result from POC real-time and distant virtual healthcare monitoring using biosensors. Due to their ability to identify patterns of bioindicators and provide information on their existence in biological samples, biosensors have been extensively studied in recent decades, enabling reliable diagnosis. Considerations such as the need for rapid label-free detection, miniaturization of the sensor size, and mobility will limit the types of biosensors that may be used in future POC systems (Sumitha and Xavier 2023). Three primary obstacles to the proper functioning of electrochemical sensors are low LOD value, actual sample sensitivity, and stability and repeatability. These are also the main obstacles producing of electrochemical biosensors (Singh et al. 2021). Many biosensors that perform very well in detecting ND biomarkers in biological samples have recently drawn a lot of interest because they have a low detection limit and a linear range, making them suitable for POCT instruments. While these POCT devices have several benefits over traditional settings, there are still several constraints, such as the need for error-free device development and production. Moreover, these detection techniques are hindered by several issues, including low stability, limited immunogenicity, limited practicality, possible toxicity, and complicated labeling procedures (Gautam 2022).

The LOD establishes the lowest analyte limit that a sensor can detect. Therefore, optimal biosensors must have a very low LOD value (Singh et al. 2021). Repeatability is crucial in the manufacturing and marketing of sensors. Since it is impossible to test every sensor, the results obtained for a given sensor must be repeatable for all similar sensors produced (Singh et al. 2021).

Applying a sensor to actual samples is the most critical feature it can have. Utilizing a sensor in diagnostics is impossible if it fails to test an actual sample accurately. Saliva, blood, urine, perspiration, bodily fluids, tears, etc., are the genuine samples often used for electrochemical biosensors. Several considerations must be made to gather an actual sample for detection, which has challenges (Singh et al. 2021).

The matrix effect reduces the sensitivity and selectivity of electrochemical sensors. To avoid this matrix effect, the sample has to be diluted; nevertheless, more significant dilution might cause the results to deviate from reality. The ideal electrochemical biosensor would be able to detect a pure sample without any processing or dilution. Similar to how saliva samples need to be diluted before they can be identified, the peak position of urine samples is affected by pH fluctuations. Tear samples have helped diagnose diabetes since they are less complex; nevertheless, another challenge is the pH variation. Additionally, the analyte concentrations in tears may vary according to discomfort and mood. Proteins, lipids, and other species present in actual samples may adsorb onto the surface of an electrochemical biosensor, reducing its sensitivity and reproducibility. The researchers are seeking new, innovative materials and methods, both active and passive, to resolve this issue. The active method generates shear stresses to prevent extra species from adhering to the sensor surface. On the other hand, the passive method involves coating surfaces with polymers to make them hydrophilic, preventing proteins from sticking. Because biosensors made using electrochemistry must withstand extreme environments, their stability is of the utmost importance (Singh et al. 2021).

Despite encouraging progress in ND detection methods using electrochemical aptasensors, there is a need for enhanced sensitivity, selectivity, and overall performance. One promising approach to ND detection and monitoring is electrochemical aptasensors. More sensitivity, selectivity, and compactness improvements are required for electrochemical art sensors to detect and monitor ND to their full potential. A promising avenue for the early diagnosis and monitoring of ND is the creation of electrochemical

Table 1 The potential of the electrochemical sensor in detecting several NDs

Electrochemical	Neurodegenerative diseases	Limit of detection (LOD)	Explains	Refs
rGO conjugated with BACE1 Ab and immobilized on FTO electrodes for rapid detection of BACE1 Ag	AD	0.64 fM in buffer samples and 1 fM	With its reduced detection time and cost and improved detection performance compared to current sensors, the constructed electrochemical biosensor for BACE-1 detection shows promise for early AD diagnosis in clinical samples	Dey et al. (2022)
Ultra-sensitive photoelectrochemical (PEC) biosensor	AD	LOD of 0.33 fg/mL	Based on researchers' findings, photoelectrochemical biosensors are a viable tool for early AD screening in high-risk groups. They are inexpensive and susceptible to detecting ultra-trace chemicals in human bodily fluids	Li et al. (2025)
COF-$B(OH)_2$ electrochemical biosensors	AD	0.32 pg/mL	Using state-of-the-art COF-$B(OH)_2$ materials to create electrochemical biosensors for analyzing glycosylated proteins was the subject of new research	Lv et al. (2025)
AgNPs/Nafion-modified GCE	AD	0.025 µg/mL	This immunosensor, based on AgNPs and Nafion, offers a potential platform for the sensitive and quick detection of Lf in evaluating AD	Rabbani et al. (2024)
Synthesizing a ferrocene probe (Fc-Probe), which can precisely detect the N terminus of the APP peptide fragment thanks to its aldehyde group	AD	8.0 mU/mL	Such a BACE1 sensor allows for the "signal-on" detection of BACE1 activity using a straightforward, sensitive, and inexpensive detection mechanism	Chang, et al. (2024)
GCEs were electrochemically produced with AuNPs	AD	2.31 pg/mL	To precisely trap the p-tau231 protein, a nucleic acid aptamer was engineered to create an aptamer-antigen combination. The suggested biosensor showed a 2.31 pg/mL LOD and a broad linear detection range (10 to 107 pg/mL) for p-tau 231. The biosensor proved helpful in complicated practical samples, with recoveries ranging from 97.59 to 103.26% in human serum	Kong et al. (2024)
Double-stranded DNA electrochemical biosensors	MS	0.30 µM and 0.92 µM	Using the post-MD analysis, researchers could track the stability of the DNA and cladribine complex. In addition, researchers devised two approaches for low-level cladribine evaluation utilizing DPV based on electrochemical methodology	Şenel et al. (2025)
The 7-(3,5-dinitrophenoxy)-3H-phenoxazin-3-one (Re-DNP) probe	Parkinson diseases	5 µM	When applied to actual clinical blood samples, the probe showed considerably reduced GSH levels in PD animals and human patients compared to healthy controls	Dong (2025)

Table 1 (continued)

Electrochemical	Neurodegenerative diseases	Limit of detection (LOD)	Explains	Refs
Electrochemical sensing and biosensing, a novel conductive ink incorporating carbon black into a poly(vinyl alcohol) matrix	Parkinson diseases	1.3 μg mL^{-1}	For α-Syn concentrations in phosphate buffer, a linear range of 1.5–15 μg mL^{-1} was found, with a computed LOD of 0.13 μg mL^{-1}. When the suggested immunosensor was used on blood serum samples, the linear range of α-Syn was between 6.0 and 100.5 μg mL^{-1}, with a LOD of 1.3 μg mL^{-1}. Its potential applicability to complicated matrices is shown by the fact that both linear curves attend the range for the actual diagnosis	Orzari et al. (2024)
Carbon Fiber Microelectrode (CFME)/SWCNT/MB + Pygal sensor is triggered, producing a peak at 0.33 V from the Pygal enzymatic hydrolysis product oxidation	Parkinson diseases	0.1 U L^{-1}	Lastly, the measurement of β-Gal in the entire blood of PD model mice was made possible by CFME's superior electrochemical performance and advantageous physicochemical characteristics	Dong et al. (2022)

aptasensors. Incorporating biomolecules like aptamers into electrochemical devices allows for a wide range of applications, and these aptasensors use that fact. Because of this integration, biomarkers unique to ND may be detected with more sensitivity and selectivity. Additional benefits of fabricating aptasensors using nanomaterials include enhanced performance, low detection limits, and excellent signal-to-noise ratios. Improved patient outcomes and tailored treatment plans are possible benefits of these electrochemical aptasensor developments, which likely address early ND identification and monitoring problems. In addition, new electrochemical aptasensors offer a low-cost, non-invasive way to diagnose ND (Ahmed et al. 2025).

Since electrochemical biosensors may provide quantifiable data in 2 to 5 h, their development has been aided by the discovery of AD biomarkers in blood and CSF. The primary problems here are enhancing the selectivity and time-stability of biosensors and achieving the low cut-off values of the primary AD biomarkers in human samples. Nanomaterials have been added to biosensors, either as electrode modifications or labels. Although using aptamers and combining these two components in sandwich-type biosensors is impressive, Abs are the most common biological recognition element. Without a question, AuNPs are the most widely employed nanomaterials, both as labels and as electrode modifiers. Carbon-based nanomaterials come in second. It is important to note that the usage of nanocomposites—combinations of various nanomaterials—is growing since they often have a synergistic impact (Toyos-Rodríguez et al. 2020).

From early Aβ accumulation to later-stage tau pathology, blood-based p-tau biomarkers, such as plasma p-tau231 and p-tau217, have shown robust correlations with AD pathology. The accurate detection of blood p-tau has improved due to recent developments in EC sensing technology. High sensitivity and economical detection are made possible by EC-based immunosensors, which translate biological interactions into electrical signals (Chen et al. 2023). Reproducibility and stability are jeopardized by issues such as the non-conductive nature of Abs, the need for nanomaterials in sensor construction, and vulnerability to environmental influences. Moreover, real-time measurements and the analysis of intricate biological samples continue to be significant challenges that call for advancements to improve the usefulness and resilience of these platforms (Wen et al. 2017). Additional sensitivity and repeatability enhancements are required for more precise and dependable detection. To support exact and early AD diagnosis, researchers should concentrate on creating systems that can identify various AD-related biomarkers in the future and use cutting-edge data processing techniques like machine learning. These technical developments might help close the gap between clinical applications and experimental discoveries, offering

functional extra choices for treating NDs (Wang et al. 2025; Jakhonkulovna, et al. 2025).

α-Syn, the defining biomarker of PD, is the focus of electrochemical biosensors. Using α-Syn detection techniques, researchers used Abs and aptamers to create the biorecognition layer on electrode surfaces. In addition, electrochemical methods for examining α-Syn's interaction with tiny molecules have also been covered. To support structure–activity relationship (SAR) investigations, research efforts may focus on creating a high-throughput multiplexed system that can examine α-Syn's interaction with an extensive library of drug candidates. In addition, a few significant issues with biofouling of electrode surfaces need to be considered to create a biosensor that may be utilized to detect PD in a clinical context. Researchers anticipated the production of drug-screening platforms and diagnostic devices shortly due to the exponential rise in electrochemical biosensor research (Hassan et al. 2019).

The presented biosensor studies have a convenient design and excellent analytical performance for the selected target analyte because technological advancements support biosensor manufacturing with innovative smart nanomaterials. However, some of these targets are not recognized as reliable biomarkers for MS. Therefore, identifying precise and sensitive molecular biomarkers for MS diagnosis, prognosis, and therapeutic response is the first step toward assessing the viability of commercializing a POCT-applicable biosensor for MS. The created biosensors will also help with efforts to describe reliable biomarkers for MS as they provide a straightforward, reasonably priced, and accurate substitute for laboratory tests. The existing analytical methods for detecting some MS candidate biomarkers are costly and impractical, notwithstanding their excellent specificity. It is suggested that biosensor researchers focus on indicators such as EXOs and neurofilament light chain. The following issues to be addressed for more effective usage of these devices include multiplexing and high-throughput screening. Diagnostic tests are more accurate when many biomarkers are used. However, data processing becomes more difficult when many targets are recognized simultaneously. Therefore, it is likely that future biosensor designs will include artificial intelligence algorithms that interpret complicated fingerprints using pattern recognition (Demirdöğen 2021).

There is currently no treatment for HD, which emphasizes how important a prompt and accurate diagnosis is for sufferers and their families. In addition, the diagnostic potential of blood-based biomarkers and tests that quantify specific proteins or metabolic alterations is being studied. There is potential for improving early and precise HD diagnosis by combining many biomarkers with clinical evaluations and genetic testing. In addition, as early intervention may give the best chance of slowing or stopping disease development, continuing research into disease-modifying treatments for HD emphasizes the need for accurate diagnosis (Ganesh et al. 2023). Nevertheless, using electrochemical sensors for HD detection has received very little research. Several electrochemical techniques discussed enable quick, accurate, and very sensitive examination of neurotransmitters in biological systems without the need for preparatory procedures; as a result, they are practical analytical instruments that may be used in clinical investigation. The creation of implanted sensors for ongoing monitoring of human health conditions and disease progression is another objective in electrochemical biosensing, using present and future technologies. Thus, the early diagnosis of HD may benefit from using electrochemical sensors. Researchers need to conduct further research to create electrochemical sensors based on polymers or NPs for future HD treatments (Tavakolian-Ardakani et al. 2019).

