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Applications of Brain-Computer Interfaces in Neurodegenerative Diseases

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Abstract: Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) are three highly prevalent, severely disabling neurodegenerative disorders. They share core pathological hallmarks: progressive degeneration and apoptosis of central neurons, persistent disconnection of intracerebral neural networks, which gradually impair memory, motor function, language, emotion and other core neurological functions. Conventional clinical treatments have notable limitations. Pharmacotherapy can only delay pathological deterioration temporarily and fails to repair damaged neural circuits, accompanied by adverse reactions such as drowsiness, dyskinesia and gastrointestinal injury after long-term administration. Traditional rehabilitation training heavily relies on patients' active limb movements, making it nearly ineffective for patients with advanced complete disability. Conventional open-loop constant deep brain stimulation (DBS) cannot dynamically adjust stimulation parameters according to real-time brain activity, resulting in insufficient regulatory precision. A brain-computer interface (BCI) establishes a bidirectional information pathway between the brain and external devices independent of muscles and peripheral nerves. By decoding neural signals and delivering multimodal feedback stimuli to form closed-loop neuromodulation, BCIs simultaneously achieve neural repair and functional compensation relying on neural plasticity. This paper stratifies five major BCI systems including EEG, fNIRS, MEG, ECoG and implantable microelectrode arrays by invasion degree. Combined with meta-analyses, multicenter randomized controlled trials (RCTs) and professional expert consensus published in the past five years, we systematically elaborate intervention protocols, clinical efficacy and intrinsic neural mechanisms of various BCIs for AD cognitive impairment, PD motor dysfunction and ALS locked-in syndrome. From hardware performance, clinical standardization, evidence-based research and data ethics four dimensions, we analyze the bottlenecks hindering clinical translation. Prospective directions including multimodal fusion, minimally invasive implantation, home-based adaptive intelligent BCIs and standardized diagnosis-treatment systems are proposed, providing evidence-based references for clinical intervention in neurology and rehabilitation, as well as related engineering and basic neuroscience research.

Keywords: Brain-computer interface; Neurodegenerative diseases; Alzheimer's disease; Parkinson's disease; Amyotrophic lateral sclerosis; Neural plasticity; Closed-loop neuromodulation

1. Introduction

Global population aging has continuously driven the rising incidence of neurodegenerative diseases. Epidemiological statistics indicate that the prevalence of Alzheimer's disease among Chinese adults aged over 60 exceeds 6%, and the incidence of Parkinson's disease reaches approximately 1.7% in individuals older than 65 years [1]. The annual incidence of amyotrophic lateral sclerosis is 1.5 per 100,000 population, with a trend of younger onset. These diseases are irreversible and progressive. In the late stage, patients lose self-care and communication abilities entirely, imposing enormous economic and psychological burdens on families while consuming massive public medical resources. Although AD [2], PD [3] and ALS [4] target distinct pathological regions, they share three universal pathological alterations: sustained neuronal loss, disrupted intracerebral excitatory-inhibitory balance and impaired synaptic plasticity. Conventional interventions cannot simultaneously address three therapeutic goals: delaying neuronal degeneration, reconstructing neural circuits and compensating lost functions [5].

For pharmacotherapy, cholinesterase inhibitors and memantine only mildly slow cognitive decline in AD patients and cannot reverse hippocampal atrophy. Levodopa-based anti-Parkinson drugs have a limited "honeymoon period", and long-term use induces motor fluctuations and dyskinesia. No disease-modifying targeted drugs are available for ALS; riluzole merely extends survival time slightly without halting motor function loss. Traditional rehabilitation training is premised on preserved limb muscle strength and voluntary motor control, which is impossible for patients with advanced ALS, severe PD and end-stage AD. Conventional constant-frequency open-loop DBS continuously suppresses basal ganglia discharge without real-time feedback, easily over inhibiting intact motor cortices and causing speech and cognitive side effects [6].

