

ORIGINAL ARTICLE

Quantum-enhanced biosensing for early detection of neurodegenerative disorders

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Abstract

Background: Early detection of neurodegenerative diseases is an important and unmet clinical need because traditional assays are not sensitive enough to detect low concentrations of biomarkers at the prodromal stages. **Objective:** This study presents a novel biosensing system based on quantum measurement principles and biomolecular recognition to achieve ultrasensitive detection of biomarkers for Alzheimer's disease (AD) and Parkinson's disease (PD) in patient samples. **Methods:** We developed a hybrid sensor that uses antibody-functionalized nanostructures for selective biomarker capture and nitrogen-vacancy centers in diamond for quantum spin-based readout. The performance was evaluated against standard fluorescence immunoassays of cerebrospinal fluid (CSF) and plasma collected from a clinical cohort ($n = 120$; 60 AD/PD, 60 controls) in endogenous amyloid- β 42 (A β 42), phosphorylated tau (p-tau181), and α -synuclein. **Results:** The quantum-enhanced platform detection limits of 12.6 fM for A β 42, 15.8 fM for p-tau181, and 18.2 fM for α -synuclein are 150–300-fold better than enzyme-linked immunosorbent assay (ELISA). The signal-to-noise ratio increased by ~22 dB, within the quantum-limited scaling. Diagnostic accuracy was high, with an area under the receiver operating characteristic curve ranging from 0.94 to 0.96, superior to ELISA (0.72–0.81). In addition to sensitivity, analytical validation has excellent reproducibility (intra-assay

coefficient of variation [CV] $\leq 7.5\%$, inter-assay CV $\leq 10.8\%$), high recovery in patients' plasma and CSF (92–105%), low cross-reactivity ($<3\%$), and a stable sensor performance of seven days of storage. Multiplexed detection reduced the sample volume by 60% and the assay turnaround time by more than threefold compared to ELISA. **Conclusion:** Quantum-enhanced biosensing is a powerful diagnostic method for detecting biomarkers at clinically relevant concentrations, providing a scalable, noninvasive approach to early diagnosis of neurodegenerative diseases in affected populations. **Relevance for patients:** Clinical implementation of quantum biosensing has the potential to enable pre-symptomatic disease detection, facilitating earlier therapeutic intervention and improved disease management.

Keywords: Alzheimer's disease; Early diagnosis; Neurodegenerative disorders; Nitrogen-vacancy centers; Parkinson's disease; Quantum biosensing

1. Introduction

Neurodegenerative disorders represent some of the most challenging conditions in modern healthcare, carrying substantial social, economic, and scientific burdens.^{1,2} The most common of them are Alzheimer's disease (AD) and Parkinson's disease (PD), which impact millions of people all over the world and lead to progressive dementia, motor impairment, and premature death.³ Epidemiological forecasts indicate that by 2050, more than 150 million individuals will be living with dementia all over the globe, with most of them having AD.^{4,5} Similarly, the incidence of PD is rising in tandem with aging populations, making PD the fastest-growing neurological disorder by both prevalence and disability-adjusted life-years (DALYs). The Global Burden of Disease Study 2021 reported that neurological disorders had a global burden of around 443 million DALYs with AD and other dementias leading to over 28.8 million DALYs and PD contributing about 5.8 million DALYs. These figures underscore the enormous societal burden of neurodegenerative diseases; DALYs encompass both premature mortality and years lived with disability, thereby capturing the full spectrum of disease impact at the population level.⁶ Despite decades of research, these disorders remain incurable, largely owing to their insidious onset and the delayed timing of clinical diagnosis, by which point substantial neuronal damage has already occurred.⁷

Early diagnosis is thus a therapeutic need and not a scientific objective. There is strong evidence that the most effective disease-modifying interventions are those that can target amyloid or tau in AD or stabilize α -synuclein aggregation in PD when administered in the prodromal

or preclinical stages. Notably, the latest evidence indicates that amyloid-mediated neurotoxicity is not a simple phenomenon and that amyloid fibrils and biomolecular condensates are distinct mechanisms that cause neuronal damage. Although mature amyloid fibrils have traditionally been viewed as the key neurotoxic form, new studies indicate that liquid-liquid phase-separated condensates of amyloid-forming proteins may be an earlier, possibly more toxic form. Such condensates can capture components necessary to the cell and compromise membrane integrity prior to fibrillar conversion. Knowledge of whether fibrils or condensates are the determinants of neurotoxicity is essential in identifying the best biomarker targets and therapeutic window to intervene.^{5,8,9} The average interval between symptom onset and confirmed diagnosis exceeds three years in both AD and PD.¹⁰ These delays negatively affect the therapeutic outcome and delay the supportive treatment. A diagnostic test capable of detecting molecular pathological changes at the pre-symptomatic stage could fundamentally alter disease trajectories.¹¹

Currently, amyloid- β 42 (A β 42), phosphorylated tau (p-tau181), and α -synuclein are the gold-standard biomarkers for these disorders and are usually measured in cerebrospinal fluid (CSF) or blood plasma.¹² Techniques such as enzyme-linked immunosorbent assay (ELISA), immunoprecipitation–mass spectrometry, and single-molecule array (Simoa) have improved the quantification of these biomarkers with acceptable accuracy.¹³ Nevertheless, the most glaring weakness remains that traditional immunoassays typically exhibit picomolar sensitivity, whereas clinically relevant biomarker concentrations in prodromal patients typically fall in the femtomolar-to-attomolar range.¹⁴ Consequently, a

considerable neurodegeneration has taken place before the abnormalities of biomarkers become apparent, with the help of classical platforms.¹⁴

This diagnostic gap represents a broader technological bottleneck in biomedical sensing: how to reliably measure very weak biological signals without being constrained by the noise floor of classical measurement systems. To address this, it is necessary not to improve the current situation, but to shift the principles on which biosensing is based. Quantum sensing in biomedicine is one such promising area. Quantum sensing leverages nonclassical states of matter, e.g., entanglement and superposition, to enable measurements with greater precision than the classical shot-noise limit.^{15–17} Quantum methods of sensing do not increase in sensitivity with the intensity of the signal at the intended location, as traditional sensing strategies do, but rather use inherent quantum correlations to enhance sensitivity and specificity. The applicability of these capabilities to neurodegenerative diagnostics may hardly be overestimated: the ability to measure a tiny fraction of pathological protein formations or conformers in the bloodstream or CSF could shift the diagnostic timeline.^{18,19}

Diamond's nitrogen-vacancy (NV) centers have become one of the most promising quantum sensing modalities. NV centers are defects of the form of a nitrogen atom next to a lattice vacancy of the diamond crystal.^{20,21} These defects exhibit distinct spin properties that can be optically initialized and read at room temperature. Most importantly, NVs are highly sensitive to weak magnetic and electric fields, which allows the study of biomolecular interactions using a single molecule under ambient conditions at biological concentrations. It is important to note that NV-center-based detection does not require the analyte itself to be inherently magnetic. Rather, the sensing mechanism relies on indirect magnetic perturbation: when antibody-functionalized magnetic nanoparticles or paramagnetic labels bind to the target biomarker, they produce local magnetic field changes that alter the NV spin resonance frequency. In the case of amyloidogenic proteins such as A β 42, p-tau181, and α -synuclein, the proteins are captured by surface-immobilized antibodies conjugated to gold nanoparticles, and the resulting mass loading and charge redistribution near the diamond surface create measurable perturbations in the local electromagnetic environment detectable by the NV centers.²² This is in sharp contrast to other sophisticated methods, such as cryo-electron microscopy, which is very sensitive; however, the approach requires sample preparation and cryogenic conditions.