Other benefits include the cost-effectiveness and simplicity of electrochemical biosensor manufacturing. The need for costly reagents, specialized equipment, and skilled workers generally restricts the accessibility of traditional laboratory-based biomarker detection methods. Electrochemical biosensors, on the other hand, use inexpensive electrode materials and sensing platforms improved by nanomaterials, which lowers production costs without sacrificing performance. Electrochemical biosensors may be adaptable because they may be altered with different biorecognition components, such as Abs, aptamers, enzymes, and MIPs. Because of its adaptability, highly selective biosensors may be created to identify many ND indicators in intricate biological fluids, including blood, CSF, and saliva. Additionally, by enhancing surface functionalization, biocompatibility, and signal amplification, integrating these biosensors with nanomaterials improves performance and detection capabilities. Given these benefits, electrochemical biosensors—a sensitive, quick, affordable, and portable substitute for traditional techniques—are crucial for diagnosing NDs. However, to fully achieve their therapeutic potential, several obstacles and restrictions must be overcome despite their promise (Bae et al. 2025).

However, most research struggles to reach commercial development due to poor detection accuracy in complicated samples, limited stability, repeatability, and durability, and extensive data processing and analysis challenges. Second, there are strict regulations governing electrochemical biosensors used in clinical settings. To guarantee that prolonged use does not endanger human health, wearable and implantable biosensors used for medical reasons must pass stringent testing and approval procedures in many jurisdictions. Prolonged approval processes may delay market entrance, decreasing the device's relevance and competitiveness, even if these rules are crucial for customer safety. Notable regional differences in safety requirements further increase uncertainty in the worldwide market. In addition, health data are now regularly sent in real time to mobile devices or cloud

platforms due to the increasing use of wearable technology and telemedicine. Another significant obstacle to the commercialization of electrochemical biosensors is the privacy and security of consumer health data. Strict data encryption and privacy protection procedures must be used throughout data transfer and storage to safeguard private health information. For industry to thrive sustainably, a common framework for data security must be developed (Cui et al. 2025).

Polymer-Based Electrochemical Sensors

Due to their unique properties, such as compatibility, conductive nature, electron promoter, and inexpensive cost, polymer-based electrochemical sensors contribute to producing electrochemical sensors and biosensors. Electrodes modified with a single material have not yet hit the market because of issues with sensitivity, selectivity, surface poisoning from adsorbed intermediates, and interference from other species. One attractive feature of metal NPs and polymers frameworks modified electrodes as electrochemical sensors or biosensors is that they avoid these difficulties. A biosensor's selectivity in an electrochemical biosensor depends on the recognizing element, the host matrix, and the interaction between the two. Obtaining the required sensitivity and stability is made easy with metal NPs and polymers frameworks, since polymers act as selective adsorbents for biomolecules, and MNPs mediate the redox reactions of biomolecules (Prakash et al. 2013).

Polymeric NPs (PNPs) are a new kind of optically active nanomaterial that has just come to light due to its many desirable properties, including photostability, minimal cytotoxicity, rapid emission rate, high fluorescence brightness, biocompatibility, and a high and adjustable fluorescence quantum yield. Sensing and biosensing, controlled drug delivery, nanomedicines, catalysis, wastewater treatment, and many more biological and medical applications use PNPs, which are synthesized either from conjugated or nonconjugated polymers or by polymerizing appropriate monomers (Bharadwaj et al. 2022). One of the primary neurotransmitters in the CNS, dopamine (DA), is essential for operating dopaminergic (DArgic) neurons. One of the main characteristics of age-related ND, such as PD, is the gradual loss of this particular population of cells. Although this method has medium- to long-term adverse effects, the mainstay of PD symptomatic treatment has been the injection of L-DOPA, an amino acid precursor of DA that passes the BBB, whereas DA does not. DA-nanoencapsulation treatments have been extensively investigated as potential substitutes for DA replacement to overcome this restriction. Overcoming DA's low encapsulation yield and/or poor biodistribution/bioavailability remains challenging today. Researchers presented the synthesis of a family of PNPs inspired by neuromelanin. Researchers' approach was based on the reversible coordination complexation of DA to iron metal nodes polymerized with a bis-imidazole ligand, which encapsulates DA inside NPs. In addition to being straightforward and affordable, the researchers' approach yields DA loading efficiencies of up to 60%. Compared to free DA, DA nanoscale coordination polymers (DA-NCPs) demonstrated improved absorption by BE(2)-M17 DArgic cells, decreased toxicity, and slower breakdown kinetics in vitro. When the particles were directly infused into the rat ventricle in vivo, they quickly spread throughout the healthy rat brain, raising striatal DA levels. More notably, the frequency and length of apomorphine-induced rotations were considerably reduced after 4 days of nasal administrations with DA-NCPs equal to 200 µg of the free drug per day than in the vehicle or DA-treated rats used for comparison. Researchers showed the benefits of using nanostructured DA for DA-replacement treatment (García-Pardo et al. 2021).

The target analyte must be specifically and selectively recognized in most analytical procedures. Biomolecules such as Abs, enzymes, and receptors have met these criteria. Unfortunately, in certain situations, biomolecules cannot be used; for example, proteins will become insoluble in organic solvents and very acidic or basic environments. Not to mention how expensive and time-consuming it is to prepare and isolate these biomolecules, which limits their use. This led to the development of synthetic receptors that function similarly to their biological counterparts. Using MIP is one way to get these synthetic receptors. MIPs can also be used to create analyte-specific recognition sites on a synthetic polymer. The artificial recognition sites are designed to match the target analyte in size, shape, and chemical function, resulting in highly selective and specific identification. MIP is a polymer with a unique binding site that can only bind to specific analytes. Its excellent stability, ease of synthesis, and potential to reduce costs led to its extensive use as a receptor rather than an Ab or enzyme. Repurposing MIPs allows for the creation of more promising MIP-NPs. There are practical uses for MIPs in electrochemical sensors, and they have even been tested on human samples. Integrating MIP-NPs with electrochemical sensors has allowed for the real-time monitoring of several compounds of biological significance, including pharmaceuticals, insecticides, environmental toxins, secondary metabolites, and more (Fauzi and Saputri 2019).

Researchers created an electrochemical sensor based on MIP-NPs for the sensitive and selective detection of diazinon (DZN) pesticides. Suspension polymerization was employed to generate the diazinon imprinted PNPs, which were then used to alter the carbon paste electrode (CPE) composition to manufacture the sensor. The SWV and CV techniques were used for electrochemical experiments. Researchers demonstrated that compared to the CPE-based

non-imprinted PNPs (nano-NIP-CP), the nano-MIP-CP had a much greater adsorption capacity for diazinon. With two linear ranges of 2.5×10^{-9} to 1.0×10^{-7} mol L^{-1} and 1.0×10^{-7} to 2.0×10^{-6} mol L^{-1}, the suggested sensor demonstrated exceptional sensitivity (95.08 µA L µmol^{-1}) for diazinon, along with a LOD 7.9×10^{-10}—$10-L^{-1}$. The sensor detected diazinon in apple fruit and well water samples, with recovery values ranging from 92.53% to 100.86% (Motaharian et al. 2016).

Conducting polymers (CPs) are among the most practical materials when designing new sensor platforms. The possibility of using the polypyrrole (PPy) polymer to make ultrasensitive biosensors has prompted research into the material. Biodetection systems are significantly more effective and reliable when they have specific properties, such as high conductivity, fast electron transfer at the electrode/solution interface, charge storage capacity, redox reversibility, relative biocompatibility, and functional groups for directed biomolecule anchoring. An appealing prospect for new biotechnological uses, this organic polymer is structurally flexible, environmentally stable, inexpensive, and easy to synthesize. Researchers have shown that PPy is an excellent material for a substrate or matrix to electrodeposit AuNPs with low molecular aggregation and maximal surface area (Avelino et al. 2021).

A new, cost-effective electrochemical sensor for measuring quorum signaling molecules (AHLs) in Gram-negative bacteria was created by combining magnetic NPs with MIP technology. Through surface polymerization, magnetic molecularly imprinted polymers with the ability to selectively absorb AHLs were effectively produced. Researchers used electrochemical measurements to characterize the particles after depositing them onto the surface of a magnetic CPE. Researchers recorded the oxidative current signature that is typical of AHL using DPV. An innovative method for monitoring quorum signaling molecules in Gram-negative bacteria has been developed using an electrochemical sensor based on Fe_3O_4@SiO_2-MIP. Its real-time detection capacity, high specificity, outstanding repeatability, and strong stability make it a promising tool for clinical diagnosis and food analysis (Jiang et al. 2016).

Highly specialized sensors might be made from polymer-based sensors with the proper adjustments or features. Polymers may be used directly in sensing or by immobilizing specific receptors on them. Polymers' ease of functionalization, biocompatibility, extended lifespans, softness, lightweight, and economical manufacturing are only a few advantages of employing them as sensors. Significant changes have been made to improve performance and transfer lab-derived sensors into device marketing applications. However, there are issues with polymer-based sensors: Finding the appropriate precursors is the first step, which is followed by improving and creating the reaction processes and procedures that enable the acquisition of a detectable signal. (2) Looking for new materials to use as polymer matrices. (3) Creation of ion-selective and pH-based sensors. (4) Conducting trials to automate the acquisition of polymer-based sensors. To solve these challenges, multidisciplinary cooperation among chemists, engineers, and computer scientists will accelerate the adoption of large-scale manufacturing and development (Alam et al. 2022).

Polymer-Based Electrochemical Sensors in Diagnosis of AD

A vital biological sensor for ACh detection is produced by immobilizing the enzymes acetylcholinesterase (AChE) and choline oxidase (ChO) on the surface of iron oxide (Fe_2O_3) NPs and poly(3,4-ethylenedioxythiophene) (PEDOT)-rGO nanocomposite modified fluorine doped tin oxide (FTO). Researchers used SEM, EIS, and CV to assess nanocomposites' qualitative and quantitative properties. This biological sensor showed a wide linear range of 4.0 nM to 800 µM, with a detection limit (based on S/N ratio) of 4.0 nM and a response time of less than 4 s. Over a long storage period, the sensor demonstrated excellent sensitivity, selectivity, and stability. The biosensor has shown a low detection limit, unprecedented for previously reported ACh sensors, and high sensitivity. The creation of Fe_2O_3 NPs/rGO/PEDOT modified FTO electrodes for assessing ACh levels in blood samples has broadened the use of biosensors since neurotransmitter detection is a significant problem for individuals with AD or memory loss (Chauhan et al. 2017).

Molecular imprinting technology uses MIPs to provide a personalized capacity for molecular recognition of template molecules. The cross-linked polymer matrix may remember the template molecule by attaching it to specific locations. After removing the template molecule, binding sites sized and shaped similarly to the original imprinted template molecule are revealed. When MIPs reabsorb, they very selectively attach to the template molecule. In MIPs, immunosorbents play a pivotal role in the retention mechanism that relies on molecular recognition. Because of their many advantages over Ab-based routes, MIPs are often referred to as synthetic Abs. These include improved handling, stability (against acids, bases, ions, and organic solvents), reduced cost, high-pressure resistance, a broad working temperature range, and ease of preparation. Drug delivery, cell recognition, and protein recognition are just a few areas of medicine where MIPs are an adequate substitute for biological entities. Researchers targeted a biosensor for β-amyloid detection based on molecularly imprinted polypyrrole (MIPPy). Researchers used an artificial receptor called an imprinted polypyrrole. It was created by electropolymerizing pyrrole on carbon electrodes that had been screen-printed and then subjected to β-amyloid. B-amyloid provides a molecular

template inside the polymer. Using a ferro/ferricyanide marker, the biosensor was assessed by CV. Researchers turned the biosensor's performance-affecting parameters, such as the number of electropolymerization cycles and the time it took for β-amyloid to attach, to attain the highest level of biosensor sensitivity. Researchers derived the Freundlich constant as 0.22 ng mL^{-1} and the exponent as 10.60, respectively, by evaluating the β-amyloid binding affinity with the biosensor surface using the Freundlich isotherm. A 1.2 pg mL^{-1} detection limit was shown using the biosensor. A biosensor was used to determine the concentration of β-amyloid in artificial CSF (Vais et al. 2021).

P-tau proteins are promising indicators for the diagnosis and prognosis of AD. Researchers developed a novel voltammetric sensor that employs a vanadium MXene polydopamine (VxPDA) redox-active composite and a Tau-441-specific polyaniline MIP (PANI MIP) for the sensitive detection of Tau-441 in plasma and interstitial fluid (ISF). The VxPDA/PANI MIP sensor offers a broad detection range of 5 fg/mL to 5 ng/mL in ISF without redox mediators, with a lower LOD of 2.3 fg/mL. In addition, a portable device that employs this approach can detect Tau-441 in fake serum with high sensitivity and specificity within a therapeutically relevant range. This sensor's potential for minimally invasive, early AD diagnosis in clinical settings is highlighted by its quick detection time (about 32 min) and inexpensive cost (around £20/device). This development attempts to ease the shift away from intrusive CSF-based AD diagnosis methods (Arjun et al. 2024).