Brain-computer interface (BCI) is an interdisciplinary frontier integrating neuroscience, rehabilitation medicine and biomedical engineering. It bypasses peripheral nerves and skeletal muscles, directly reads neural electrical, hemodynamic and magnetic signals related to motor and cognitive activities, and delivers visual, auditory, tactile and electrical feedback to the brain, constructing a closed-loop regulatory framework of "brain intent recognition – external device execution – neural feedback adjustment" [7]. BCIs are categorized into non-invasive, semi-invasive and fully invasive types based on surgical trauma, matching patients with mild, moderate and severe functional impairment at different disease stages. Domestic expert consensus on non-invasive BCI rehabilitation (2026) and numerous international meta-analyses over the past five years have validated that closed-loop BCI training actively induces long-term potentiation (LTP) and long-term depression (LTD), remodels broken neural networks, and acts as a vital supplementary therapy to conventional drugs and rehabilitation [8, 9].

This paper integrates 32 authoritative Chinese and English literatures, systematically dissects the principles, advantages, disadvantages and applicable populations of diverse BCI modalities, elaborates stratified clinical protocols and quantitative therapeutic effects for each disease, deeply analyzes translational obstacles, and proposes comprehensive prospects for device development and clinical standardization, offering systematic references for clinical practice and basic experimental research [10].

2. Classification, Principles and Applicable Populations of Complete BCI Systems

BCIs are divided into three major categories according to intracranial implantation invasiveness, with multiple signal acquisition modalities under each type featuring unique signal characteristics,

equipment costs and clinical application boundaries.

2.1 Non-invasive Brain-Computer Interfaces (Mainstream for Clinical Popularization)

No surgical operation is required; sensors only attach to the scalp without intracranial hemorrhage or infection risks, supporting long-term home and community rehabilitation. Three mainstream acquisition modalities are widely adopted:

2.1.1 EEG-Based BCI

Core Mechanism: Synchronized neuronal firing generates subtle scalp potentials. Electrodes capture mu (8–12 Hz), beta (13–30 Hz), theta (4–7 Hz) and gamma (>30 Hz) rhythms. Algorithms decode variations associated with motor imagery, attention and visual evoked potentials to generate device control commands. Major Clinical Paradigms

(1) Motor Imagery (MI): Patients imagine hand or lower-limb grasping/stepping to elicit cortical event-related desynchronization/synchronization (ERD/ERS), primarily for motor rehabilitation;

(2) P300 Speller: Character flickering evokes a positive 300-millisecond cortical potential to realize text input for communication-disabled patients;

(3) Steady-State Visual Evoked Potential (SSVEP): Periodic light stimuli produce stable brain responses with faster decoding speed than P300;

(4) Neurofeedback Training: Real-time visualization of brain oscillations guides patients to voluntarily modulate theta-gamma coupling and alpha power for cognitive and emotional intervention. Advantages: Lightweight wireless dry-electrode headbands with low cost and sampling rate $\geqslant$250 Hz, easy to deploy in primary hospitals and households. Limitations: Signals are attenuated by skull and scalp tissues, leading to low signal-to-noise ratio (SNR); eye blinks, mastication and head motion introduce massive electromyographic/ocular artifacts; decoding accuracy for lower limbs and deep brain regions only ranges 55%–70%. Approximately 20% of patients are "BCI illiterates" who cannot generate identifiable brain signals. Applicable Populations: Mild AD, early-stage PD, mild ALS and patients with mild cognitive impairment (MCI).

2.1.2 fNIRS-Based BCI (Functional Near-Infrared Spectroscopy)

Core Mechanism: Near-infrared light penetrates scalp and skull to detect cortical oxyhemoglobin (HbO) and deoxyhemoglobin fluctuations. Increased regional cerebral blood flow upon neuronal activation elevates HbO levels to form detectable hemodynamic signals. Advantages: Highly resistant to ocular and myogenic artifacts with superior spatial resolution for targeting prefrontal and motor cortices; zero electromagnetic radiation with excellent long-term safety. Drawbacks: Hemodynamic lag of 2–5 seconds disables high-speed real-time control; poor temporal resolution fails to capture millisecond-scale neural oscillations; bulkier hardware than simple EEG headsets. Application Scenarios: AD memory training, PD gait rehabilitation and pediatric neurodevelopmental intervention.