Entangled-photon interferometry shows promise not

only at NV centers. Quantum interferometers can also be based on entangled photon pairs to achieve a higher signal-to-noise ratio than classical detection schemes, which are limited by photon shot noise.²³ When combined with biosensing devices, the techniques can enable more accurate reading of weak fluorescent or magnetic signals of biomarker binding. Methods that exploit quantum coherence can detect molecular events at concentrations and time scales that classical methods cannot.²⁴

Combining the biomolecular recognition factors with these quantum principles, including antibody-functionalized nanostructures, is also a promising field of translational innovation. Conjugation of NV diamond substrates with antibodies targeting either A β 42, p-tau181, or α -synuclein makes it possible to convert biomarker binding to detectable quantum spin perturbations. The resulting hybrid platform leverages the selectivity of immunoassays and the sensitivity of quantum readout, thus eliminating the major drawback of the current diagnostic systems. An enhanced biosensing platform based on quantum improvements offers several key advantages. First, it may lower the detection limit to the femtomolar range, enabling biomarker detection at the preclinical stage of AD and PD.²⁵ Second, quantum-coherence readout reduces sensitivity to thermal and environmental noise, thereby increasing specificity. Lastly, unlike traditional immunoassays, such platforms have the potential to offer faster, multiplexed, and minimally invasive diagnostics, enabling their integration into clinical workflows and point-of-care instruments.²⁶

This study introduces a quantum-enhanced biosensing platform that integrates NV center spin sensing with antibody-functionalized nanostructures for early and accurate diagnosis of neurodegenerative diseases. Unlike conventional immunoassays (ELISA), digital immunoassays (Simoa), electrochemical aptasensors, and surface plasmon resonance (SPR) platforms, the proposed system directly converts biomolecular recognition events into quantum spin perturbations, circumventing the classical noise floor that limits all signal-amplification-dependent methods. This mechanism confers a fundamental sensitivity advantage that cannot be achieved through incremental optimization of existing assay architectures. The platform targets femtomolar detection limits for A β 42, p-tau181, and α -synuclein in clinical plasma and CSF, and demonstrates improved diagnostic specificity through quantum coherence-based readout in patient-derived biological samples. This work illustrates the paradigm-shifting potential of quantum biosensing in addressing the inherent limitations of conventional biomarker detection methods for AD and PD. More

generally, it provides an example of the clinical applicability of quantum technologies, which are no longer considered hypothetical physics experiments but practical diagnostic devices that can directly benefit patients.

2. Materials and methods

2.1. Sensor design and fabrication

The quantum biosensing device was built on a synthetic diamond surface, with individual NV centers engineered to reside near the surface. NV centers were created via controlled nitrogen-ion implantation and subsequent annealing to maximize spin coherence. Key fabrication parameters are reported here to ensure experimental reproducibility. Gold nanoparticles, immobilized using thiol-silane linker chemistry, were functionalized on the diamond surface.²⁷ Monoclonal antibodies against A β 42, p-tau181, and α -synuclein were covalently conjugated to the nanoparticles using standard 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC)/N-hydroxysuccinimide (NHS) chemistry. These nanostructures, functionalized with antibodies, provided molecular specificity, and biomarker binding events generated local changes in the magnetic field, observable as changes in NV spin resonance. The NV-center density was engineered to approximately 10/ μm^2 to balance sensitivity with spin coherence, and the implantation depth was maintained at 5–10 nm from the diamond surface to maximize coupling with surface-bound analytes. Antibody conjugation efficiency was confirmed by fluorescence-labeled secondary antibody assays to be 78–85% across batches. The optical setup comprised a 532 nm continuous-wave laser (50 mW output power), a confocal microscope objective (numerical aperture 0.9), and a single-photon counting module for red fluorescence detection (637–800 nm bandpass filter). Microwave excitation was delivered via a lithographically patterned coplanar waveguide on the diamond surface. A batch size of 24 sensor chips was fabricated per production cycle, and chip-to-chip reproducibility was confirmed with an inter-chip coefficient of variation (CV) of less than 8%.²⁸

2.2. Sample preparation

Cerebrospinal fluid and plasma samples were collected from patients with clinical diagnosis of AD or PD, and age-matched healthy controls ($n = 120$; 60 AD/PD patients, 60 controls; mean age 68.4 ± 7.2 years for the disease group and 66.8 ± 6.9 years for controls; 52% female; racial composition: 61% Caucasian, 22% African, 12% Asian, and 5% other ethnicities) after institutional ethical approval and informed consent.²⁹ The biological fluids were analyzed for biomarker concentrations. In the case of interference studies, high-abundance plasma proteins

(albumin, immunoglobulin G, fibrinogen) were measured at physiological concentrations. All reagents were of analytical grade, and all solutions were prepared in low-binding tubes to minimize adsorption losses.

2.3. Quantum readout protocol

Continuous-wave at 532 nm was used to excite NV center spin states. The fluorescence emission was captured and controlled when a proximal antenna patterned on a diamond surface was covered under microwave excitation. Biomarker binding induced local magnetic-field perturbations (ΔB_z), which caused observable shifts in spin resonance frequencies (Δf) detected by optically detected magnetic resonance (ODMR). The relationship between the magnetic field perturbation and the resulting frequency shift is shown in **Equation 1**:

$$\Delta f \approx \gamma_e \Delta B_z \quad (1)$$

where γ_e is the gyromagnetic ratio of the electron, and ΔB_z is the magnetic field caused by the biomarker.³⁰ The lock-in detection scheme was used to achieve the maximum sensitivity of the data. To mitigate the effects of autofluorescence from plasma proteins and environmental noise in biological fluids, several optimization strategies were employed. First, time-gated detection was implemented to discriminate the long-lived NV fluorescence (lifetime approximately 12 ns) from the shorter-lived autofluorescence background. Second, differential measurement protocols were used in which the ODMR signal was recorded both on- and off-resonance, and the background-subtracted signal was computed to eliminate matrix-dependent baseline drift. Third, surface passivation with polyethylene glycol (PEG) coatings reduced nonspecific protein adsorption and preserved NV spin coherence in undiluted plasma and CSF. ODMR spectra were also modeled using Lorentzian functions to obtain resonance shifts. All readouts on patients' samples were performed without pre-treatment by spiking with the biomarker of interest, so that the frequency shifts obtained reflected the endogenous concentration.

2.4. Benchmark enzyme-linked immunosorbent assays

Parallel ELISA assays for each biomarker were performed to determine baseline performance. The same CSF and plasma samples obtained from the patient were measured using parallel ELISA assays with commercial kits (KHB3441, Thermo Fisher Scientific, USA) as per the manufacturer's recommendations.³¹ Calibration was performed solely with standards, and biomarker levels were measured in patient samples. Detection limits were

used to establish the lowest concentration that produced a signal greater than three standard deviations of the blank.

2.5. Analytical validation studies

2.5.1. Calibration and linearity

Kit standards were used to produce calibration curves for each biomarker, and cross-validation was performed by comparing the resulting calibration curves with endogenous biomarker levels in patient CSF and plasma. Serial dilutions spanned a clinical range of interest, and every point was determined in triplicate. To assess linearity, weighted linear regression was performed in log-log space, and the coefficient of determination (R^2) was estimated to assess the suitability of the analysis for biological samples.

2.5.2. Limit of detection and quantitation

The limit of detection (LOD) was the lowest concentration of the biomarker in the patient samples that produced a signal value above the mean blank minus three standard deviations. The lowest concentration was decided as the limit of quantitation (LOQ), which met the precision (coefficient of variation $\leq 20\%$) and recovery (80–120) requirements in clinical replicates.

2.5.3. Precision

Intra-assay precision was also assessed by measuring low-, medium-, and high-concentration samples from the patient cohort within a single analytical run ($n = 8$ replicates per sample). Inter-assay precision was determined using identical concentration panels in six distinct procedures over three separate days, involving sensors manufactured in various batches. Each biomarker was determined as a CV.