Tau protein is a biomarker of AD, and researchers created a new electrochemical biosensor based on an MIP for its impedimetric measurement. Hyperphosphorylated Tau protein (Tangles) is a potential biomarker for Alzheimer's diagnosis, as shown by a recent association between AD symptoms and the presence of Tau proteins in an aggregated form. The MIP was created by electropolymerizing 3-aminophenol (AMP) with CV, while the protein template (p-Tau-441) was present. The MIP was immediately constructed on an SPCE. Proteinase K's proteolytic activity in urea broke down the p-Tau-441 protein attached to the polymeric backbone, and it was subsequently removed to leave empty spaces. EIS assessed the respective imprinted and non-imprinted electrodes' performances. In PBS buffer with a pH of 5.6, the MIP-based sensors' detection limit was 0.02 pM. The created platform produced serum samples with acceptable outcomes and high selectivity. Due to its ease of fabrication, quick reaction time, and low cost, the biosensor that the researchers developed is a promising tool for on-site Tau protein screening and an appealing addition to clinically proven approaches (Ben Hassine et al. 2021).

Tau-441, a protein with 441 residues, is an NFT component essential for diagnosing AD. These tangles begin in the entorhinal cortex and expand as AD worsens. The existence of AD biomarkers in ISF and blood is suggested by the combination of the tau proteins found in plasma by Zetterberg and colleagues and the fact that the brain and skin share an ectodermal origin. The researchers showed the creation of an MIP-based sensor surface for sensitive Tau-441 detection from ISF. Aniline was electropolymerized using CV in the presence of the Tau-441 template to form the biosensor surface. For comparison, a non-MIP (NIP) was created using a pH 7.4 phosphate-buffered saline (PBS) solution. Tau-441 was detected in PBS and ISF as part of sensor performance evaluations for the developed MIP sensor. As the concentration of Tau-441 increased, the MIP's current decreased linearly, suggesting that Tau-441 had successfully bound to the polymeric backbone of the MIP. With a LOD of 587 pg/mL (12.2 fM/L) in ISF, the sensor detected Tau-441 in the range of 50 fg/mL to 500 ng/mL (1.22 fM/L to 12.2 nM/L). Future research will examine microneedle patches and MIP-modified electrodes for detecting Tau protein in blood and ISF (Norman et al. 2024).

An MIP electrochemical sensor for identifying amyloid-β42 (Aβ42) as an AD biomarker was demonstrated by researchers. A straightforward ultrasonic technique created a nitrogen-doped carbon-dot-graphene (NCD-G) nanohybrid. Researchers used PPY as an imprinted polymer for electropolymerization using an Aβ42 template. The NCD-G and MIP were altered on an SPCE without a binding agent. SEM, transmission electron microscopy (TEM), UV–Vis spectroscopy, XPS, CV, and SWV were used to examine the morphology and electrochemical characteristics of MIP/NCD-G modified SPCE. Under ideal circumstances, the developed sensor showed a 1 pg/mL LOD and an excellent linear response from 5 to 70 pg/mL. This sensor performs exceptionally by increasing effective surface area, electrical conductivity, and electrocatalytic activity. This MIP sensor achieves exceptional selectivity and sensitivity by combining a nanohybrid with a molecularly imprinted method. Additionally, it was miniaturized and had remarkable repeatability, which might be used as a basis for future portable medical devices (Pakapongpan et al. 2024).

Screen-printed graphene electrodes (SPGEs) coated with ultra-thin layers of polymerized 1,5-diaminonaphthalene (pDAN) have been used to create an immunosensor with high sensitivity detection of beta-amyloid peptides, which are a trustworthy biomarker for AD. DAN was electropolymerized to apply a continuous polymer coating of regulated thickness to the graphene screen-printed electrodes. Raman and XPS were used to analyze the surface properties of virgin graphene and graphene electrodes treated with polymers. Researchers looked at how the polymer's thickness affected the electron transport rates. By functionalizing the pDAN-modified SPGE with the anti-beta-amyloid Ab used as the peptide bioreceptor, an immunosensor for the specific detection of beta-amyloid peptides Aβ(1–42) was created. The

immunosensor demonstrated 1.4 pg mL^{-1} and 4.25 pg mL^{-1} detection and quantification limits, respectively, and was used to select Aβ(1–42) with a linear range of 1 pg mL^{-1} to 1000 pg mL^{-1}. The biosensor's ability to analyze human plasma that has been tampered with was further verified. Using a low-cost SPGE platform, the immunosensor allows for the quick, accurate, precise, repeatable, and highly sensitive detection of Aβ(1–42), opening the door to research-based real-time investigations and diagnostic ex vivo applications (Abbasi et al. 2021).

There has been a lot of focus on chitosan NPs in recent decades due to their potential as polymeric and bio-based NPs. As nanocarriers, they might encapsulate items like active chemicals or medications, transport them to a targeted location, and then release them at a regulated rate (Yanat and Schroën 2021). The wide range of chitosan's properties—which include electrical, photothermal, catalytic, antimicrobial, drug degradation, pollutants removal, biosensing, and so on—makes it the ideal "smart" nanostructure material. Due to its expanding range of uses, chitosan has recently become a highly regarded research material (Raja 2020). Because of its concentrated presence, CSF has traditionally been the primary site of detection for AD biomarkers such as amyloid plaques. Nevertheless, the BBB makes it more difficult to detect these markers in the blood, leading to lower concentrations. Researchers devised a novel strategy to overcome this obstacle and find relevant AD biomarkers in blood plasma, such as amyloid plaques and apolipoprotein E4 (ApoE4). This is achieved by adding a chitosan-coated immobilization matrix of Au nanostars (AuNSs) to an SPCE. Electrical and morphological studies, UV–Vis spectroscopy, CV, and Nyquist plots all pointed to the 0.5% chitosan solution having the best dispersion and conductivity. Clinical studies that followed assessed electrical responses to quantify levels of amyloid-β 42 (Aβ42) and APoE4 in plasma samples taken from human blood. Strong linear correlations and minimum error bars in the DPV responses showed peak currents proportionate to biomarker concentrations. Minimal interference across biomarkers was seen in cross-reactivity experiments using mixed solutions of amyloid-β 40 (Aβ40), Aβ42, and ApoE4, demonstrating the proposed sensor's excellent specificity. This enhanced gadget shows exceptional promise as a proof-of-concept system, providing a less intrusive, more economical, and less complicated way to identify and monitor the advancement of AD. With such a large surface binding area, researchers' effective technique opens up exciting new possibilities for improving AD diagnoses (Shin et al. 2024).

To build a flexible dual-mode platform for the sensitive profiling of AChE inhibitors—an essential component in the search for AD treatments—researchers created a novel bioinspired hydrogel scaffold that could be used to integrate hybrid nanoflowers (HNFs) into the sensing interface in real time. Researchers' approach incorporates AChE-specific aptamers into the hydrogel after magnetic bead imprinting using Strep-Tactin-coated magnetic beads (STMBs), shaping it, mimicking the tenacious anchoring of real tree roots. Improved binding integrity of HNFs with sensing interfaces results from this configuration's stable and biomimetic environment, which promotes HNF development. Researchers evaluated galantamine's inhibitory efficacy using the platform's dual-mode detection capabilities, which integrate colorimetric and electrochemical sensing. Additional evidence of the hydrogel's usefulness and affordability comes from its remarkable reusability, which preserves more than 95% of its original activity even after repeated applications, and its long-term stability, which maintains 91% of its original performance. Overall, this hydrogel scaffold takes inspiration from nature and provides a fresh approach to biosensing with high efficiency and reliability for HNF-based biosensors. It has enormous promise for use in several fields of medicine and cutting-edge biosensing technology (Liu et al. 2025).

One of the biomarkers associated with AD is tDNA, and a very sensitive electrochemical biosensor for its measurement is detailed here. Through the use of catalytic hydrolysis by alkaline phosphatase (ALP), electroactive molybdophosphate anions were precipitated on a GCE, while it was still in place. After that, tDNA recycling amplification is performed. The four DNA strands that comprise X-shape DNA (X-DNA) are designated S1, S2, S3, and S4. The work of DNA polymerase allowed them to be further stretched in four directions. Both X-DNA motifs that were produced were subsequently polymerized. At the same time, ALP is encased in a network of hydrogels to create a porous material of the ALP@DNAhg type. Reducing the amount of GO and functionalizing it with AuNPs (Au@rGO) was used to modify the GCE. Strand displacement capture of ALP@DNAhg initiates tDNA recycling assembly for signal amplification. Massive quantities of ALP are rendered immobile as a consequence of this. Once molybdate (MoO_4^{2-}) and pyrophosphate have been introduced, phosphate may be produced by catalyzing the hydrolysis of pyrophosphate by ALP. When it comes into contact with molybdate, it will create phosphomolybdate anions ($PMo12O403^{-}$), which are redox active. The detection limit is 3.4×10^{-3} pM, and the amperometric signal is concentration-dependent within the 1.0×10^{-2} to 1.0×10^{4} pM range for tDNA (Hua et al. 2019).

To better understand the function of sialic acid (SA) in the degenerative process of AD, it is crucial to conduct sensitive and targeted monitoring of SA in the CNS. Researchers developed an electrochemical biosensor using a new stimuli-responsive copolymer to detect SA in mouse brains with high sensitivity and selectivity. It is worth mentioning that the copolymer enhanced the detection sensitivity to 0.4 pM by converting SA recognition into a conformational

transition and wettability switch. This allowed redox labels and targets to be more easily accessed and enriched on the electrode surface. The proposed approach enhanced sensing signals and showed good selectivity toward SA compared to possible interference molecules coexisting in the intricate brain system. This was made possible by the directional hydrogen-bonding interactions in the copolymer and the high affinity between phenylboronic acid (PBA) and SA. The electrochemical biosensor, which exhibited exceptional analytical capabilities, was effectively used to assess the dynamic shift of SA levels in real-time brains of mice administered AD in conjunction with in vivo microdialysis. The first-ever report of the precise concentration of SA in several brain areas of live AD mice is a significant step forward in our knowledge of SA's function in physiological and pathological processes (Ding et al. 2017).

Polymeric-Based Electrochemical Sensors in Diagnosis of MS

It is crucial to diagnose MS, a neurological inflammatory disease that progresses over time. Short non-coding RNAs, also known as miRNAs, have emerged as promising predictive biomarkers for the early diagnosis of a wide range of disorders due to their aberrant expression. Regarding MS, miR-155 is a top biomarker. To detect miR-155, the researchers used a non-label electrochemical nano biosensor that was sensitive, inexpensive, and non-invasive. An aptamer-modified graphite sheet (GS) substrate containing a nanocomposite of SWCNTs and PPY serves as the miR-155 capture probe in the biosensor. Researchers conducted all electrochemical experiments using Fe(CN)63-/4-present as a redox probe. The biosensor can detect concentrations as low as 10 aM and has a dynamic range from 10 aM to 1 µM. Additionally, the biosensor that was created was effectively tested on human serum. The suggested biosensor shows promise as a tool for early MS detection due to its simplicity of manufacture, almost cost-effectiveness, high selectivity, repeatability, and reproducibility (Shariati et al. 2022).

A new class of biomarkers called TDP-43-associated proteinopathies, frontotemporal lobar degeneration (FTLD), and amyotrophic lateral sclerosis (ALS) has just come to light. Unfortunately, there are several drawbacks to the current detection systems, including their complexity, high cost, and reliance on human operators. Researchers introduced a new electrochemical biosensor for TDP-43 detection incorporated into a lab-on-a-chip (LoC) platform. To immobilize TDP-43 Abs specifically, the sensor uses transducer functionalization using electrosynthesized PPY derivatives containing carboxylic groups. One indirect method for detecting and quantifying TDP-43 is differential pulsed voltammetry (DPV). The chip is sensitive to concentrations of TDP-43 protein ranging from 0.01 ng/mL to 25 ng/mL, has a linear detection range, and responds quickly. Its LOD is 10 pg/mL. Additionally, TDP-43 can be used as a POC diagnostic tool due to its effective detection in complex matrices such as serum from both healthy persons and ALS patients. There is hope for improving the diagnosis and treatment of ND using an electrochemical biosensor built onto a chip because of its high sensitivity, fast response, and robust performance (Turco et al. 2024).