2.1.3 Wearable OPM-MEG (Optically Pumped Magnetoencephalography)

Traditional SQUID-MEG demands cryogenic helium shielding rooms with tens of millions of dollars in construction costs and limited laboratory use. New-generation OPM magnetometers operate at room temperature with scalp-fitted sensors capturing neuronal magnetic fields. Advantages: Magnetic signals barely attenuated by skull tissue, delivering simultaneous high spatial

and temporal resolution to distinguish superficial and hippocampal deep-layer activity for cognitive mechanistic research. Shortcomings: Expensive hardware requiring magnetic shielding, susceptible to ambient electromagnetic interference, unsuitable for home rehabilitation. Applications: Basic research on AD hippocampal memory circuits and PD basal ganglia mechanisms, not yet deployed for routine clinical rehabilitation.

2.2 Semi-invasive ECoG-Based BCI (Electrocorticography)

Surgical Modality: Minimally invasive craniotomy; flexible thin-film electrode arrays are attached to the dura mater without penetrating brain parenchyma to record cortical potentials. Core Advantages: Avoid scalp signal attenuation with drastically reduced motion/ocular artifacts; much faster decoding and text output speed than EEG; lower surgical risk than fully invasive implants. Limitations: Still requires neurosurgical craniotomy with minor intracranial hemorrhage and anesthesia risks; cerebrospinal fluid encapsulation gradually attenuates signals over long-term implantation. Applicable Populations: Moderate-to-late ALS patients with unstable scalp EEG signals and drug-refractory moderate-severe Parkinson's disease patients.

2.3 Fully Invasive Microelectrode Array BCI

Representative Systems: BrainGate, domestic Beina No.1, Neuralink. Micrometer-scale multi-channel microelectrodes are surgically implanted into motor and language cortices to record single-unit neuronal spikes. Core Advantages: Single-cell signal resolution enables fine finger movement and speech decoding, supporting multi-degree-of-freedom prosthetic manipulation and real-time voice synthesis — the only viable modality for end-stage locked-in patients to conduct complex communication. Critical Drawbacks: Craniotomy carries intracranial hemorrhage, infection and epilepsy risks; chronic implantation triggers glial scarring that attenuates signals within 6–24 months; built-in batteries require secondary craniotomy for replacement with extremely high overall implantation and maintenance costs. Applications: Clinical trials exclusively for end-stage locked-in ALS patients, no routine clinical promotion available.

3. Stratified Clinical Applications of BCIs in Three Neurodegenerative Diseases

3.1 Cognitive and Emotional Rehabilitation for Alzheimer's Disease

AD's core pathological features include massive hippocampal neuronal loss, overactivated default mode network (DMN) and decoupled theta-gamma oscillations. Clinical manifestations are divided into MCI, moderate AD and severe AD, with distinct BCI intervention protocols and therapeutic effects across stages.

3.1.1 Mild Cognitive Impairment / Early AD (MMSE ≥ 20)

Patients retain intact attention and memory regulation capacity; EEG/fNIRS neurofeedback BCI serves as the first-line intervention targeting hippocampal theta-gamma coupling repair. Standardized Intervention Protocol: 8–16-channel electrodes covering prefrontal and parietal cortices; training paradigms include n-back working memory, virtual reality scene memory and facial recognition. Single session: 20–30 min, 3–5 sessions weekly, full intervention cycle ≥4 weeks with total training duration ≥300 min. Real-time feedback of theta and gamma spectral power guides patients to upregulate gamma oscillations and suppress abnormal low-frequency theta waves to normalize overactive DMN. Evidence-Based Outcomes: Meta-analysis integrating 11 RCTs revealed

significant improvements in MoCA and MMSE scores (weighted mean difference MD=2.12, 95%CI [1.03, 3.21], P<0.001). Working and short-term memory, executive function were enhanced, while apathy, irritability and nocturnal agitation incidence dropped by 35%. Underlying Neural Mechanisms: Sustained closed-loop feedback facilitates hippocampal LTP, strengthens hippocampal-prefrontal functional connectivity, suppresses DMN overactive self-referential processing and reduces neuroinflammatory factors to slow neuronal degeneration. It also elevates prefrontal dopamine and serotonin levels to relieve comorbid depression and anxiety.