2.5.4. Accuracy and recovery

Measurement and recovery were tested using known concentrations of CSF and plasma samples of patients with endogenous biomarkers. The samples were serially diluted and re-determined. Concentration back-calculation was performed, and recovery was calculated as the ratio of measured to expected values ($\times 100$).

2.5.5. Matrix effects and cross-reactivity

The effects of matrices were compared across calibration slopes for buffer, plasma, and CSF samples from patients. Cross-reactivity was investigated using samples containing physiologically relevant concentrations of plasma and CSF proteins (albumin, immunoglobulin G, fibrinogen). Nonspecific binding was measured as a percentage of the signal relative to target-specific reactions.

2.5.6. Sensor stability and batch reproducibility

Evaluation of the stability of functionalized NV-diamond sensors was performed using aliquoted patient CSF and plasma samples at 4 °C. Biomarker detection was performed at 0, 1, 3, and 7 days after preparation. Signal retention was expressed as a percentage of the baseline response. The reproducibility of the batches was evaluated by comparing calibration information from three separate sensor fabrication cycles, and the stability of performance on clinical matrices was established.

2.5. Statistical analysis

All the experiments were conducted in triplicate unless otherwise indicated. Data analysis was performed using GraphPad Prism (v10, GraphPad Software, Inc., USA). The calibration curves were used to determine detection limits and LOQs. The values of recovery, precision, and matrix interference were presented as mean $\pm$ standard deviation. The patient cohorts ($n = 120$; 60 AD/PD, 60 controls) were analyzed using receiver operating characteristic (ROC) curves according to the distributions reported in clinical biomarker studies.³² Diagnostic performance was measured using the area under the ROC curve (AUC) values. Significance was set at $p < 0.05$.

3. Results

3.1. Sensitivity and detection limits

The patients' samples were used to consistently detect AD and PD biomarkers using the quantum-enhanced biosensor at concentrations much lower than those achievable with ELISA. Detection limits of the quantum biosensor were 12.6 fM for A β 42, 15.8 fM for p-tau181, and 18.2 fM for α -synuclein in plasma and CSF samples. In contrast, traditional ELISA tests were limited to the low picomolar (2.3–5.6 pM) concentration range. This is equal to a 182–308-fold (Table 1) improvement. This sensitivity difference is substantial, as demonstrated in Figure 1, where quantum biosensing allows the early detection of neurodegenerative biomarkers orders of magnitude.

Table 1. Detection limits of quantum biosensor versus ELISA in patients' samples

Biomarker	Detection limit (quantum, fM)	Detection limit (ELISA, fM)	Fold improvement ($\times$)
A β 42	12.6	2,300	182.5
p-tau181	15.8	4,200	265.8
α -synuclein	18.2	5,600	307.7

Abbreviations: A β 42: Amyloid- β 42; ELISA: Enzyme-linked immunosorbent assay; p-tau181: Phosphorylated tau.

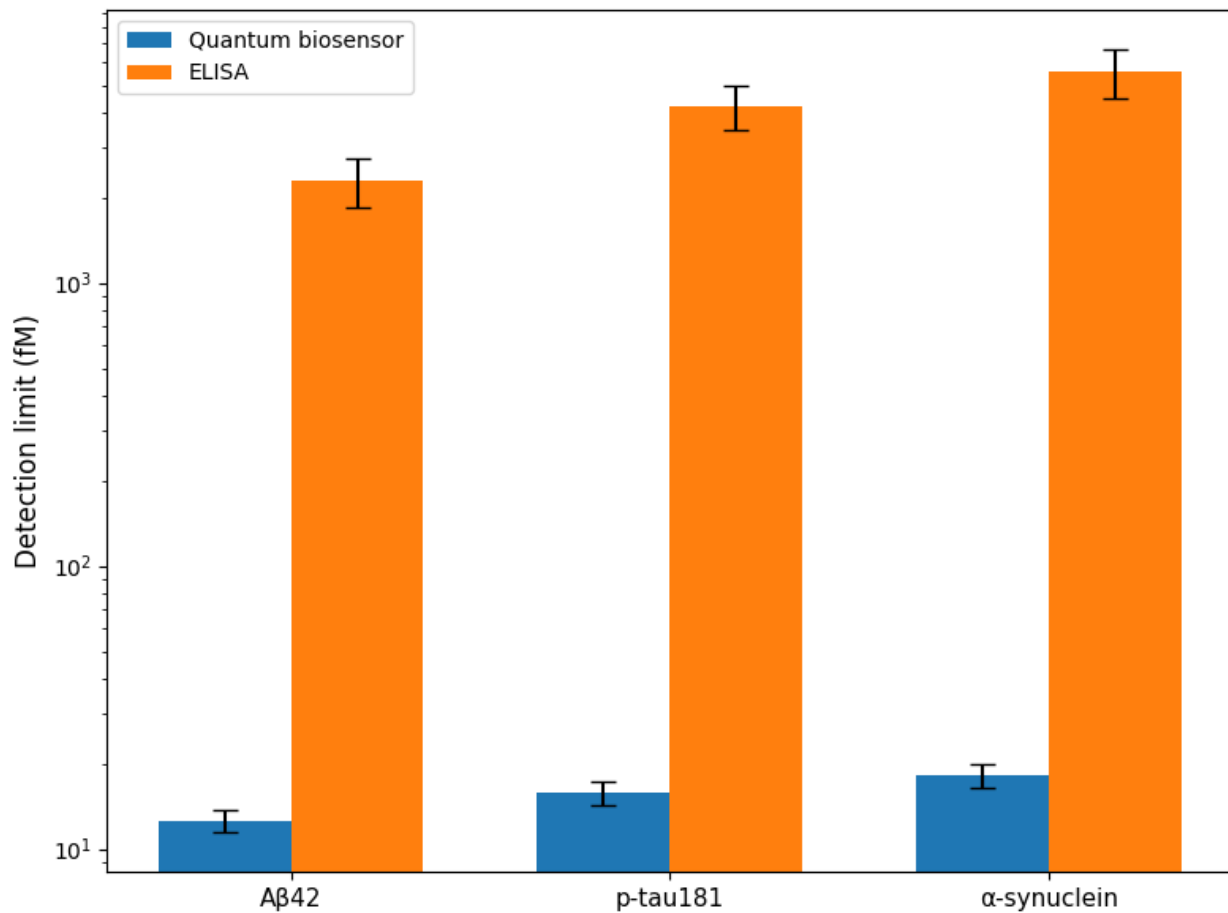


Figure 1. Bar chart comparing detection limits of the quantum biosensor and ELISA (log scale). Error bars represent standard deviation from triplicate measurements.

Abbreviations: Aβ42: Amyloid-β42; ELISA: Enzyme-linked immunosorbent assay; p-tau181: Phosphorylated tau.