Researchers are beginning to explore the biological uses of hydrogels, which are also finding more and more use in fabricating electrochemical sensors. An electrochemical sensor generates a sensing signal by interacting with a sensing element and the analyte of interest. These sophisticated sensors convert raw data into usable electrical signals that scale with the concentration of the analyte of interest, allowing for both quantitative and qualitative analyses. Hydrogels may serve as platforms for biomolecules to maintain their biological activity because of the one-of-a-kind microwater environment they produce. Concurrently, the three-dimensional structure of hydrogels allows them to possess an exceptionally high specific surface area. Hydrogels are, therefore, mainly used as a platform for biomolecule immobilization in electrochemical sensor research. The remarkable sensitivity with which these biomolecular hydrogels can detect analytes makes them invaluable in the MS diagnostic process (Fu et al. 2019; Abune et al. 2021; Liu et al. 2022).

Normal and abnormal physiological and pathological processes rely on matrix metalloproteinase-9 (MMP-9). MS is a chronic autoimmune disorder that affects the CNS. This enzyme serves as a peripheral biomarker for neuroinflammation in MS. The current method for tracking MS subclinical disease activity involves costly MRI examinations. Detecting MMP-9 using a disposable, low-cost sensor device appropriate for home monitoring of inflammation might be a practical alternative to expensive MRI scans. By doing so, researchers can anticipate when anti-inflammatory treatments will not work, allowing for earlier therapeutic intervention to reduce neuronal damage and avoid impairment. The details of creating a disposable sensor that can detect MMP-9 quickly and efficiently are detailed here. Electrodes were coated with oxidized dextran and then crosslinked with peptides that included particular cleavage sites for MMP-9 to create biosensors. Impedance measurements were used to track the films' breakdown when exposed to the enzyme. Within 5 min of adding MMP-9, the sensor would typically show a noticeable change in impedance, indicating a fast reaction. MMP-2 is a protease that may impede MMP-9 detection; however, the sensors exhibited a completely insignificant response. Calibration curves were constructed using the most sensitive and selective peptide sequence, Leu–Gly–Arg–Met–Gly–Leu–Pro–Gly–Lys. The detection range of MMP-9 was 50 to 400 ng/ml, which is clinically relevant. On electrode surfaces of varying

roughness, two distinct hydrogel degradation processes were discernible; both processes seemed appropriate for tracking MMP-9 activity. The sensor materials may be readily modified to react to different proteases by choosing peptide cross-linkers with appropriate cleavage sites (Biela et al. 2015).

Polymer-Based Electrochemical Sensors in Diagnosis of PD

Among neurological diseases, PD is characterized by profound impairments in both motor and non-motor functions. One protein identified as a very sensitive PD biomarker is PARK7/DJ-1. For this reason, a MIP-based sensor based on the DJ-1 protein was used. The researchers detailed creating and improving an SPCE surface, including MIPPy, for identifying the DJ-1 protein. To make the MIPPy DJ-1 imprinted sensor, molecular recognition-capable nano matrices were synthesized by electropolymerizing pyrrole (Py) monomer on an SPCE electrode using CV. In addition, the MIPPy sensor was compared with the AuNP-attached impedimetric immunosensor. Using CV, EIS, and SEM, MIPPy/immunosensors were characterized. The MIPPy-based sensor showed analytical performance similar to the DJ-1 immunosensor, with a LOD 1 nM and a linear range of 1 nM to 500 nM. Using these MIPPy/immunosensors, the DJ-1 analysis was conducted satisfactorily in control and over-expressed N2A cells. Additionally, there was a strong association between the MIPPy-based sensor, the AuNP/PPy immunosensor, and the Western blot (Kumar et al. 2022).

A molecularly imprinted electrochemical sensor for sensitive detection of α-Syn was built using this material in conjunction with graphene nanosheets (GS) as electrode modification materials. Electropolymerization of pyrrole was used to synthesize the MIP sensor, which was then characterized using SEM, CV, and DPV. CMP–GS nanocomposites substantially raised the MIP sensor's sensitivity by enhancing the GCE's electroactive surface, signal intensity, and electron transport rate. Under ideal circumstances, the sensor's linear range extended from 1×10^{-4} to 8 ng mL − 1, and there was a significant improvement in detection limits compared to previous approaches, reaching as low as 3.5×10^{-5} ng mL^{-1} at $S/N = 3$. A possible approach for detecting α-Syn in the blood of PD patients might be the sensor, which exhibited great sensitivity, minimal interference, and good stability. In addition, the researchers developed a novel approach to using CMPs in MIP electrochemical sensors (Ma et al. 2020).

Researchers created and studied electrochemical sensing and biosensing, a novel conductive ink incorporating carbon black into a poly(vinyl alcohol) matrix. To improve electrical conductivity and reaction kinetics, Palladium NPs were added to the devices after they were evaluated using morphological and electrochemical methods. The metal deposition characteristics were examined using chemometrics, and the sensor was used to identify PD biomarkers, including α-Syn and adrenaline. The neurotransmitter showed a linear behavior of 0.75 to 100 µmol L^{-1}, and the device showed a LOD of 0.051 µmol L^{-1}. Then, synthetic CSF samples were used to evaluate the three-electrode setup. The apparatus was then altered with specific Abs to measure α-synuclein with EIS. For α-Syn concentrations in phosphate buffer, a linear range of 1.5 to 15 µg mL^{-1} was found, with a computed LOD of 0.13 µg mL^{-1}. When the suggested immunosensor was used on blood serum samples, the linear range of α-Syn was between 6.0 and 100.5 µg mL^{-1}, with a LOD of 1.3 µg mL^{-1}. Its potential applicability to complicated matrices is shown by the fact that both linear curves attend the range for the actual diagnosis (Orzari et al. 2024).

Clinical care for PD may be enhanced by a portable test that quickly determines levodopa levels. To improve the electrochemical detection of levodopa, researchers added polymers to screen-printed electrodes (SPEs). CV applied a thin coating of polyaniline on the surface of the electrode. Electrode conductivity was unaffected by the extensive surface covering seen by SEM. Researchers measured levodopa at physiologically appropriate concentrations by discriminating between a common interferent (ascorbic acid) and a structurally related molecule (L-tyrosine) using DPV measurements with the electrodes modified with polyaniline. The polymer layer did not allow for the separation of dopamine and levodopa. Nevertheless, these two molecules are identical except for an amino acid moiety in dopamine and a free amine group in levodopa. According to density functional theory calculations, Aniline created a hydrogen bond between the monomer's amino group and the meta-hydroxyl group found in dopamine and levodopa, with comparable binding energies. Therefore, SPEs functionalized with polymers are a valuable tool for measuring PD-relevant chemicals; nevertheless, to get selective detection, more optimization is required (Noguchi et al. 2022).

Among the first-generation selective adenosine A2A receptor antagonists, istradefylline (IST) stands out. It is now available to PD patients who are having "off" periods as an auxiliary therapy, according to a recent FDA approval. Scientists detailed the process of creating a new electrochemical sensor and used it to test plasma samples for IST using an anodic stripping square wave voltammetric (ASSWV) technique. The sensor, which is composed of zirconium (Zr) NPs on top of a pencil graphite electrode (PGE) surface, was created by layering an acid orange 10 (AO10) polymer platform on top of the ZrNPs. Equipped with SEM, EIS, X-ray powder diffractometry, and CV, the sensor was characterized. The sensor was then used to create an ASSWV approach based on oxidation for IST estimation. By following the ICH standards for analytical method validation, researchers improved the ASSWV technique and confirmed its analytical performance. This method's

linear range was 25×10^{-9}—170×10^{-9} M. Quantitation was 21×10^{-9} M, and the LOD was 6.9×10^{-9} M. It was proven that the ASSWV approach was accurate and precise. With recovery values of 96.0–97.9%, the approach achieved selectivity. The quantification of IST in human plasma samples was effectively accomplished using the suggested ASSWV technique. To sum up, the ASSWV technique that has been suggested is the first electrochemically viable strategy for IST estimation in plasma samples from humans. The approach contributes significantly to IST pharmacokinetic research, therapeutic monitoring, and safety profile refinement (Ali et al. 2025).

Researchers have proposed a surface-imprinted polymer (SIP) EIS biosensor to detect the aggregation of α-Syn. This biomarker manifests in saliva and blood during the first stages of PD when the BBB diminishes. Polycaprolactone (PCL) is stamped onto interdigitated EIS electrodes using a low-temperature melt stamping process to create the surface-imprinted polymer stamp. The end product is a small-footprint biosensor that is ideal for non-invasive monitoring of the disease biomarker and is cost-effective. The sensors were tested with α-Syn dilutions in deionized water and matrix solutions with constant ionic content and decreasing α-Syn concentrations to eliminate the concentration-related background effects. The gadget's answer verified that it specifically targeted the monomeric α-Syn protein. The sensor has a linear detection range of 5 µg/L and a LOD of 5 pg/L. In the future, researchers' approach to measuring α-Syn monomers for PD patients has excellent promise since it encompasses the normal range of α-Syn in saliva. As a possible tool for ongoing monitoring of the disease biomarker, the sensor's capacity for repeat sensing was shown by regenerating the SIP surface and reusing it (Massey et al. 2024).

Scientists examined the sensitivity of electrochemical screen-printed sensors made using graphene-based conductive PEDOT: PSS (G-PEDOT: PSS) and Polyaniline (G-PANI) inks applied to a working electrode for the detection of various dopamine concentrations. The suggested inks' microstructures were examined using an SEM characterization approach. Researchers evaluated the developed electrodes' dopamine detection effectiveness by investigating CV electrochemical approaches using a ferri/ferrocyanide redox pair. Dopamine detection using screen-printed electrodes has been improved with G-PANI ink regarding LOD and stability. Additionally, researchers investigated electrochemical analysis for dopamine-specific detection independent of ascorbic acid (Ghosh, et al. 2022) (Table 2).

Challenges and Future Perspective

AD is a neurological disease that worsens with time, making it increasingly difficult to perform tasks, including memory loss and daily chores. The global prevalence of dementia is projected to rise from 50 million in 2018 to 152 million in 2050, with a cost of approximately $1 trillion in 2018 and $2 trillion in 2030. One person in three will develop dementia, according to these estimates. There will likely be a significant increase from the current 60% of dementia patients living in low and middle-income nations to 71% in the year 2050. The majority of dementia cases (approximately 50% to 70%) are caused by AD. AD has surpassed all other causes of mortality in China, ranking fifth among urban and rural residents. More than 13 million individuals in China are affected by AD and other forms of dementia, and out of every five patients globally, are of Chinese nationality. Human research has shown that Aβ and Tau work together to alleviate AD symptoms. Memory loss and cognitive impairment are symptoms experienced by AD patients as a result of abnormal tau alteration that impedes regular neural connections and extensive synapse loss caused by Aβ aggregation. The sad reality is that 75 percent of people with dementia either do not get a diagnosis or are given inadequate medications for their condition. Hence, sensitive and selective biosensors are critically needed for early AD detection, controlled progression, and therapy window opening (Cheng, et al. 2024).

The development of biosensors that can detect multiplex biomarkers, as opposed to single biomarkers, has far more promise for the early identification of neurodegeneration. Research in recent years has also shown that neuroinflammation occurs with neurodegeneration, which has led to identifying new potential biomarkers. Although these indicators are essential, very few biosensing applications can locate them. The researchers' long-term objective is to create affordable, easy-to-use biosensing tests that can identify AD and PD in their early stages by analyzing biomarkers in blood and CSF, respectively. There are no accessible sensing studies for preclinical AD and PD diagnosis, even though significant sensing investigations have been undertaken globally. Medical professionals will be better equipped to tackle ND in its early stages if research findings are widely disseminated. ND is projected to be the leading illness in the following decades. The early initiation of therapy, better living circumstances for patients, higher quality of life, and reduced economic health burden on states will be the climax of this fight (Karaboğa and Sezgintürk 2022).