3.1.2 Moderate AD (MMSE 10–19)

Patients lose capacity for voluntary brain wave modulation; passive multimodal stimulation BCI is adopted instead. Auditory and tactile Oddball stimuli evoke event-related potentials (ERP) without active mental imagery. Intervention Scheme: Dual-channel audio-tactile stimulation with real-time P300 detection and audio-visual positive feedback; training difficulty is gradually downgraded, single session shortened to 15–20 min to avoid fatigue and agitation. Clinical Value: Objectively assess residual cognitive capacity to compensate subjective bias of clinical scales, improve circadian rhythm disorders and reduce nocturnal wandering; however, long-term memory improvement is limited, only used as palliative adjuvant therapy.

3.1.3 Severe AD (MMSE < 10)

Patients exhibit fragmented consciousness and cannot cooperate with training; active BCI paradigms yield negligible effects, only applicable for residual consciousness evaluation. Invasive BCIs lack human clinical data and remain limited to AD animal memory research, far from clinical translation.

3.1.4 Auxiliary Early Screening Value

Resting-state EEG combined with machine learning extracts theta/gamma ratio and prefrontal connectivity features to differentiate healthy elderly, MCI and early AD with over 83% classification accuracy, enabling cognitive decline warning 2–3 years earlier than traditional scales to capture optimal intervention windows.

3.2 Motor and Cognitive Intervention for Parkinson's Disease

PD arises from midbrain dopaminergic neuron loss and disrupted basal ganglia circuits with pathologically elevated beta oscillations, manifesting as resting tremor, rigidity, bradykinesia and freezing of gait, frequently accompanied by mild cognitive impairment (PD-MCI). BCI applications fall into non-invasive motor rehabilitation and invasive closed-loop DBS two branches.

3.2.1 Non-invasive MI-BCI Combined Therapy for Early-to-Mid PD

Indicated for patients with intact drug efficacy without severe dyskinesia; mainstream combinations: motor imagery BCI + functional electrical stimulation (FES), BCI + lower-limb exoskeletons. Standardized Training Protocol: Record mu and beta rhythms at C3/C4/Cz central electrodes; patients imagine unilateral/bilateral hand lifting or foot dorsiflexion. Upon successful MI decoding, FES or exoskeleton delivers synchronized limb assistance. 30 min per session, 5 sessions weekly, full cycle $\geqslant$4 weeks with cumulative training $\geqslant$20 sessions. Meta-Analysis Results: Eight included RCTs demonstrated reduced UPDRS motor scores (MD=-6.34, P<0.0001), 47% decreased

freezing-of-gait episodes, and alleviated rigidity/tremor. The therapy corrects bilateral cortical overexcitation imbalance and suppresses contralateral hypercompensation. Neural Pathways: Synchronous activation of upper and lower motor neurons elevates motor evoked potential (MEP) amplitude and shortens central motor conduction time; multimodal feedback re-synchronizes cortical-basal ganglia circuits and reduces pathological beta power.

3.2.2 Closed-Loop BCI-DBS for Advanced Parkinson's Disease

Conventional constant-frequency DBS cannot distinguish physiological and pathological brain states and frequently induces dysarthria and dyskinesia. Closed-loop BCI-DBS monitors basal ganglia beta oscillations intracranially, automatically boosting stimulation upon abnormal beta elevation and lowering output as rhythms normalize. Clinical Trial Data: 84.21% motor symptom improvement rate and 60% reduction in dyskinesia adverse effects; oral levodopa dosage can be moderately tapered. This intervention receives Grade A high-strength clinical recommendation.

3.3 Intervention for PD Combined Mild Cognitive Impairment

Prefrontal alpha/theta neurofeedback BCIs regulate executive control networks to ameliorate attention and spatial memory deficits, enabling reduced donepezil dosage and alleviating somnolence and gastrointestinal side effects.

3.4 Stratified Communication Compensation for Amyotrophic Lateral Sclerosis

ALS causes progressive degeneration of upper and lower motor neurons, advancing to locked-in syndrome in late stages: full paralysis, limited eye movement and complete loss of verbal communication. BCIs are stratified by residual motor and ocular function to construct thought-based communication channels.