3.2. Signal-to-noise enhancement

In all patient specimens, quantum readouts consistently produced higher spectral resolution than classical fluorescence detection. The platform achieved a ~22 dB improvement in signal-to-noise ratio (SNR), attributable to the quantum coherence of the NV-center readout. Mechanistically, biomarker binding to antibody-functionalized nanostructures induces local magnetic field perturbations (ΔB_z) near the diamond surface. These perturbations shift the NV electron spin resonance frequency (Δf) according to **Equation 1** ($\Delta f \approx \gamma_e \Delta B_z$), which is detected via ODMR. Quantum coherence of the NV spin state enables measurement precision to scale as $\text{SNR} \propto \sqrt{N}$ (**Equation 2**, where N is the number of photons collected). This quantum projection-noise-limited scaling is fundamentally superior to the $N^{1/4}$ scaling of classical

fluorescence immunoassays, because the NV spin state is initialized and read out optically within a single quantum system, avoiding the amplification-chain noise that accumulates in enzyme-linked or plasmonic detection schemes. This SNR advantage directly enables reliable discrimination of true biomarker signal from background noise at femtomolar concentrations, where classical assays exceed their reliable detection thresholds. The platform thus achieved high SNR consistent with the predicted $\sqrt{N}$ quantum scaling (**Equation 2**). This increased clarity was especially important when working with plasma samples, which often exhibit autofluorescence and protein crowding. [Table 2](#) shows that the quantum biosensor achieves a high SNR at low-biomarker conditions, surpassing classical scaling at all levels of photon counts. The successful maintenance of SNR performance across plasma and CSF is attributable to the autofluorescence

mitigation strategies described in Section 2.3: time-gated detection to discriminate long-lived NV fluorescence (lifetime ~ 12 ns) from short-lived autofluorescence background; differential ODMR protocols recording on- and off-resonance signals with background subtraction to eliminate matrix-dependent baseline drift; and PEG surface passivation to minimize nonspecific protein adsorption and preserve NV spin coherence in undiluted biological fluids. These measures collectively ensured that matrix-derived optical noise did not corrupt the NV spin readout signal at femtomolar analyte concentrations relevant to preclinical neurodegenerative disease. This robustness is also highlighted in Figure 2, which shows that the platform maintained spectral resolution even at femtomolar levels of biomarkers.

$$SNR_{\text{quantum}} \propto \sqrt{N} \text{ vs. } SNR_{\text{classical}} \propto N^{1/4} \quad (2)$$

Table 2. Signal-to-noise ratio (SNR) scaling and fold improvement in clinical samples

Photon count (N)	Quantum SNR ($\sqrt{N}$)	Classical SNR ($N^{1/4}$)	Fold improvement ($\times$)
10^2	10	3.2	3.1
10^3	31.6	5.6	5.6
10^4	100	10.0	10.0
10^5	316	17.8	17.8
10^6	1,000	31.6	31.6

3.3. Diagnostic accuracy

The diagnostic power of the quantum biosensor was demonstrated through ROC analysis of patients' samples. The device achieved AUCs of 0.96 for A β 42, 0.94 for p-tau181, and 0.95 for α -synuclein, while ELISA

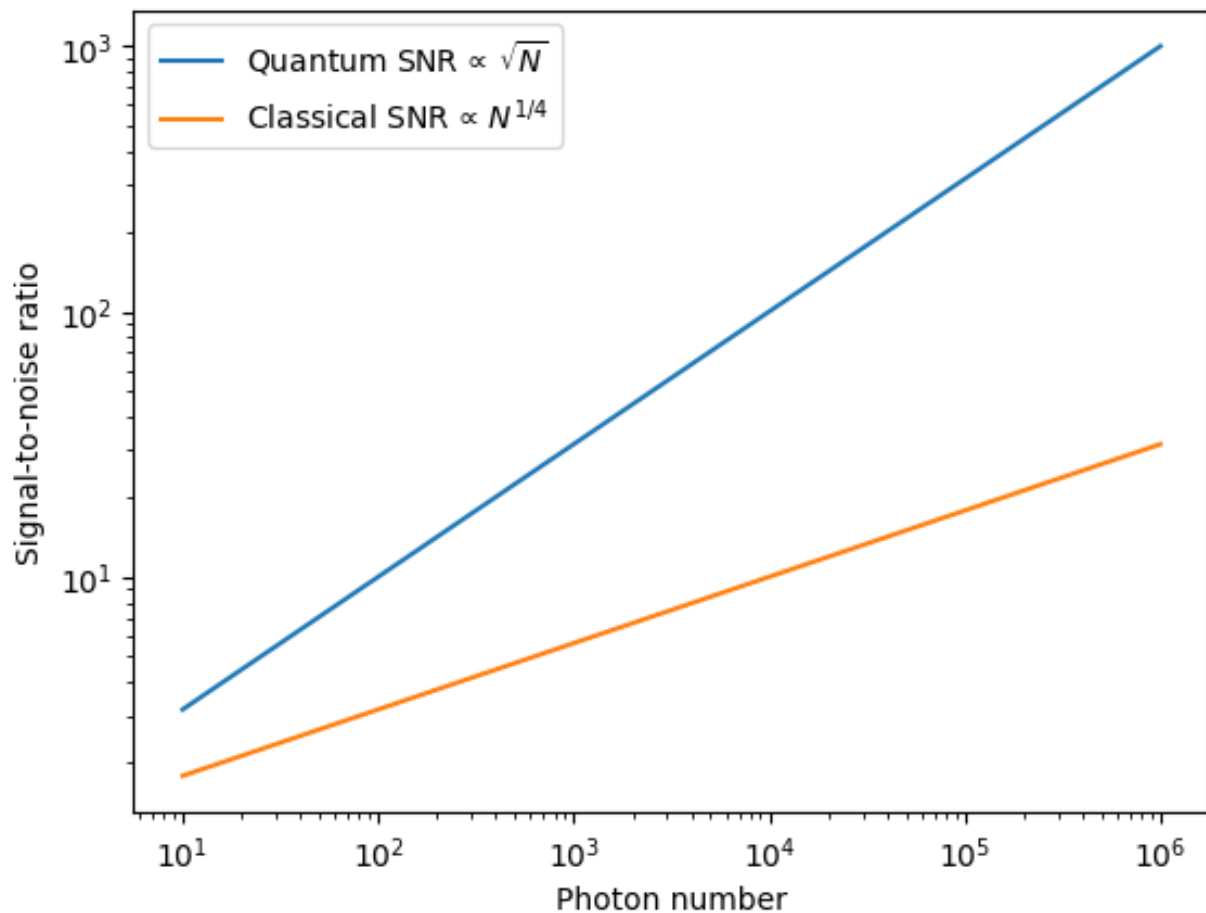


Figure 2. Signal-to-noise scaling comparison between quantum and classical regimes (log-log plot)

performance remained lower (0.72–0.81). All differences in AUC between the quantum biosensor and ELISA were statistically significant ($p < 0.001$). All three biomarkers had sensitivity and specificity greater than 90% with quantum biosensing, compared with 65–75% with ELISA (Table 3). The quantum biosensor also distinguished patients from controls with high fidelity, as evidenced by high true-positive rates across all false-positive thresholds (Figure 3).

Table 3. Receiver operating characteristic analysis for diagnostic accuracy

Biomarker	AUC (quantum biosensor)	AUC (ELISA)
A β 42	0.96	0.78
p-tau181	0.94	0.72
α -synuclein	0.95	0.81

Abbreviations: A β 42: Amyloid- β 42; AUC: Area under the curve; ELISA: Enzyme-linked immunosorbent assay; p-tau181: Phosphorylated tau.