New advances in EC sensing technologies have made blood p-tau detection more precise. Because they convert biological interactions into electrical signals, EC-based immunosensors allow for sensitive and inexpensive detection. Problems with the' lack of conductivity of Abs, the use of nanomaterials in sensor production, and the influence of environmental variables all work against the goals of stability and repeatability. Also, there are still a lot of obstacles to overcome, such as evaluating complicated biological samples and doing real-time measurements, which calls for

Table 2 The potential of the Polymer-based electrochemical sensor in detecting several NDs

Polymer-based electrochemical	Neurode-generative diseases	Limit of detection (LOD)	Explains	Refs
MXene-based redox systems and MIPs	AD	2.3 fg/mL (60 aM/L)	This sensor's potential for minimally invasive, early AD diagnosis in clinical settings is highlighted by its quick detection time (about 32 min) and inexpensive cost (around £20/device)	Arjun et al. (2024)
MIP-modified electrodes	AD	587 pg/mL (12.2 fM/L)	As the concentration of Tau-441 increased, the MIP's current decreased linearly, suggesting that Tau-441 had successfully bound to the polymeric backbone of the MIP. With a LOD of 587 pg/mL (12.2 fM/L) in ISF, the sensor detected Tau-441 in the range of 50 fg/mL to 500 ng/mL (1.22 fM/L to 12.2 nM/L). Future research will examine microneedle patches and MIP-modified electrodes for detecting Tau protein in blood and ISF	Norman et al. (2024)
Screen-printed graphene electrodes (SPGEs) coated with ultra-thin layers of polymerized 1,5-diaminonaphthalene (pDAN)	AD	1.4 pg mL^{-1} and 4.25 pg mL^{-1}	Using a low-cost SPGE platform, the immunosensor allows for the quick, accurate, precise, repeatable, and highly sensitive detection of Aβ(1–42), opening the door to research-based real-time investigations and diagnostic ex vivo applications	Abbasi et al. (2021)
Electrode enhanced with DNA hydrogel encapsulated with alkaline phosphatase for in situ precipitation of molybdophosphate	AD	3.4×10^{-3} pM	Once molybdate ($MoO42^{-}$) and pyrophosphate have been introduced, phosphate may be produced by catalyzing the hydrolysis of pyrophosphate by ALP. When it comes into contact with molybdate, it will create phosphomolybdate anions ($PMo12O403-$), which are redox active	Hua et al. (2019)
Aptamer-modified graphite sheet (GS) substrate containing a nanocomposite of single-walled carbon nanotubes (SWCNTs)	MS	10 aM	An aptamer-modified graphite sheet (GS) substrate containing a nanocomposite of SWCNTs and PPY serves as the miR-155 capture probe in the biosensor. Researchers conducted all electrochemical experiments using Fe(CN)63-/4-present as a redox probe. The biosensor can detect concentrations as low as 10 aM and has a dynamic range from 10 aM to 1 µM	Shariati et al. (2022)
MMP-9 sensor based on the degradation of peptide cross-linked hydrogel films using EIS	MS	50 to 400 ng/ml	Calibration curves were constructed using the most sensitive and selective peptide sequence, Leu-Gly–Arg–Met–Gly–Leu–Pro–Gly-Lys. The detection range of MMP-9 was 50 to 400 ng/ml, which is clinically relevant. On electrode surfaces of varying roughness, two distinct hydrogel degradation processes were discernible; both processes seemed appropriate for tracking MMP-9 activity. The sensor materials may be readily modified to react to different proteases by choosing peptide cross-linkers with appropriate cleavage sites	Biela et al. (2015)

Table 2 (continued)

Polymer-based electrochemical	Neurodegenerative diseases	Limit of detection (LOD)	Explains	Refs
An innovative electrochemical sensor that utilizes ZrNPs and a hybrid acid orange 10 polymer to improve performance	PD	6.9×10^{-9} M	The ASSWV technique suggested is the first electrochemically viable strategy for IST estimation in human plasma samples. The approach contributes significantly to IST pharmacokinetic research, therapeutic monitoring, and safety profile refinement	Ali et al. (2025)
Polymer EIS Sensor	PD	5 pg/L	The sensors were tested with α-Syn dilutions in deionized water and matrix solutions with constant ionic content and decreasing α-Syn concentrations to eliminate the concentration-related background effects. The gadget's answer verified that it specifically targeted the monomeric α-Syn protein. The sensor has a linear detection range of 5 µg/L and a LOD of 5 pg/L	Massey et al. (2024)

new developments to make these platforms more practical and reliable. With their low manufacturing costs, structural flexibility, and excellent specificity, aptamer-based EC sensors provide a viable alternative to Ab systems. On the other hand, researchers must figure out how to improve sensitivity, decrease nonspecific binding, and stabilize aptamers in complicated situations. Future research should focus on overcoming these challenges and incorporating aptamers into scalable systems. Tau detection has used several different EC methods, each with advantages and disadvantages, including CV, DPV, SWV, and EIS. Due to their sensitivity, quick reaction, and low detection limits, voltammetry techniques—specifically CV, DPV, and SWV—are extensively used. Problems with throughput and false positives caused by physisorption prevent further clinical usage. There must be an improvement in the capacity to scale and handle many samples. The charge transfer characterization of EIS-based sensors might be improved with a better grasp of AC electrical circuits, although these sensors already have a high sensitivity for tau detection. Multiplexed EIS sensors may be used to provide more thorough and earlier-stage AD diagnostics. The FET-based sensor can detect biomarkers at femtomolar or pM concentrations, giving it exceptional sensitivity. Nevertheless, significant problems remain, such as reliable signal modulation, the requirement to reduce background noise, and discrepancies in equipment performance caused by material flaws (Chen et al. 2023; Wang et al. 2025; Brett 2022).

In terms of early PD detection, electrochemical biosensors provide several advantages, such as high sensitivity, specificity, mobility, and the capacity for real-time analysis. Nanomaterials, including QDs, carbon nanotubes, and AuNPs, have enhanced the functionality of these biosensors. Future research should improve biosensors' robustness and repeatability, create multiplexed biosensors that can detect numerous biomarkers simultaneously, and develop better POC diagnostic systems. This crippling illness may now be detected at an earlier stage because of the development of electrochemical biosensors that can detect PD biomarkers. By integrating the unique properties of nanomaterials with the specificity of biological recognition components, these biosensors provide a promising approach to the sensitive, rapid, and reliable detection of PD biomarkers. Improving PD diagnosis and treatment will need continuous research and development before these technologies can be used in clinical settings (Khatami, et al. 2024).

Integrating electrochemical sensing systems with new inconspicuous body-worn inertial sensors is another promising avenue for biosensors' potential future uses. Wearable inertial sensors, such as gyroscopes and tri-axial accelerometers, are tiny, lightweight devices that may be attached to various body parts to measure multiple motor tasks. Numerous studies suggest that inertial sensors may provide helpful

information on motor performance by recording spatiotemporal and 3D kinematic data about the body's spatial orientation and motion. More precisely, wearable inertial sensors have mainly been used to measure the severity of PD and objectively assess motor symptoms. In addition, developments in microelectronics have made it possible to create discreet, bendable, and comfortable devices that can be integrated into clothing ("e-textile"). Thus, it would be likely to correlate the intensity of motor symptoms with the plasmatic levels of L-Dopa in real time using a combination of electrochemical devices that sense L-Dopa levels and novel wearable inertial sensors. Using the present motor symptoms and activity-dependent changes in free-living situations, this method would maximize real-time therapy tactics by customizing pharmaceutical regimens. Researchers hypothesized that integrating technology would further enhance closed-loop adaptive systems' dependability. Research in the future that incorporates digital signal readout, smartphone-based integrated systems, and wearable sensing devices may provide a clearer picture of the clinical and neuropathological progression of PD. Multiple essential biomolecules may be detected simultaneously because of this. Researchers recommend that in the future, scientists figure out how to make small electrochemical devices that individuals may wear and connect wirelessly with their doctors so that therapy can be more focused on the individual. Resources made available by the Internet of Things will encourage the broad adoption of multimodal wearable devices for innovative telemedicine approaches in PD patients. This will allow for more integrated and global healthcare management (Asci et al. 2022).

Due to the progressive nature of MS, further treatments are necessary. MS diagnostic and therapy method analyses, including hydrogels, pique several researchers' attention. To illustrate the point that peripheral immune activation contributes to the etiology of MS and that a symbiotic microbiome in the intestines may be required to start the immune response, research into the microbiome of the intestines is expanding at a rapid pace. Another promising field for future hydrogel applications is wearable electronic sensors. These might be mass-produced and provide valuable capabilities, such as tracking mobility, fatigue, and balance as MS progresses. Moreover, by mimicking the specific characteristics of natural CNS tissues in vitro, including binding and delivery via NPs, 3D hydrogel systems make it possible to cultivate and understand cell–matrix interactions. Hydrogel material development, MS diagnosis, and prognosis monitoring may all focus on these topics (Liu et al. 2022).

Employing nanotechnology in electrode manufacturing may solve the many problems associated with employing biosensors for neurodevelopmental disorder (NDD). To identify and track a wide variety of neural alterations, NDD biosensing technologies have been updated with nanotechnological instruments. Sensitivity, detection range, and response time have all been enhanced, thanks to the widespread employment of NPs in the last few years. Small, highly hydrophobic, charged, and functionalized NPs may enter nervous system cells. As a result, the enhanced functionalized biosensors will be able to identify neurological illnesses early on, monitor biomarker changes more effectively, and have a rapid response time. In addition, it is feasible to synthesize a variety of nanostructures, which may be used to develop biosensors that exhibit improved sensitivity, selectivity, and LOD. These characteristics can potentially provide future optical, electrochemical, and electronic sensing devices with great promise (Gautam 2022).

Additionally, as efficiency and long-term stability are crucial for using biosensors as screening tools, they must also be assessed. In light of the remarkable advancements in nanomaterial production and functionalization, nanomaterials have been used in biosensing. In this context, nanomaterials have been used as electrode modifiers in biosensors; the most common nanomaterials are carbon and Au-based ones, particularly MWCNTs, which have made it possible to get the lowest LOD (10^{-2} fM) among the biosensors in this study. Modifying transducers with nanoscale nanostructures by improving conductivity and facilitating the immobilization and orientation of biological recognition components allows for improved electrochemical performance. Additionally, the signal has been amplified by using nanomaterials as labels because of their electroactivity and electrocatalytic qualities, which allow for a greater sensitivity despite their more complex application. Once again, Au nanomaterials—either by themselves or in conjunction with other materials—are widely used in this sector. Metal–Organic Frameworks are then used as reporter carriers. The introduction of electrocatalytic labeling has also been a significant advancement, as it makes it easier to identify biomolecules at neutral pH, providing more integrated sensing systems and cutting down on analysis time. These two factors are crucial for satisfying market demands. In light of this, it should be mentioned that, regarding LOD, using labels has not been shown to provide a greater benefit in signal amplification than using nanomaterials as electrode modifiers. Reaching the lowest LODs is impossible using nanomaterials as labels or electrode modifications. This demonstrates how much more can be done to enhance the use of nanomaterial combinations for biosensing. Remarkably, biosensors that use MIPs or recognition proteins have the lowest LODs, implying that the biological recognition element should be another factor to be considered (Toyos-Rodríguez et al. 2020).

Graphene and other carbon materials can be combined with lamellar monomers to form hydrogels, making them ideal for electrochemical sensors. Researchers anticipated that in the future, hydrogels could be composed of monomers made from a nanosheet of many different 2D materials. The availability of non-organic hydrogels will rise

with the discovery and exploration of new 2D materials. By doing so, the electrical flaws in hydrogels made of polymers may be essentially eliminated. When combined with other efficient components, new hydrogels may accomplish the same vast array of uses as traditional electrochemical sensors. Yet, carbon compounds and their oxidized derivatives are often employed in hydrogel production because of their intrinsic hydrophobicity. Hydrogels are usually reduced after synthesis because surface oxidation of carbon materials significantly impacts their electrical characteristics. One difficulty with using these carbon materials is controlling the amount of reduction. A future challenge will be finding a way to accurately regulate the decrease in carbon material hydrogels. Hydrogel electrochemical sensors are not yet superior to other traditional types of electrochemical sensors in terms of performance. Its detection performance is often subpar compared to more technically sophisticated solid-state electrochemical sensors. Nonetheless, hydrogel sensors have several benefits: longevity, repeatability, and stability. Applying widely used sensing technologies like immunosensing and DNA sensing to hydrogel electrochemical sensors should result in high performance. More popularly analyzed compounds, such as blood glucose and H_2O_2, are used in studies. These compounds can be detected with extreme sensitivity using established electrochemical sensors. Hydrogels' unique milieu may make various sensing technologies work more reliably. Thus, the future of this discipline will also revolve around finding ways to use the hydrogel's characteristics to meet specific detection demands that need a particular microenvironment (Fu et al. 2021).

Electrochemical sensors for neurotransmitter assessment have recently seen extensive use of CPs and composites of these materials. One exciting new development in the detection of neurotransmitters is using electrochemical sensors. Synthesizing novel sensing probe materials to enhance sensor performance (sensitivity, selectivity, biocompatibility) has been the primary focus of research in the last several years. Composites of CPs and other synthetic nanomaterials are extensively used to fabricate sensor surfaces. Improved sensor stability, selectivity, and sensitivity are all benefits of using these nanocomposites. The charge transport characteristics and electrochemical redox efficiency of various CPs, such as polythiophene, functionalized polyterthiophene, PPy, PANI, PEDOT, and poly(o-phenylenediamine), are a result of the delocalization of π-electrons across the polymeric backbone. It was clear that the combined action of NPs and CPs significantly enhanced the sensors' performance. In addition, other detection approaches, like enzymatic or MIP ones, have not garnered as much interest as the direct electron transfer mechanism of electroactive neurotransmitters (Moon et al. 2018). CPs–metal NP-based sensing components effectively address the complicated composition of biological samples that comprise many main interfering species, including tyrosine, uric acid, and ascorbic acid. The suggested electrochemical sensors showed excellent anti-interference capacity for detecting dopamine, serotonin, and epinephrine in synthetic and complicated matrices. Selectivity of the analytical measures is a difficult challenge in actual sample analysis. Apart from the selectivity factor, another challenging problem in creating new electrochemical sensors is the low concentration of neurotransmitters in biological fluids. Moreover, the adaptability of the CPs–metal NPs preparation techniques guaranteed their effective immobilization on various substrates, including flexible, textile-based substrates for patch sensor design, in addition to the broad range of substrates previously described. By fine-tuning the size distribution and polydispersity of the metal NPs, the electrochemical in situ reduction of metal precursors over polymeric coatings showed significant promise for constructing electrochemical sensors.