3.4.1 Early ALS (Preserved Limb Function)

Non-invasive P300/SSVEP speller serves as first-line therapy. Patients only gaze at screen characters to generate text output at 5–10 characters per minute; MI modules additionally control wheelchairs and household smart devices for daily self-care. Advantages: Fully non-invasive, long-term home usability without surgical risk; Grade B moderate evidence recommendation.

3.4.2 Moderate ALS (Severely Weakened Limbs, Unstable Scalp EEG)

ECoG semi-invasive BCIs are adopted for enhanced anti-artifact capacity, boosting text output speed to 30 characters per minute to support complete sentence communication and reduce communication latency.

3.4.3 End-Stage Locked-In Syndrome

Only fully invasive microelectrode arrays deliver viable intervention. Implants decode language and motor single-unit signals to synthesize natural speech and drive multi-joint prosthetics for drinking and feeding. A 2025 Nature clinical trial reported stable sentence generation at 80 words per minute. Nevertheless, critical drawbacks persist: craniotomy hemorrhage/infection risks, progressive glial scar signal attenuation within 1–2 years, and battery replacement requiring repeat craniotomy. This modality is restricted to specialized clinical trial centers without widespread clinical access.

4. Universal Neural Mechanisms of BCI Intervention in Neurodegenerative Diseases

Synthesizing animal experiments, fMRI and electrophysiological clinical data, four core shared mechanisms underpin BCI therapeutic effects:

(1) Induction of Synaptic Neuroplasticity Repetitive closed-loop "imagery-feedback" stimulation triggers LTP and LTD to repair degenerated cortical-spinal, hippocampal and basal ganglia synapses, boosting synaptic density and slowing neuronal apoptosis. For AD it remodels memory circuits; for PD it rebalances inhibitory basal ganglia pathways; for ALS it preserves residual motor neuron viability.

(2) Restoration of Interhemispheric Excitatory-Inhibitory Balance Neurodegenerative disorders feature pathological overactivation of contralateral cortex (PD) or DMN (AD). Targeted oscillatory modulation suppresses hyperactive regions and reactivates impaired cortices to restore synchronized bilateral neural activity and eliminate pathological oscillation output.

(3) Enhanced Corticospinal Conduction Efficiency Coordinated motor imagery and peripheral electrical stimulation co-activate upper/lower motor neurons, increasing MEP amplitude and shortening central motor conduction time to remediate impaired motor output pathways for rigidity and gait dysfunction.

(4) Limb-Independent Active Neural Training Paradigm Traditional rehabilitation requires voluntary limb movement, which is impossible for end-stage disabled patients. BCIs activate functional cortices purely via internal mental imagery, maximizing residual neuroplastic reserves without physical movement prerequisites.

5. Five Core Barriers to Clinical Translation

5.1 Intrinsic Hardware Limitations

Non-invasive BCIs suffer low SNR with poor decoding of lower-limb and deep hippocampal signals; head motion and sweat generate severe artifacts, and ~20% patients are "BCI illiterates" with no therapeutic response. Semi/fully invasive devices require craniotomy with hemorrhage/epilepsy hazards; chronic implantation induces glial scarring that attenuates signals within months to two years. High procurement and maintenance costs restrict deployment at primary and community rehabilitation institutions.

5.2 Absence of Standardized Clinical Protocols

Existing literatures adopt inconsistent training duration, frequency, electrode configurations and feedback paradigms. No stratified standardized guidelines for MCI/AD, early/mid/late PD and progressive ALS are established. Outcome evaluation lacks unified standards (scales vs electrophysiological biomarkers), hindering cross-study comparison. Clear stratification criteria for non/semi/invasive BCI eligibility remain undefined for clinicians.

5.3 Insufficient High-Quality Evidence Base

Most trials are single-center small-sample studies; large-scale multicenter RCTs are scarce. Long-term follow-up data ($\geqslant$1 year) are lacking to validate sustained therapeutic effects. High interstudy heterogeneity (I^2 >50 in many meta-analyses) downgrades most interventions to Grade C/D evidence, with only PD motor rehabilitation reaching Grade B.