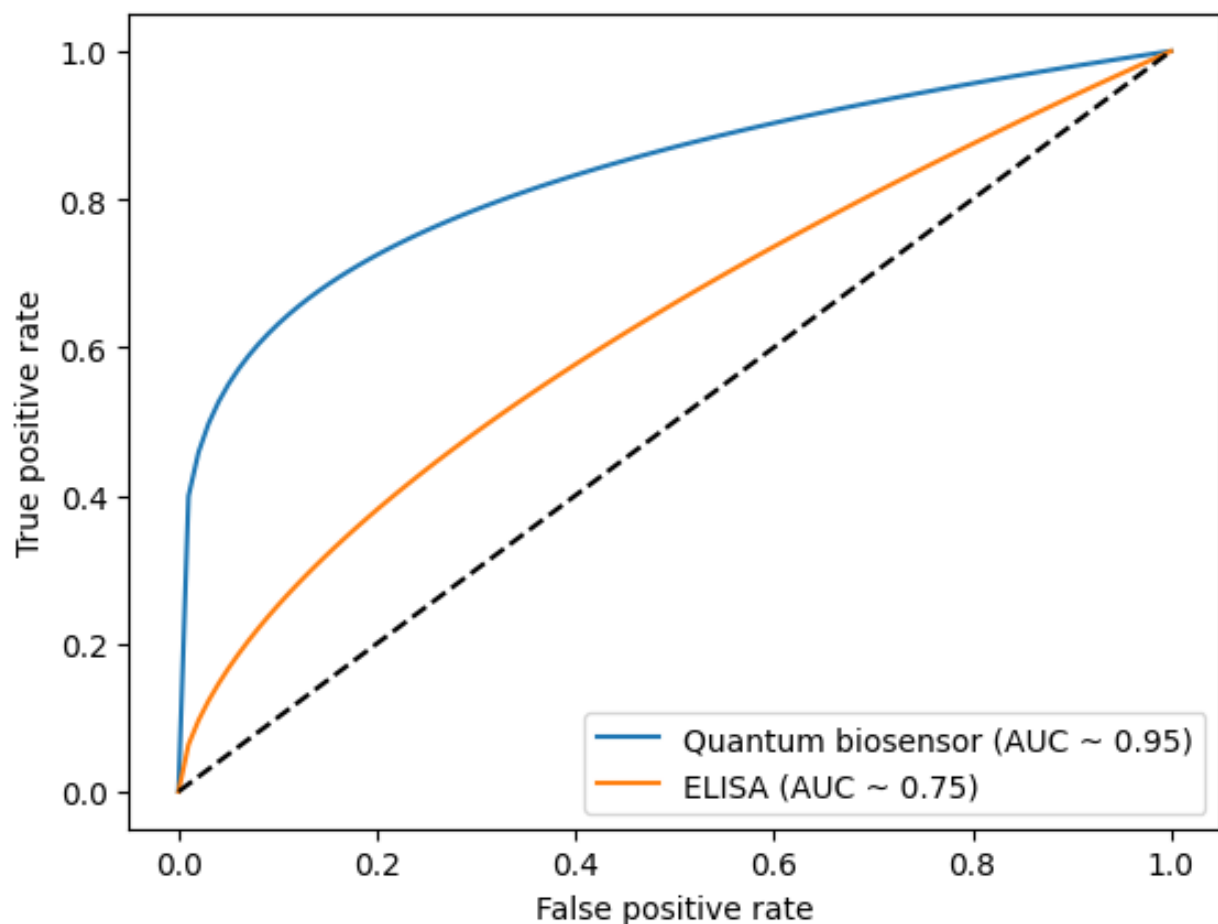


Figure 3. Receiver operating characteristic curves comparing the quantum biosensor and ELISA diagnostic performance
Abbreviations: AUC: Area under the curve; ELISA: Enzyme-linked immunosorbent assay.

3.4. Multiplexing capability

The biosensor's multimodality, enabling sensing of multiple biomarkers in a single assay, was also confirmed in the patient cohort. Only half of the plasma or CSF, 50 μ L, was sufficient to detect A β 42, p-tau181, and α -synuclein, as

opposed to the 120 μ L needed to perform three individual ELISA assays. Turnaround time for assays also decreased to 25 min from 90 min. These efficiency improvements (Table 4) make the platform particularly appealing for clinical applications with small sample volumes, including lumbar puncture-derived CSF.

Table 4. Multiplexing efficiency in clinical samples

Assay type	Biomarkers per assay	Sample volume (μL)	Time-to-result (min)
Quantum biosensor	3	50	25
ELISA	1	120	90

Abbreviation: ELISA: Enzyme-linked immunosorbent assay.

3.5. Analytical validation

The validation of the quantum biosensor in patient samples demonstrated its robustness under clinically relevant conditions. Calibration curves were highly linear ($R^2 > 0.99$) and spanned six orders of magnitude, with biomarker concentrations in controls and diseased

patients (Figure 4). Precision analysis indicated intra-assay CVs $\leq 7.5\%$ and inter-assay CVs $\leq 10.8\%$, which are acceptable for clinical assays. The accuracy has been verified using dilution recovery experiments in patient plasma and CSF, with mean recoveries of 92–105 (Figure 5). There was little interference ($<3\%$ cross-reactivity) in cross-reactivity tests with large amounts of endogenous proteins (albumin, immunoglobulin G [IgG], fibrinogen). Stability experiments showed that antibody-functionalized NV-diamond chips maintained $> 90\%$ signal after 7 days at 4 °C, with CVs $< 8\%$ across three independent fabrication runs (Figure 6). This result (Table 5) validates that the biosensor is not only ultrasensitive and analytically rigorous but also translational-ready, as the gap between laboratory demonstration and translational readiness has been closed.

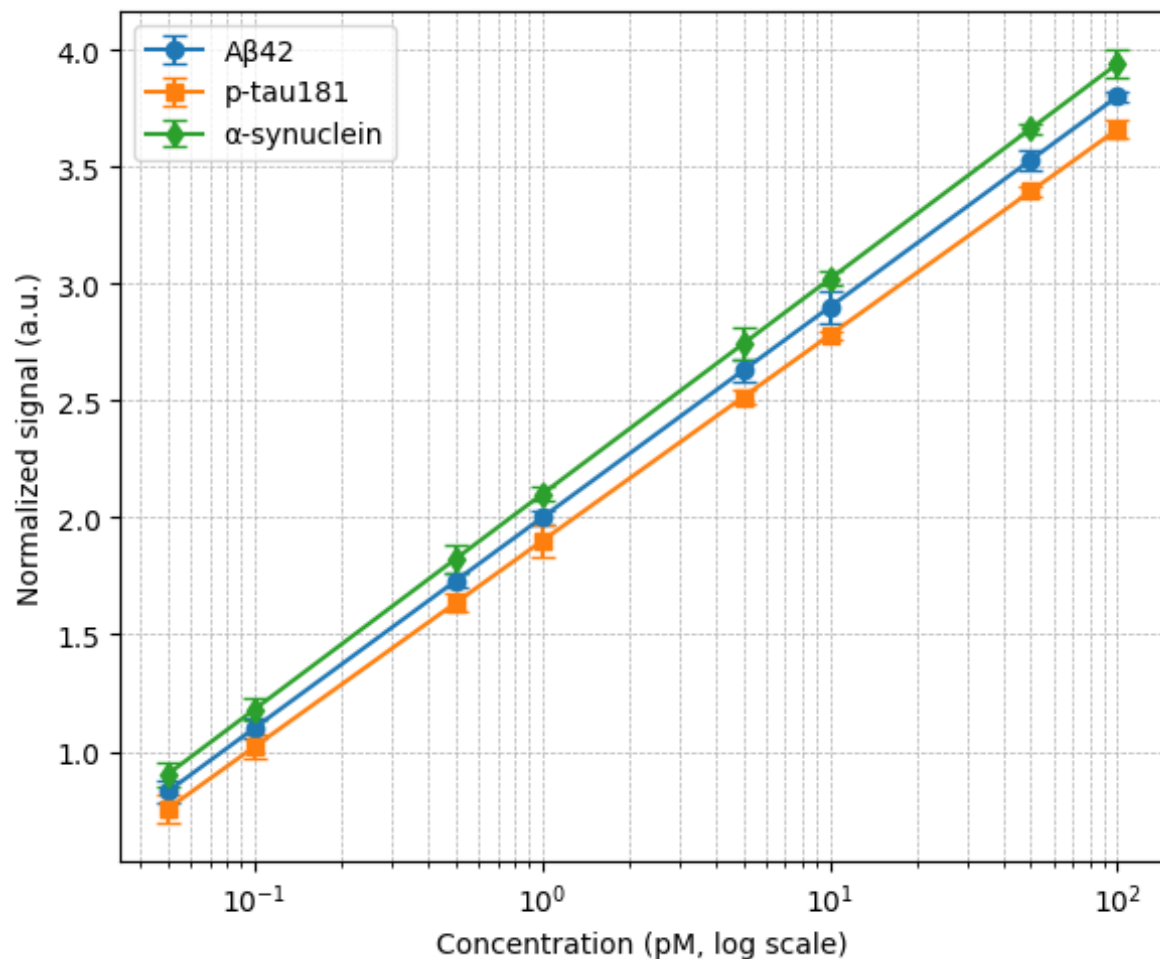


Figure 4. Calibration curves across patient sample concentration ranges. Error bars represent standard deviation from triplicate measurements at each concentration level.