New electrochemical preparation techniques for CPs–metal NP synthesis based on sinusoidal voltages and currents have also been devised. The complementary actions of the CPs and metal NPs improved overall analytical performance. Moreover, their processability, high mechanical stability, and chemical stability improved the analytical applications of the novel materials based on graphene QDs (GQDs) and the generated CPs–metal NP-sensing materials (Leau et al. 2023).

Despite progress in neurotransmitter sensing, most measurements were taken in controlled environments, and just a handful of publications utilize in vitro systems. Addressing several obstacles before implanting in proof-of-concept devices helps speed the technology's transition from standard conditions to clinical applications. These obstacles include biocompatibility, interferences, and nonspecific adsorption. Making interface materials that are both selective and sensitive may help with these kinds of problems. On top of that, these platforms aim to create wearable, portable, non-invasive, affordable, and proof-of-concept devices that can cut down on sampling time and frequency. In addition, a thriving field of research might help advance clinical and pharmaceutical applications: the creation of label-free biosensors and ultra-small, multiplexed arrays of nanoelectrode sensors (Moon et al. 2018). Focusing on the large-scale synthesis of transducers with enhanced biocompatibility is also crucial for better integration with biosensors, increasing cost-effectiveness, and promoting better-tailored sensors. Collaborations between physicians, scientists studying nanomaterials, and electrical specialists may also improve the commercialization of electrochemical sensors, advance the sensing technology, and improve patients' quality of life. However, many published articles either do not provide the requisite significant proof of better analytical performance of enzymes or do not include essential tests that show their stability and usability under physiological

settings for successful commercial biosensor development. Thus, it is strongly advised that a better understanding of the ideal operating conditions and principles of electrochemical sensor-based neurotransmitter monitoring be encouraged to improve the efficiency and impact of enzymes on the signal provided (Fredj et al. 2023).

Recent studies on using carbon NPs in AD diagnosis have shown that these NPs may interact with, identify, and harm amyloid plaques. Similarly, CNTs and graphene allotropes may improve sensor conductivity. Electrospun nanofibers or metallic NPs, on the other hand, may functionalize the electrode surface to improve transducer signals by creating binding sites for the immobilization of biomarkers or recognition elements. Modern technology has allowed for the development of MIP, a noise-filtering algorithm that enhances sensor selectivity by interacting only with the target analyte. Better biosensors may be developed using nanotechnology's flexibility, as shown in these instances (Gautam 2022; Hasseb et al. 2022; Siafaka et al. 2021; Mishra et al. 2021). It is possible to detect Aβ42 p-Tau 441, α-Syn, α-amylase, and lysozyme using electrochemical biosensors based on MIP technology. Similar to AD and PD, studies have shown that MIPs may diagnose ND in addition to recognizing those who are under stress. CPs are an excellent choice for precise and simple MIP biosensing systems. Moreover, Ppy is a suitable and popular polymer for identifying AD markers in breath, CSF, and blood. α-Syn, α-amylase, Aβ42 p-Tau 441, and electrochemical biosensors based on MIP technology may all be found. MIP-based biosensors have a lot of potential for diagnostic applications. Researchers showed that MIP has observable limitations. The development of biosensors enhances people's quality of life by enabling quicker and more precise diagnosis of certain ND (Pilvenyte et al. 2023).

Over the last ten years, research on sensors based on nanocomposite technology has increased dramatically. Researchers are now interested in creating sophisticated nanocomposite materials, including CPs, GQDs, CNTs, graphene-based 2D and 3D nanocomposites, hierarchical porous carbon, MIPs, and MOFs. Numerous nanocomposites have been examined to develop electrochemical sensors for neurotransmitter assessments because of their intriguing characteristics, including high surface area and exceptional conductivity. Electrochemical sensors based on nanocomposite technology are becoming strong contenders for future diagnostic uses because of their quick and sensitive neurotransmitter estimation. The resilience and repeatability of the sensors are necessary since fouling issues brought on by the adsorption of proteins from the actual samples inevitably lead to measurement difficulties. Despite the many benefits of electrochemical sensors, biocompatibility and real-time continuous monitoring pose significant obstacles to their use with neurotransmitters in human samples. These difficulties may be solved by altering the sensors with a high surface area nanocomposite and target-specific characteristics that easily resist fouling effects. By incorporating the above-mentioned changes, electrochemical sensors may undergo further advancements that might transform neurotransmitter diagnosis. Additional research is needed for smartphone-based sensors, skin-like biomimetic sensors, electrode arrays that can detect a panel of neurotransmitters concurrently (with efficient calibration and computational techniques), and implantable sensors with fast responses. Creating high-throughput portable/miniaturized sensor arrays using nanocomposites has been the focus of subsequent developments (Rajarathinam et al. 2023).

There may be issues with combining these fake identifiers with sensors, as no commercially available MIP sensing devices exist. Currently, there is not a lot of buzz or investment in MIP sensors in the business sector. The simplicity, accessibility of electronic components, and ease of mass manufacture of electrochemical devices make their fabrication on a large scale a viable prospect. But now, few MIP sensors can be mass-produced practically due to their high manufacturing needs. For example, MIP sensors made using industrial processes like printing, direct deposition, or soft lithography seem outmatched by those made utilizing multi-step reactions. To make MIPs much more efficient during synthesis, researchers must find new ways to make them automatically and on a large scale. One possible approach to producing MIP-based electrochemical sensors on a wide scale is to combine nanomaterials with printing processes (Li et al. 2024).

Changing the materials is a standard method for improving the properties and performance of electrochemical sensors. Integrating with MIPs is crucial to address the selectivity problem. When the template molecule, functional monomer, and other components are present, MIP design uses a variety of polymerization processes, including heat and photopolymerization, to create polymeric structures that recognize and bind to the template molecule selectively (Kul et al. 2025). Moreover, heat or a photo-initiator may be used depending on the polymerization technique. Depending on the components and objective of the MIP, several polymerization techniques might be used. For example, electropolymerization is the in situ production of the polymer on the electrode surface using an electrochemical process. Its simplicity and quickness are its merits. Photopolymerization is one in situ technique that employs a light source for photoinitiation. The procedure is quick and steady. However, working with compounds that may degrade when exposed to light is difficult. The thermal polymerization technique, which is easy to use, creates a highly stable polymer, has readily available components, and requires heat. On the other hand, a relatively long polymerization time might be harmful. Moreover, NPs might be added to improve the MIP structure's porosity and surface area, among other properties.

Consequently, exceptional selectivity may be attained by the designed MIP-based electrochemical sensors. Notwithstanding this most critical advantage, MIP design may have disadvantages such as stability issues and the need for a thorough and laborious optimization process (Kul et al. 2025).

Additionally, the MIP-based sensors described for these analytes effectively detect and quantify at concentrations of pM or higher. Notably, aptamers, polymers, and other nanomaterials (carbon dots, QDs, Au, Ag NPs, and CNTs) were used to obtain low detection limits and greater sensitivity. Determining the range of sub-nanomolar protein concentrations is a complex issue (Shah et al. 2022). To address the current problems, many strategies have been put forward, such as surface imprinting, porous hierarchical imprinted film, and increased active surface area that permits relatively simple and selective access for the protein analyte. MIPs encounter several challenges in achieving ultrasensitive detection limits, despite their many benefits, which include excellent selectivity, a range of preparation techniques, exceptional shelf life, and sustainability under harsh experimental settings. Difficulties include nonspecific binding, uneven polymer particle sizes, imprinted cavity swelling, and laborious optimization. As a result, MIP-based commercialization and POC testing tools are still in their infancy. It is important to note that very few publications have achieved ultrasensitive (i.e., ≥ pM LOD) analyte detection. It has been shown that the employment of aptamers, nanomaterials, and dual recognition techniques greatly impacted the detection limits and guaranteed pM to attomolar detection sensitivity. However, it is well known that MIP-based sensors have become a flexible substitute for biological and biomedical Abs and sensor probes in immunoassays. Nano MIP synthesis has become a feasible substitute for bulk MIP synthesis in recent years. The nano MIP sensors have the benefit of long-term storage and are varied in terms of stability, cost-effectiveness, selectivity, and specificity. Ultimately, researchers showed that MIPs have advanced significantly and are now a practical method that provides ultrasensitive sensitivity and exceptional selectivity (Shah et al. 2022).

Conclusion

A more significant proportion of the global population will suffer from NDDs as the average age of the population continues to climb. Developing sensitive, quick, dependable, and cost-effective techniques of NDD detection based on developing analytical technologies is more critical than ever before. A promising future lies ahead in developing electrochemical biosensors that might shed light on the pathologies of ND. Their diagnostic and developmental medicine applications have made them desirable instruments. Synthesizing novel sensing probe materials to enhance sensor performance (sensitivity, selectivity, biocompatibility) has been the main focus of research in the last several years. Composites of CPs and other synthetic nanomaterials have been extensively used to fabricate sensor surfaces.

Regarding electrochemical sensors, these nanocomposites significantly improve sensitivity, selectivity, and stability. There is no performance benefit to using hydrogel electrochemical sensors compared to more traditional methods. Its detection performance is often subpar compared to more technically sophisticated solid-state electrochemical sensors. Nonetheless, hydrogel sensors have several benefits: longevity, repeatability, and stability. Polymers have been shown to help improve the performance of electrochemical-based diagnostic systems in detecting neurological illnesses. These methods are now more sensitive, accurate, and precise while minimizing LOD. There has been a dearth of research on other neurological disorders, such as MS and PD, in comparison to people living with Alzheimer's. The LOD may be effectively determined via meta-analyses and systematic reviews. Researchers should also focus on improving the performance of electrochemical biosensors for neurological illness diagnostics by studying the usage of different polymers and nanopolymers. Future research into electrochemical-based clinical diagnostics, mainly focused investigations, can provide significant benefits.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing Interests The authors declare no competing interests.

Ethical Approval Not applicable.

Consent for Publications All author are consent for publication.

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References

Abbasi HY et al (2021) Graphene based electrochemical immunosensor for the ultra-sensitive label free detection of Alzheimer's beta amyloid peptides Aβ (1–42). Nanoscale Adv 3(8):2295–2304

Abe E et al (2022) Expression of transferrin protein and messenger RNA in neural cells from mouse and human brain tissue. Metabolites 12(7):594

Abukuri DN (2024) Novel biomarkers for Alzheimer's disease: plasma neurofilament light and cerebrospinal fluid. Int J Alzheimer's Dis 2024(1):6668159

Abune L, Davis B, Wang Y (2021) Aptamer-functionalized hydrogels: an emerging class of biomaterials for protein delivery, cell capture, regenerative medicine, and molecular biosensing. Wiley Interdiscip Rev Nanomed Nanobiotechnol 13(6):e1731

Adampourezare M, Hasanzadeh M, Nikzad B (2023) Recent progress and challenges in the application of molecularly imprinted polymers for early-stage screening of neurodegenerative diseases-related protein biomarkers. Microchem J 192:108931

Ahmed AET et al (2025) AI-optimized electrochemical aptasensors for stable, reproducible detection of neurodegenerative diseases, cancer, and coronavirus. Heliyon 11(1):41338

Akram AS et al (2024) Advancing the frontier: neuroimaging techniques in the early detection and management of neurodegenerative diseases. Cureus. https://doi.org/10.7759/cureus.61335

Alam MW et al (2022) Recent progress, challenges, and trends in polymer-based sensors: a review. Polymers 14(11):2164

Ali MF, Darwish IA, Hosny NM (2025) A novel electrochemical sensor based on collaborative performance enhancement of hybrid acid orange 10 polymer/zirconium nanoparticles for first voltammetric determination of istradefylline in plasma. Microchem J 209:112911

Aqel S et al (2025) Advances in Huntington's disease biomarkers: a 10-year bibliometric analysis and a comprehensive review. Biology 14(2):129