5.4 Pronounced Interindividual Variability with No Pre-Screening Biomarkers

Age, disease duration, cerebral atrophy, scalp thickness and cerebral blood flow all alter EEG quality. Identical protocols yield divergent therapeutic responses across patients, and no baseline neural biomarkers exist to pre-screen responders for personalized treatment stratification.

5.5 Neuro-Privacy, Ethical and Regulatory Gaps

Brain signals contain subconscious memory and emotional information far more sensitive than routine physiological data, without dedicated medical data storage/de-identification regulations. Invasive implants carry risks of external malicious neural modulation. Domestic supervision fails to clearly demarcate therapeutic medical BCIs and consumer cognitive enhancement devices; standardized ethical review workflows for trials remain incomplete.

6. Multidimensional Future Development Directions

6.1 Multimodal Fusion BCI Hardware Innovation

Dual-modal EEG-fNIRS synchronous acquisition integrates high temporal resolution of electrical signals and high spatial resolution of hemodynamics to suppress motion artifacts and raise decoding accuracy. Lightweight, low-cost OPM-MEG will be gradually deployed for precise AD cognitive assessment.

6.2 Minimally Invasive Biocompatible Implant Technology

Intravascular stent BCIs deliver electrodes via endovascular catheters without craniotomy, representing next-generation minimally invasive solutions. Biodegradable flexible polymers reduce intracranial inflammation and glial scarring, extending implant service life and eliminating repeat battery replacement surgery.

6.3 Home-Based Adaptive Intelligent BCIs

Dry-electrode wireless all-in-one headbands replace conductive gel hardware. On-device local AI real-time decoding paired with cloud remote clinician parameter adjustment supports home tele-rehabilitation. Adaptive algorithms auto-modulate training difficulty and stimulus intensity based on real-time brain states for personalized therapy.

6.4 Stratified Standardized Clinical Guidelines

Develop tiered intervention specifications by disease stage and functional impairment, unifying electrode layouts, training schedules and combined scale-electrophysiology outcome metrics. Establish clear eligibility boundaries for non/semi/fully invasive BCIs to form universal neurology/rehabilitation clinical workflows and integrate BCI into routine rehabilitation care.

6.5 Expanding Evidence and Medical Insurance Coverage

Launch national multicenter long-term RCTs with 1–3 year follow-ups to upgrade evidence grades. Promote reimbursements for validated motor imagery BCI rehabilitation under rehabilitation medical insurance systems to reduce patient financial burden.

6.6 Refined Neurodata Security and Ethical Supervision

Release specialized regulatory documents distinguishing therapeutic medical BCIs and civilian cognitive enhancement devices. Formulate standardized brain signal de-identification, storage and

access protocols, and uniform human subject protection rules for clinical trials to prevent neural privacy leakage and unauthorized brain modulation risks.

7. Conclusion

No curative therapies currently exist for Alzheimer's, Parkinson's and amyotrophic lateral sclerosis, while conventional pharmacotherapy and rehabilitation carry inherent drawbacks. BCIs feature unique advantages of limb-independent closed-loop neuromodulation and targeted neuroplastic remodeling, delivering irreplaceable benefits for AD cognitive remediation, PD motor rehabilitation and ALS communication restoration. Non-invasive EEG/fNIRS BCIs are mature, safe and recommended as adjuvant therapy for mild-to-moderate neurodegenerative patients. Semi-invasive ECoG and fully invasive microelectrode arrays improve quality of life for moderate/end-stage critically ill patients, yet remain limited to clinical trials due to surgical risks, hardware instability and high costs.

At present, BCI clinical translation is hindered by hardware defects, lack of clinical standards, insufficient high-quality evidence, interindividual heterogeneity and incomplete ethical frameworks. In the future, integrated advances in multimodal signal fusion, minimally invasive electrodes, home intelligent devices and standardized clinical guidelines will enable BCIs to combine with drugs and conventional rehabilitation into full-cycle stratified comprehensive regimens for neurodegenerative diseases, delaying functional decline and improving patients' self-care and communication capacity, opening a novel therapeutic avenue amid global population aging.

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