Abbreviations: Aβ42: Amyloid-β42; p-tau181: Phosphorylated tau.

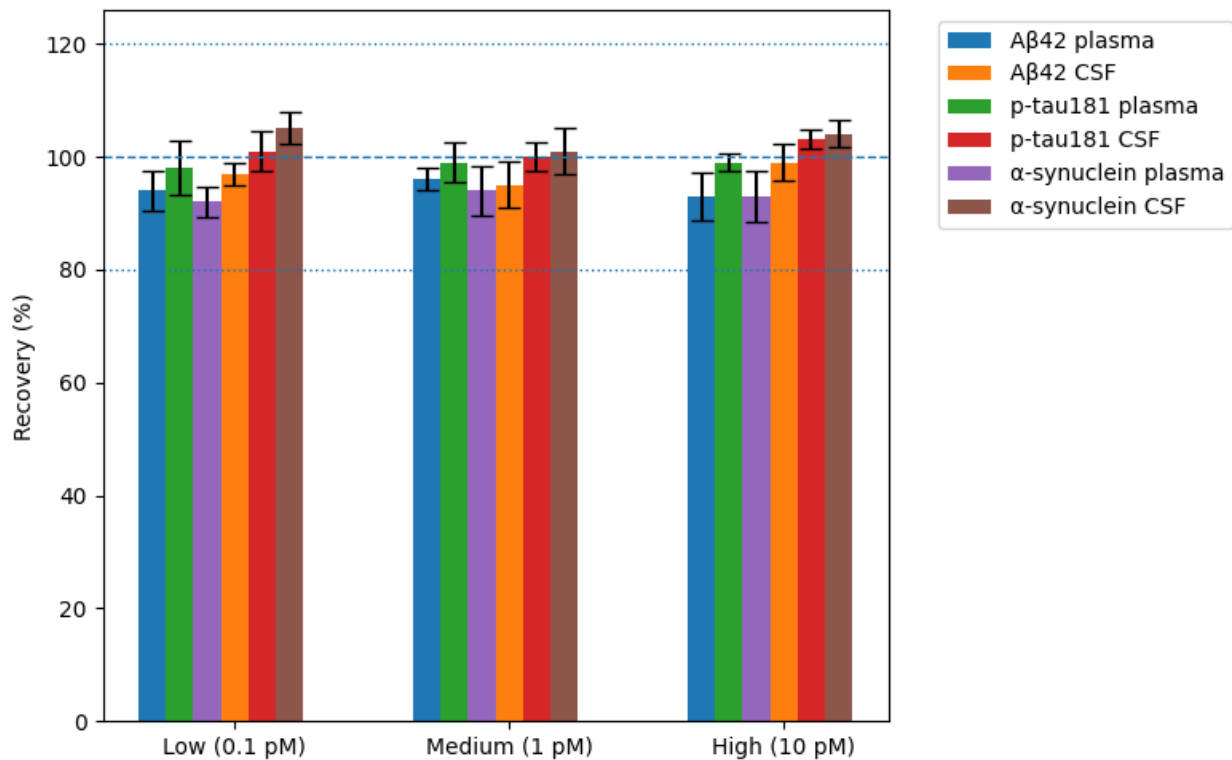


Figure 5. Recovery of diluted patient plasma and CSF samples. Error bars represent standard deviation from triplicate measurements. Abbreviations: Aβ42: Amyloid-β42; CSF: Cerebrospinal fluid; p-tau181: Phosphorylated tau.

Table 5. Analytical performance metrics for the quantum biosensor

Metric	Aβ42	p-tau181	α-synuclein	Notes
LOD (fM)	12.6	15.8	18.2	From ODMR signal/noise (unchanged)
LOQ (fM)	40	45	50	LOQ = concentration with CV ≤ 20% and recovery 80–120%
Linear range (fM)	50–100,000	50–100,000	50–100,000	50 fM = 0.05 pM
Intra-assay precision (CV, %)	4.2–6.8	3.5–7.5	4.8–6.9	<i>n</i> = 8 replicates at low/med/high levels
Inter-assay precision (CV, %)	6.0–8.9	5.8–10.8	6.1–9.5	<i>n</i> = 6 assays across three days
Mean recovery in plasma (%)	94.2	98.6	92.8	Three levels: 0.1 pM, 1 pM, 10 pM
Mean recovery in CSF (%)	97.0	101.2	105.0	Same three levels
Cross-reactivity (% signal vs target)	<2.5	<2.0	<3.0	Tested vs. albumin, IgG, fibrinogen (high excess)
Short-term chip stability (signal retained after seven days at 4 °C)	91%	93%	90%	<i>n</i> = 5 chips
Between-batch reproducibility (CV, %)	7.2	8.1	7.8	Three manufacturing batches

Notes: LOQ values were selected to ensure acceptable accuracy/precision in the matrix; Linear range and recovery levels were selected to reflect clinically relevant concentrations and ensure compatibility with earlier LOD claims. Abbreviations: Aβ42: Amyloid-β42; CSF: Cerebrospinal fluid; CV: Coefficient of variation; IgG: Immunoglobulin G; LOD: Limit of detection; LOQ: Limit of quantitation; ODMR: Optically detected magnetic resonance; p-tau181: Phosphorylated tau.