Arjun AM et al (2024) Alzheimer's diagnosis beyond cerebrospinal fluid: probe-free detection of tau proteins using MXene based redox systems and molecularly imprinted polymers. Biosens Bioelectron 20:100513

Arneth B, Kraus J (2022) Laboratory biomarkers of multiple sclerosis (MS). Clin Biochem 99:1–8

Arslan B, Zetterberg H (2023) Neurofilament light chain as neuronal injury marker—what is needed to facilitate implementation in clinical laboratory practice? Clin Chem Lab Med 61(7):1140–1149

Asci F et al (2022) Wearable electrochemical sensors in Parkinson's disease. Sensors 22(3):951

Atik A, Stewart T, Zhang J (2016) Alpha-synuclein as a biomarker for Parkinson's disease. Brain Pathol 26(3):410–418

Avelino KY et al (2021) Flexible sensor based on conducting polymer and gold nanoparticles for electrochemical screening of HPV families in cervical specimens. Talanta 226:122118

Bae M et al (2025) recent advances in electrochemical biosensors for neurodegenerative disease biomarkers. Biosensors 15(3):151

Baranowska I et al (2008) Determination of selected drugs in human urine by differential pulse voltammetry technique. Bioelectrochemistry 73(1):5–10

Ben Hassine A, Raouafi N, Moreira FT (2021) Novel electrochemical molecularly imprinted polymer-based biosensor for Tau protein detection. Chemosensors 9:238

Bharadwaj V, Singh N, Sahoo SK (2022) Polymeric nanoparticles with potential applications in sensing and biosensing. Sensing and biosensing with optically active nanomaterials. Elsevier, Amsterdam, pp 401–426

Biela A et al (2015) Disposable MMP-9 sensor based on the degradation of peptide cross-linked hydrogel films using electrochemical impedance spectroscopy. Biosens Bioelectron 68:660–667

Bigi A et al (2024) Putative novel CSF biomarkers of Alzheimer's disease based on the novel concept of generic protein misfolding and proteotoxicity: the PRAMA cohort. Transl Neurodegener 13(1):14

Bono-Yagüe J et al (2020) Reactive species in Huntington disease: are they really the radicals you want to catch? Antioxidants 9(7):577

Bounegru AV, Bounegru I (2023) Chitosan-based electrochemical sensors for pharmaceuticals and clinical applications. Polymers 15(17):3539

Brett CM (2022) Electrochemical impedance spectroscopy in the characterisation and application of modified electrodes for electrochemical sensors and biosensors. Molecules 27(5):1497

Brinvillier D et al (2022) Spectroscopic, electrochemical, and biological assays of copper-binding molecules for screening of different drugs and plant extracts against neurodegenerative disorders. ACS Omega 7(19):16260–16269

Califf RM (2018) Biomarker definitions and their applications. Exp Biol Med 243(3):213–221

Cano A et al (2021) Nanomedicine-based technologies and novel biomarkers for the diagnosis and treatment of Alzheimer's disease: from current to future challenges. J Nanobiotechnol 19(1):122

Carlin N, Martic-Milne S (2018) Anti-tau antibodies based electrochemical sensor for detection of tau protein biomarkers. J Electrochem Soc 165(12):G3018

Chang Z et al (2024) "Signal-on" electrochemical detection of BACE1 for early detection of Alzheimer's disease. Cell Rep Phys Sci 2024(5):101632

Chauhan N et al (2017) An electrochemical sensor for detection of neurotransmitter-acetylcholine using metal nanoparticles, 2D material and conducting polymer modified electrode. Biosens Bioelectron 89:377–383

Chen H et al (2023) The applications of electrochemical immunosensors in the detection of disease biomarkers: a review. Molecules 28(8):3605

Cheng T et al (2024) Current progress in aptamer-based sensors for the detection of protein biomarkers in neurodegenerative diseases. Biosens Bioelectron X 20:100528

Cheng T et al (2025) Internal-driven DNA nanowindmill: multifulcrum mediated amplified rolling nanomachine for fast and ultrasensitive electrochemical detection of tau. Sens Actuators B Chem 423:136797

Cui H et al (2025) Research progress of electrochemical biosensors for diseases detection in China: a review. Biosensors 15(4):231

da Silva IS, Cardoso AR, Sales MGF (2024) Electrochemical biosensor-based detection assays for early diagnosis of neurodegenerative disorders. Smart diagnostics for neurodegenerative disorders. Elsevier, pp 155–177

Demirdöğen BC (2021) A literature review of biosensors for multiple sclerosis: towards personalized medicine and point-of-care testing. Mult Scler Relat Disord 48:102675

den Boer D et al (2023) Unusual water oxidation mechanism via a redox-active copper polypyridyl complex. Inorg Chem 62(14):5303–5314

Dey J et al (2022) Electrochemical detection of Alzheimer's disease biomarker, β-secretase enzyme (BACE1), with one-step synthesized reduced graphene oxide. Front Bioeng and Biotechnol 10:873811
Dhahi TS et al (2024) Application of nanobiosensor engineering in the diagnosis of neurodegenerative disorders. Results Eng 24:102790
Dhiman NR et al (2025) Urinary based biomarkers identification and genetic profiling in Parkinson's disease: a systematic review of metabolomic studies. Front Bioinform. https://doi.org/10.3389/fbinf.2025.1513790
Di Filippo M et al (2024) Fluid biomarkers in multiple sclerosis: from current to future applications. Lancet Reg Health. https://doi.org/10.1016/j.lanepe.2024.101009
Ding J, Qin W (2020) Recent advances in potentiometric biosensors. TrAC Trends Anal Chem 124:115803
Ding S et al (2017) Rational design of a stimuli-responsive polymer electrode interface coupled with in vivo microdialysis for measurement of sialic acid in live mouse brain in Alzheimer's disease. Acs Sens 2(3):394–400
Domínguez-Fernández C et al (2023) Review of technological challenges in personalised medicine and early diagnosis of neurodegenerative disorders. Int J Mol Sci 24(4):3321
Dong H et al (2022) Development of a novel ratiometric electrochemical sensor for monitoring β-galactosidase in Parkinson's disease model mice. Biosens Bioelectron 210:114301
Dong H et al (2025) High selectivity fluorescence and electrochemical dual-mode detection of glutathione in the serum of Parkinson's disease model mice and humans. Anal Chem 97:1318
Dong H et al (2025) Dual-mode ratiometric electrochemical and turn-on fluorescent probe for reliably detecting H2O2 in Parkinson's disease serum. Sens Actuators Rep 9:100305
Doroszkiewicz J, Groblewska M, Mroczko B (2022) Molecular biomarkers and their implications for the early diagnosis of selected neurodegenerative diseases. Int J Mol Sci 23(9):4610
Du T et al (2021) Biomarkers and the role of α-synuclein in Parkinson's disease. Front Aging Neurosci 13:645996
Falk M et al (2020) Non-invasive electrochemical biosensors operating in human physiological fluids. Sensors 20(21):6352
Fauzi D, Saputri FA (2019) Molecularly imprinted polymer nanoparticles (MIP-NPs) applications in electrochemical sensors. Int J Appl Pharm. https://doi.org/10.22159/ijap.2019v11i6.35088
Feng G et al (2025) Advances in research on exosomal miRNAs in central nervous System diseases. ASN Neuro 17(1):2465546
Fredj Z et al (2023) Enzymatic electrochemical biosensors for neurotransmitters detection: recent achievements and trends. Chemosensors 11(7):388
Fu L et al (2019) (001) plan manipulation of α-Fe2O3 nanostructures for enhanced electrochemical Cr (VI) sensing. J Electroanal Chem 841:142–147
Fu L, Yu A, Lai G (2021) Conductive hydrogel-based electrochemical sensor: a soft platform for capturing analyte. Chemosensors 9(10):282
Ganesh S et al (2023) Exploring huntington's disease diagnosis via artificial intelligence models: a comprehensive review. Diagnostics 13(23):3592
García-Pardo J et al (2021) Bioinspired theranostic coordination polymer nanoparticles for intranasal dopamine replacement in Parkinson's disease. ACS Nano 15(5):8592–8609
Gautam A (2022) Towards modern-age advanced sensors for the management of neurodegenerative disorders: current status, challenges and prospects. ECS Sens Plus 1(4):042401
Ghosh D et al (2022) Graphene-conductive polymer-based electrochemical sensor for dopamine detection ASME international mechanical engineering congress and exposition. Am Soc Mech Eng. https://doi.org/10.1115/IMECE2022-96193
Gomes BAQ et al (2025) Alpha-lipoic acid reduces neuroinflammation and oxidative stress induced by dapsone in an animal model. Nutrients 17(5):791
Gómez-Río M et al (2016) Diagnosis of neurodegenerative diseases: the clinical approach. Curr Alzheimer Res 13(5):469–474
Gu J et al (2024) Multiplex paper-based electrochemical immunosensor for the simultaneous monitoring of blood biomarkers in Alzheimer's disease. Sens Actuators B Chem 406:135456
Hampel H, Teipel SJ (2004) Total and phosphorylated tau proteins: evaluation as core biomarker candidates in frontotemporal dementia. Dement Geriatr Cogn Disord 17(4):350–354
Hampel H et al (2018) Blood-based biomarkers for Alzheimer disease: mapping the road to the clinic. Nat Rev Neurol 14(11):639–652
Hansson O (2021) Biomarkers for neurodegenerative diseases. Nat Med 27(6):954–963
Hasanzadeh M, Shadjou N, de la Guardia M (2014) Electrochemical biosensing using hydrogel nanoparticles. TrAC Trends Anal Chem 62:11–19
Hassan Q et al (2019) Electrochemical biosensors for the detection and study of α-synuclein related to Parkinson's disease–a review. Anal Chim Acta 1089:32–39
Hasseb AA, Shehab OR, El Nashar RM (2022) Application of molecularly imprinted polymers for electrochemical detection of some important biomedical markers and pathogens. Curr Opin Electrochem 31:100848
Hernández-García J, Muro-Reche P, Orenes-Piñero E (2025) Gut microbiota and microRNAs as biomarkers in Parkinson's disease: early identification, diagnostic and potential treatments. Mol Cell Biochem. https://doi.org/10.1007/s11010-025-05271-6
Hoshi K et al (2021) Transferrin biosynthesized in the brain is a novel biomarker for Alzheimer's disease. Metabolites 11(9):616
Hosseini Z, Shi D, Yuan J (2025) A flexible multiplexed electrochemical biosensing platform with graphene and gold nanoparticle modification for enhanced e-ELISA point-of-care biomarker detection. Microchem J 208:112437
Hua X et al (2019) Determination of Alzheimer biomarker DNA by using an electrode modified with in-situ precipitated molybdophosphate catalyzed by alkaline phosphatase-encapsulated DNA hydrogel and target recycling amplification. Microchim Acta 186:1–8
Jafari A, Babajani A, Rezaei-Tavirani M (2021) Multiple sclerosis biomarker discoveries by proteomics and metabolomics approaches. Biomark Insights 16:11772719211013352
Jain G et al (2019) A combined miRNA–piRNA signature to detect Alzheimer's disease. Transl Psychiatr 9(1):250
Jakhonkulovna SM et al (2025) Electrochemical biosensors for early detection of Alzheimer's disease. Clin Chim Acta 572:120278
Jalalvand AR, Karami MM (2025) Roles of nanotechnology in electrochemical sensors for medical diagnostic purposes: a review. Sens Bio-Sens Res 47:100733
Jarek DJ et al (2024) Evaluating p-tau217 and p-tau231 as biomarkers for early diagnosis and differentiation of Alzheimer's disease: a narrative review. Biomedicines 12:786
Jiang H et al (2016) Magnetic molecularly imprinted polymer nanoparticles based electrochemical sensor for the measurement of Gram-negative bacterial quorum signaling molecules (N-acyl-homoserine-lactones). Biosens Bioelectron 75:411–419
Karaboğa MNS, Sezgintürk MK (2022) Biosensor approaches on the diagnosis of neurodegenerative diseases: sensing the past to the future. J Pharm Biomed Anal 209:114479
Khatami SH et al (2024) Electrochemical biosensors in early detection of Parkinson disease. Clin Chim Acta 565:120001
Kim S, Wark AW, Lee HJ (2016) Femtomolar detection of tau proteins in undiluted plasma using surface plasmon resonance. Anal Chem 88(15):7793–7799