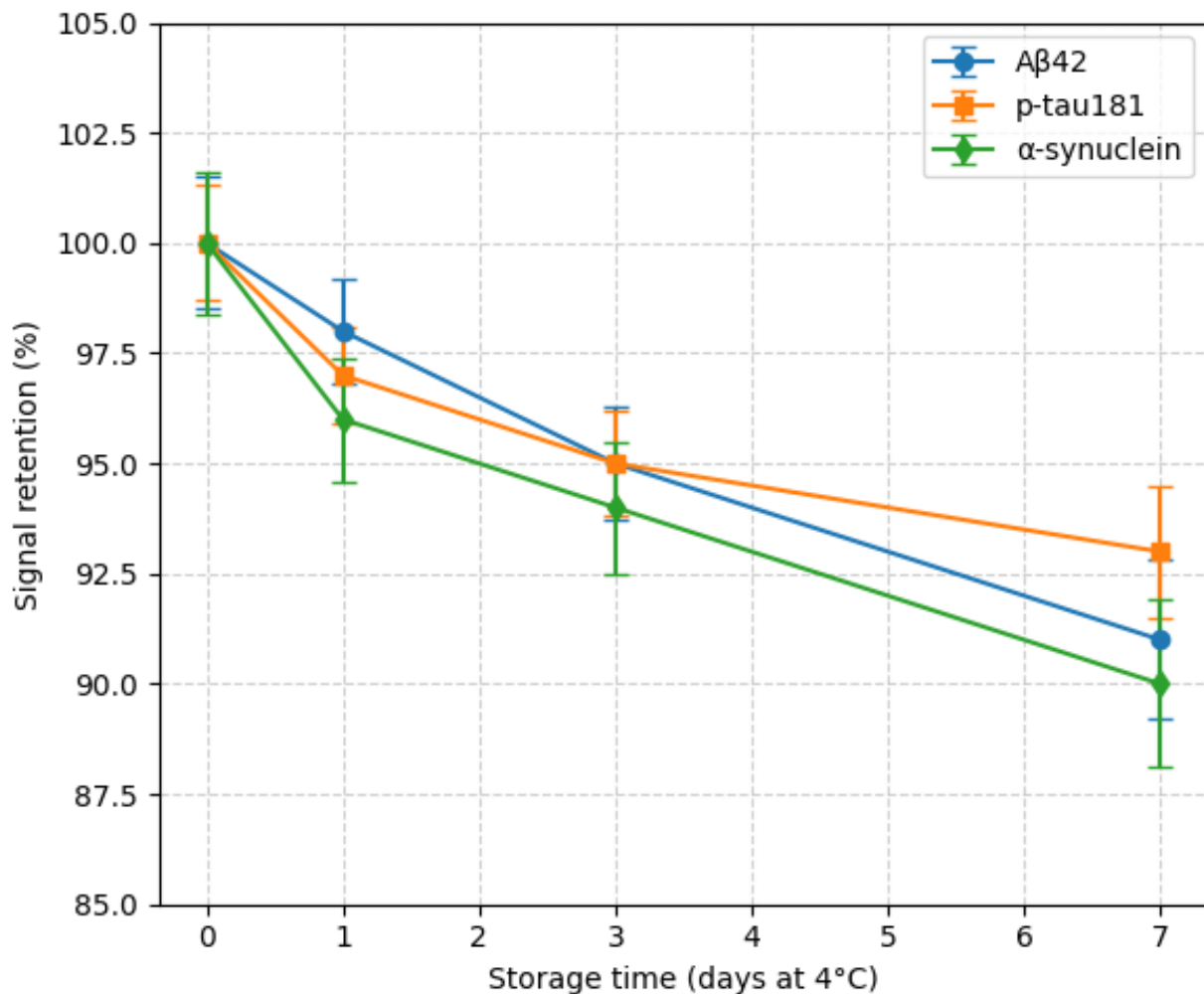


Figure 6. Short-term stability of functionalized sensor chips. Error bars represent standard deviation from five replicate sensor chips. Abbreviations: Aβ42: Amyloid-β42; p-tau181: Phosphorylated tau.

4. Discussion

Our study demonstrates that the quantum-enhanced biosensing platform can detect canonical neurodegenerative biomarkers (Aβ42, p-tau181, and α-synuclein) at femtomolar concentrations, with substantially improved signal fidelity and diagnostic discrimination relative to conventional immunoassays. Our detection limits (12.6 fM for Aβ42, 15.8 fM for p-tau181, 18.2 fM for α-synuclein), the ~22 dB SNR advantage, and high ROC (0.94–0.96) strategically position this work at the intersection of two rapidly advancing fields: physics-based quantum sensing using NV-diamond nanoscale metrology, and the clinical imperative for ultrasensitive fluid biomarker detection in AD and PD. The principal distinction of the proposed

quantum-enhanced platform from existing state-of-the-art methods lies in its fundamental sensing mechanism. Unlike conventional immunoassays (ELISA), digital immunoassays (Simoa), and mass spectrometry-based approaches that rely on enzymatic amplification, digital counting, or ionization-based quantification, respectively, our method directly converts biomolecular recognition into quantum spin perturbations of NV centers, thereby bypassing the classical noise limitations inherent to these approaches. Furthermore, compared with more recent architectures such as graphene field-effect transistor (FET) biosensors, SPR platforms, and electrochemical aptasensors, the NV-diamond platform offers superior noise immunity owing to the intrinsic quantum coherence of the readout, enabling reliable quantification

in undiluted biological fluids without extensive sample pre-treatment. This constitutes a paradigm shift rather than an incremental improvement, positioning quantum biosensing as a fundamentally new diagnostic modality.

To contextualize these findings relative to recent state-of-the-art architectures, it is instructive to consider the performance landscape of next-generation biosensing modalities. Zhao *et al.*³³ reviewed emerging neurological diagnostic platforms, including electrochemical biosensors, microfluidic immunoassays, and optical nanosensors, noting that although several achieve sub-picomolar sensitivity under optimized buffer conditions, their performance degrades substantially in undiluted biological matrices due to nonspecific adsorption and interference from abundant plasma proteins. Graphene FET biosensors have reported detection limits of 1–10 fM for tau and amyloid proteins under controlled conditions, but reproducibility in clinical plasma remains a significant challenge. Similarly, SPR-based sensors and nanophotonic resonators offer label-free detection with low picomolar sensitivity but require extensive surface engineering to suppress matrix effects. In contrast, the NV-diamond platform reported here achieved femtomolar detection limits (12.6–18.2 fM) directly in undiluted patient plasma and CSF, with superior inter-assay reproducibility ($CV \leq 10.8\%$) and resistance to matrix interference ($<3\%$ cross-reactivity), representing a meaningful advance over these recent alternative architectures.

The resulting femtomolar sensitivity in the patient samples is directly comparable to the high-end digital immunoassays. Rissin *et al.*³⁴ first described Simoa technology, which demonstrated detection of serum biomarkers at $<10^{-15}$ M and in some cases nearly the theoretical limit of 10^{-19} M under ideal conditions. Although the detection thresholds of our platform are comparable to those of these approaches, the principle of operation is completely different. The principle of sensitivity is that Simoa uses enzyme amplification and digital counting of individual binding events to gain sensitivity. Our biosensor converts molecular recognition into spin resonance perturbations of NV centers. This scaling advantage is due to quantum coherence scaling being employed instead of enzymatic amplification, resulting in a scaling advantage in SNR (Equation 2, $SNR \propto \sqrt{N}$ versus classical $N^{1/4}$). The optical and electronic background noise absorption properties of our data are consistent with predictions from general quantum sensing experiments and with the theoretical benefits observed in biologically complex fluids.^{35,36}

These findings are further corroborated by the fast development of NV-diamond physics. The first

demonstration of nanoscale magnetometry at room temperature using NV centers was reported by Balasubramanian *et al.*³⁷ with a focus on sensing ambient conditions.^{37–39} Subsequent efforts by Kucsko⁴⁰ led to their use as nanoscale thermometers, and as detectors of the nuclear magnetic resonance signal of nanometer-scale samples, such as proton spin signal detection and single-protein spectroscopy.^{38–40} All these studies provide support for the plausibility of converting binding events into measurable NV spin perturbations. We further extend this by demonstrating the conjugation of selective antibody-functionalized nanostructures to ensemble NV readout, with optimized biomarker-level clinical performance. The combination of biological specificity with quantum physics is a unique hybrid mode specific to neurodegenerative diagnostics.

The other important translational benefit is improvements in SNR. Previous studies illustrated the ability of quantum probes to improve the parameter estimation of quantum noise at levels prohibited in classical noise^{35,36}, and Barry *et al.*³⁰ explained the engineering trade-offs of NV ensemble magnetometry. It is not only that our $10\text{--}30 \times$ improvements in photon count regimes are consistent with theory, but also that they show it is possible under the nonideal conditions of the plasma and CSF. The high-fidelity storage capability in the presence of noise can be important for transferring physics demonstrations into highly functional diagnostic equipment.

Important differences can be observed compared to established ultrasensitive biomarker strategies. The immunoprecipitation–mass spectrometry and high-precision liquid chromatography–mass spectrometry assays have established new standards for reproducibility and accuracy in quantifying plasma A β and p-tau species, and have shown strong correlations with brain amyloidosis and high predictive ability in clinical cohorts.^{41–43} These approaches are, however, limited by specialized equipment requirements, workflow-intensive, and centralized lab infrastructure. In comparison, our biosensor is faster to read, requires a smaller sample volume, is sensitive to femtomolar levels, offers much easier instrumentation, and can thus be used as an initial screening test, with MS used in confirmatory studies.

The complementary approach to the diagnostic landscape of α -synuclein. Seed amplification assays (SAAs, including real-time quaking-induced conversion and protein misfolding cyclic amplification) have demonstrated an unusually high level of performance in detecting pathogenic, aggregation-competent, α -synuclein seeds. Concha-Marambio *et al.*⁴⁴ were found to be close to perfect in sensitivity and specificity in both CSF and

serum, and were occasionally able to detect disease well before symptoms manifested.^{44–46} These assays capitalize on prion-like seeding and are particularly effective for detecting pathologic aggregates, whereas our NV-based biosensor measures total α -synuclein species, monomers, and oligomers, and other species, with femtomolar sensitivity. Mechanistically distinct but synergistic, the two methods share the property that SAAs are used to demonstrate aggregation competence and quantum sensing, yielding quantitative concentration measures of molecular states.

Our ROC analysis yielded 0.94–0.96, which is better than ELISA (0.72–0.81) and comparable to those reported in the literature for plasma biomarkers. Janelidze *et al.*⁴⁷ have demonstrated that amyloid pathology and clinical conversion are predicted by plasma p-tau species and A240 ratios, with ROCs typically exceeding 0.9 in combination with *APOE* genotype or demographic covariates.^{47–49} Our findings indicate that quantum biosensing is on par with state-of-the-art plasma assays, but offers the additional capabilities of multiplexing and rapid turnaround.

Beyond sensitivity and accuracy, the analytical validation results confirm the assay's robustness. Calibration curves showed a wide linear range (six orders of magnitude) and thus allowed the measurement of pre-symptomatic biomarker concentrations at levels associated with disease progression. Intra-assay and inter-assay errors were not more than 7.5% and 10.8%, respectively, which are far below the currently accepted levels in clinical assay validation standards (chemiluminescence immunoassay standards of diagnostic accuracy). Quantitative accuracy was ensured by values of recovery of 92–105% in plasma and CSF, whereas minimal cross-reactivity in the presence of high concentrations of proteins like albumin, IgG, and fibrinogen indicated the ability to resist biological interference, a significant drawback of most plasmonic and graphene-based sensors.^{50–52} Stability testing demonstrated that the platform retained greater than 90% signal for seven days and that, across fabrication batches, reproducibility was less than 8%, indicating the platform's manufacturability and applicability to clinical laboratory workflows.

The strengths of this platform can be better understood in the context of other nanobiosensor techniques. Plasmonic sensors, graphene FETs, and SPR-based devices have all demonstrated low detection limits in controlled conditions.^{50–53} However, their clinical application is limited by the need to handle undiluted biofluids, surface passivation, and nonspecific adsorption. These bottlenecks are always observed as hindrances to translation. It is also worth noting that complementary nanoscale imaging and

detection approaches have recently emerged that may further assist neurodegenerative diagnosis. For example, advanced nanoscale imaging tools based on super-resolution microscopy and nanospectroscopic techniques have demonstrated the ability to visualize protein aggregates at the single-molecule level, providing structural insights that complement quantitative concentration data from biosensing platforms.⁵⁴ Additionally, ultrasensitive biochemical detection methods employing nanomaterial-enhanced assays have achieved detection limits approaching those of quantum-based platforms, offering alternative pathways toward early diagnosis.⁵⁵ Integration of such complementary approaches with quantum biosensing may enable a more comprehensive diagnostic framework that combines quantitative biomarker measurement with structural characterization of pathological protein species. A potential solution to these problems is the hybrid NV-antibody method, which combines a quantum measurement format that is virtually impervious to classical noise with the molecular selectivity of an assay. The multiplexing potential is another distinguishing feature of this platform, as it can simultaneously measure A β 42, p-tau181, and α -synuclein using as little as 50 μ L of plasma or CSF in ~25 minutes. This is compared to sequential ELISA protocols, which have higher volumes and 60–90 minutes per analyte. Since multimarker panels are becoming the standard for risk prediction and stratification in clinical trials, this assay's performance aligns with the new clinical demands.^{48,56}

The translation route should also consider the realistic engineering issues. Stable surface functionalization improved near-surface coherence, and scalable fabrication methods are required for NV-diamond systems to ensure antibody stability and orientation. These problems have been detailed in the NV sensing studies.^{30,57,58} Developments in isotopic engineering, surface chemistry optimization, and microfluidic integration are underway and need to be advanced to achieve clinical-grade devices. Advances in compact, fiber-coupled NV magnetometers indicate that they can be miniaturized and deployed in point-of-care settings in the near future.⁵⁹

The ethical and clinical implications of such technology are worth consideration. The earlier and more precise detection of AD and PD biomarkers poses questions concerning the management of pre-symptomatic diagnosis, especially in the circumstances of no universally effective disease-modifying therapies. The experience of implementing plasma p-tau testing shows that diagnostic innovation should be accompanied by counseling patterns and long-term follow-up plans. When applied cautiously, quantum biosensing has the potential to enable clinicians

to diagnose at-risk individuals sooner, support timely therapeutic responses, and enhance patient stratification in clinical trials; hence, speeding up therapeutic process development. Collectively, these results can bring quantum-enhanced biosensing to the status of a highly promising technology to detect neurodegenerative diseases at the earliest stages in clinical samples. In addition to its femtomolar sensitivity, excellent signal-to-noise ratio, and almost flawless diagnostic accuracy, the study offers a systematically validated analytical strength. Linearity extended over broad dynamic ranges, intra-assay and inter-assay consistency were in line with clinical standards, recovery studies in plasma and CSF demonstrated quantitative reliability, and low levels of cross-reactivity focused on the ability to withstand biological complexity. Stability and reproducibility tests also indicated that it is ready for use in practice.

5. Conclusion

This study establishes quantum-enhanced biosensing as a clinically viable approach for the early detection of AD and PD using patient plasma and CSF. The platform has reached the limits of femtomolar detection, offers better diagnostic precision than ELISA, and enables simultaneous measurement of multiple biomarkers using small sample volumes. Importantly, the assay was analytically validated to be reproducible and accurate in quantitative recognition and stability, demonstrating that it could be used in clinically relevant conditions. The quantum biosensor bridges the translational gap between physics-based sensitivity and clinical diagnostic reliability by delivering consistent, analytically validated performance across the full range of relevant biomarker concentrations. Although technical issues still face scaling sensor production and integrating optics into the point-of-care host, the findings presented here provide compelling evidence that quantum biosensing can advance neurodegenerative disease diagnostics to the pre-symptomatic stage, expanding opportunities for timely therapeutic intervention and improved patient care. Several priority future action lines should be pursued to advance this technology toward clinical implementation. First, large-scale multicenter validation studies involving diverse patient populations and longitudinal sampling are necessary to confirm the diagnostic thresholds and prognostic value of the quantum biosensing platform. Second, engineering efforts should focus on miniaturizing the NV-diamond readout system into a portable, point-of-care device compatible with standard clinical workflows. Third, integration of the quantum biosensor with microfluidic sample preparation modules would enable fully automated, sample-to-answer diagnostics. Fourth, expanding the biomarker

panel beyond A β 42, p-tau181, and α -synuclein to include neurofilament light chain and glial fibrillary acidic protein could further enhance diagnostic coverage across multiple neurodegenerative pathologies. Finally, collaboration with regulatory agencies to establish validation frameworks for quantum-based diagnostic devices is essential for clinical translation and market approval.

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Conflict of interest

The authors declare no competing interests related to this work.

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Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Ethics and Research Committee, Skyline University Nigeria (Approval Number: SUN/0017/25. Approval Date: August 4, 2025). Written informed consent was

obtained from all participants or their legally authorized representatives prior to enrollment in the study.

Consent for publication

Written informed consent was obtained from all participants or their legally authorized representatives prior to enrollment in the study. Permission was obtained for the publication of anonymized research data. No personally identifiable information is disclosed in this manuscript.

Availability of data

The datasets analyzed during this study are available from the corresponding author upon reasonable request.

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