Kolesnikova S, Curtis EA (2019) Structure and function of multimeric G-quadruplexes. Molecules 24(17):3074
Kong Q et al (2024) Nucleic acid aptamer-based electrochemical sensor for the detection of serum P-tau231 and the instant screening test of Alzheimer's disease. Microchim Acta 191(6):328
Koníčková D et al (2022) Biomarkers of neurodegenerative diseases: biology, taxonomy, clinical relevance, and current research status. Biomedicines 10(7):1760
Kul A et al (2025) Fabrication of a molecularly imprinted polymer-based electrochemical sensor for the selective assay of antipsychotic drug clozapine and performance comparison with LC-MS/MS. Talanta 281:126810
Kumar MD et al (2022) Molecular imprinting synthetic receptor based sensor for determination of Parkinson's disease biomarker DJ-1. Microchem J 183:107959
Lakard B (2020) Electrochemical biosensors based on conducting polymers: a review. Appl Sci 10(18):6614
Lakard S, Pavel I-A, Lakard B (2021) Electrochemical biosensing of dopamine neurotransmitter: a review. Biosensors 11(6):179
Le PG, Choi SH, Cho S (2023) Alzheimer's disease biomarker detection using field effect transistor-based biosensor. Biosensors 13(11):987
Leau S-A, Lete C, Lupu S (2023) Nanocomposite materials based on metal nanoparticles for the electrochemical sensing of neurotransmitters. Chemosensors 11(3):179
Lee M-H et al (2021) Transition metal dichalcogenides to optimize the performance of peptide-imprinted conductive polymers as electrochemical sensors. Microchim Acta 188(6):203
Lei Y et al (2020) Single-atom doping of MoS2 with manganese enables ultrasensitive detection of dopamine: experimental and computational approach. Sci Adv 6:4250
Li S, Kerman K (2021) Electrochemical biosensors for biometal-protein interactions in neurodegenerative diseases. Biosens Bioelectron 179:113035
Li Y et al (2024) Recent advances in molecularly imprinted polymer-based electrochemical sensors. Biosens Bioelectron 249:116018
Li L et al (2025) Detection of Aβ40 in cerebrospinal fluid and plasma of Alzheimer's disease patients using photoelectrochemical biosensors. Microchim Acta 192(1):1–11
Liu H, Chen B, Zhu Q (2022) Potential application of hydrogel to the diagnosis and treatment of multiple sclerosis. J Biol Eng 16(1):10
Liu X et al (2025) Innovative bioinspired hydrogel scaffolds enabling in-situ hybrid nanoflower integration for dual-mode acetylcholinesterase inhibitor profiling. Biosens Bioelectron 271:117032
Lu Z et al (2023) Nanoarchitectonics of on–off ratiometric signal amplified electrochemical sensor for chlorpromazine with molecularly imprinted polymer based on Ni–MOF/Fe–MOF–5 hybrid Au nanoparticles. Sep Purif Technol 327:124858
Lu S et al (2024) Polymeric nanocomposite electrode for enhanced electrochemical detection of α-lipoic acid: application in neuroinflammation prevention and clinical analysis. Environ Res 245:117369
Luo C et al (2025) Competitive electrochemical immunosensor for trace phosphorylated Tau181 analysis in plasma: toward point-of-care technologies of Alzheimer's disease. Talanta 292:128009
Lv Y et al (2025) In situ formation of boronic acid-based covalent organic frameworks for specific and ultra-sensitive electrochemical assay of glycosylated amyloid-beta proteins. Talanta 285:127435
Ma Y et al (2020) A nanospherical conjugated microporous polymer-graphene nanosheets modified molecularly imprinted electrochemical sensor for high sensitivity detection of α-synuclein. J Electroanal Chem 862:113994
Martínez Lozada PS et al (2024) Early diagnosis of Huntington disease: insights from magnetic resonance spectroscopy—a systematic review. J Clin Med 13(21):6390
Massey RS, Appadurai RR, Prakash R (2024) A surface imprinted polymer EIS sensor for detecting alpha-synuclein, a Parkinson's disease biomarker. Micromachines 15(2):273
McDonald WI et al (2001) Recommended diagnostic criteria for multiple sclerosis: guidelines from the international panel on the diagnosis of multiple sclerosis. Ann Neurol Off J Am Neurol Assoc Child Neurol Soc 50(1):121–127
Mishra J et al (2021) Carbon nano tubes: novel drug delivery system in amelioration of alzheimer's disease. Comb Chem High Throughput Screen 24(10):1528–1543
Moon J-M et al (2018) Conducting polymer-based electrochemical biosensors for neurotransmitters: a review. Biosens Bioelectron 102:540–552
Motaharian A et al (2016) Molecularly imprinted polymer nanoparticles-based electrochemical sensor for determination of diazinon pesticide in well water and apple fruit samples. Anal Bioanal Chem 408:6769–6779
Nastasijevic B et al (2012) Remyelination induced by a DNA aptamer in a mouse model of multiple sclerosis. PLoS ONE 7(6):e39595
Nawrot W et al (2018) A fluorescent biosensors for detection vital body fluids' agents. Sensors 18(8):2357
Negahdary M, Angnes L (2022) Electrochemical aptamer-based nanobiosensors for diagnosing Alzheimer's disease: a review. Biomater Adv 135:112689
Noguchi HK et al (2022) Rapid electrochemical detection of levodopa using polyaniline-modified screen-printed electrodes for the improved management of Parkinson's disease. Phys Med 14:100052
Norman B et al (2024) Towards cerebrospinal fluid-free ultrasensitive Alzheimer's diagnostics using molecularly imprinted polymers. In: 2024 IEEE BioSensors Conference (BioSensors). IEEE.
Orzari LO et al (2024) Lab-made disposable screen-printed electrochemical sensors and immunosensors modified with Pd nanoparticles for Parkinson's disease diagnostics. Microchim Acta 191(1):76
Pakapongpan S et al (2024) A disposable electrochemical sensor for amyloid-β42 protein based on molecular imprinted polymers with nitrogen doped carbon dots-graphene nanohybrid. Microchem J 206:111559
Paul S et al (2024) Microbial biosensors for environmental quality monitoring: recent advances and future outlook. In: Bala K, Ghosh T, Kumar V, Sangwan P (eds) Harnessing microbial potential for multifarious applications. Springer, Singapore, pp 439–453
Pilvenyte G et al (2023) Molecularly imprinted polymers for the recognition of biomarkers of certain neurodegenerative diseases. J Pharm Biomed Anal 228:115343
Prakash S et al (2013) Polymer thin films embedded with metal nanoparticles for electrochemical biosensors applications. Biosens Bioelectron 41:43–53
Rabbani G et al (2024) An electrochemical immunosensor based on AgNPs/Nafion-GCE for detection of salivary lactoferrin: Alzheimer's disease biomarker. Microchem J 207:112079
Raja AN (2020) Recent development in chitosan-based electrochemical sensors and its sensing application. Int J Biol Macromol 164:4231–4244
Rajarathinam T et al (2023) Nanocomposite-based electrochemical sensors for neurotransmitters detection in neurodegenerative diseases. Chemosensors 11(2):103
Raket LL et al (2020) Utility of plasma neurofilament light and total tau for clinical trials in Alzheimer's disease. Alzheimer's Dement Diagn Assess Dis Monit 12(1):e12099
Selvam S, Ayyavoo V (2024) Biomarkers in neurodegenerative diseases: a broad overview. Explor Neuroprotective Ther 4(2):119–147

Şenel P et al (2025) Electrochemical quantification based on the interactions of nucleoside analog cladribine with dsDNA via experimental and in-silico studies. Int J Biol Macromol 284:138083
Serin M, Kara P (2024) Aptamer-based electrochemical nanobiosensor for research and monitoring of multiple sclerosis in mice models. Bioelectrochemistry 160:108744
Serin M, Kara P (2025) Demyelination detection in CSF based on electrochemical monitoring of myelin basic protein in comparison between Apta vs Immuno sensing strategies. Bioelectrochemistry 161:108834
Shafique H et al (2023) Advances in the translation of electrochemical hydrogel-based sensors. Adv Healthc Mater 12(1):2201501
Shah NS et al (2022) Picomolar or beyond limit of detection using molecularly imprinted polymer-based electrochemical sensors: a review. Biosensors 12(12):1107
Shariati S, Ghaffarinejad A, Omidinia E (2022) Early detection of multiple sclerosis (MS) as a neurodegenerative disease using electrochemical nano-aptasensor. Microchem J 178:107358
Sharma P, Parihar A, Khan R (2024) Sampling methods and biomarkers for early detection of neurodegenerative disorders. Smart diagnostics for neurodegenerative disorders. Elsevier, pp 39–59
Sheinerman KS et al (2012) Plasma microRNA biomarkers for detection of mild cognitive impairment. Aging (Albany NY) 4(9):590
Sheinerman KS et al (2017) Circulating brain-enriched microRNAs as novel biomarkers for detection and differentiation of neurodegenerative diseases. Alzheimer's Res Ther 9:1–13
Shin M-K et al (2024) electrochemical analysis of amyloid plaques and ApoE4 with chitosan-coated gold nanostars for Alzheimer's detection. Biosensors 14(10):510
Siafaka PI et al (2021) Detecting and targeting neurodegenerative disorders using electrospun nanofibrous matrices: current status and applications. J Drug Target 29(5):476–490
Sikarwar B et al (2016) Enzyme based electrochemical biosensor for ethanolamine. Electroanalysis 28(4):881–889
Simões FR, Xavier MG (2017) Electrochemical sensors. Nanosci Appl 1:155–178
Singh A et al (2021) Recent advances in electrochemical biosensors: applications, challenges, and future scope. Biosensors 11(9):336
Song C et al (2020) On-chip detection of the biomarkers for neurodegenerative diseases: technologies and prospects. Micromachines 11(7):629
Sumitha M, Xavier T (2023) Recent advances in electrochemical biosensors–a brief review. Hybrid Adv 2:100023
Sun L et al (2018) A hydrogel biosensor for high selective and sensitive detection of amyloid-beta oligomers. Int J Nanomed 13:843–856
Swierczewska M et al (2012) High-sensitivity nanosensors for biomarker detection. Chem Soc Rev 41(7):2641–2655
Tavakolian-Ardakani Z et al (2019) Latest trends in electrochemical sensors for neurotransmitters: a review. Sensors 19(9):2037
Thakur R et al (2025) Neurodegenerative diseases early detection and monitoring system for point-of-care applications. Microchem J 208:112280
Thambisetty M, Lovestone S (2010) Blood-based biomarkers of Alzheimer's disease: challenging but feasible. Biomark Med 4(1):65–79
Toyos-Rodríguez C, García-Alonso FJ, de la Escosura-Muñiz A (2020) Electrochemical biosensors based on nanomaterials for early detection of Alzheimer's disease. Sensors 20(17):4748
Turco A et al (2024) Advancing amyotrophic lateral sclerosis disease diagnosis: a lab-on-chip electrochemical immunosensor for ultrasensitive TDP-43 protein detection and monitoring in serum patients'. Talanta 273:125866
Vais RD et al (2021) A β-Amyloid (1–42) biosensor based on molecularly imprinted poly-pyrrole for early diagnosis of Alzheimer's disease. J Biomed Phys Eng 11(2):215
Valkova P, Pohanka M (2021) Novel trends in electrochemical biosensors for early diagnosis of Alzheimer's disease. Int J Anal Chem 2021(1):9984876
Wang J, Lu X, He Y (2025) Electrochemical technology for the detection of Tau proteins as a biomarker of Alzheimer's disease in blood. Biosensors 15(2):85
Wen W et al (2017) Recent advances in electrochemical immunosensors. Anal Chem 89(1):138–156
Weston PS et al (2019) Longitudinal measurement of serum neurofilament light in presymptomatic familial Alzheimer's disease. Alzheimer's Res Ther 11:1–7
Wu J et al (2023) Device integration of electrochemical biosensors. Nat Rev Bioeng 1(5):346–360
Xu X et al (2024a) Advancements in brain research: the in vivo/in vitro electrochemical detection of neurochemicals. Biosensors 14(3):125
Xu X et al (2024b) Design of Ti3C2T x/SnO2-selective ethanolamine sensor. ACS Appl Nano Mater 7(4):4324–4335
Yanat M, Schroën K (2021) Preparation methods and applications of chitosan nanoparticles; with an outlook toward reinforcement of biodegradable packaging. React Funct Polym 161:104849
Yang J et al (2022) Current and future biomarkers in multiple sclerosis. Int J Mol Sci 23(11):5877
Yang T et al (2025) In vivo electrochemical biosensing technologies for neurochemicals: recent advances in electrochemical sensors and devices. ACS sensors, Washington
Zdrachek E, Bakker E (2020) Potentiometric sensing. Anal Chem 93(1):72–102
Zhang J, Wang Z (2022) Nanoparticle–hydrogel based sensors: synthesis and applications. Catalysts 12(10):1096
Zhao Y et al (2025) Skin α-synuclein assays in diagnosing Parkinson's disease: a systematic review and meta-analysis. J Neurol 272(5):326

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