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ADAPTIVE DEEP BRAIN STIMULATION FOR PARKINSON'S DISEASE: NEURAL BIOMARKERS, GAIT-SYNCHRONIZED CONTROL, AND PATIENT-SPECIFIC NETWORK NEUROMODULATION

Abstract

Background. Conventional deep brain stimulation provides continuous therapy for Parkinson's disease, but fixed stimulation cannot accommodate medication cycles, sleep–wake transitions, gait freezing, dyskinesia, or biomarker drift. Adaptive deep brain stimulation offers closed-loop neuromodulation by adjusting stimulation according to sensed neural or behavioral signals.

Materials and methods. A structured narrative review used randomized and nonrandomized trials, prospective cohorts, documents, neurophysiological studies, and investigations published through July 2026. Evidence was organized by biomarker validity, control architecture, programming feasibility, effectiveness, safety, energy efficiency, generalizability, and human-factor integration. A multicenter crossover study is proposed for adults with levodopa-responsive Parkinson's disease and motor fluctuations despite optimized conventional stimulation.

Results. Subthalamic beta amplitude and beta-burst duration remain the most mature control variables, whereas stimulation-entrained gamma activity, cortical signals, wearable-derived gait events, and multimodal decoders may better capture dyskinesia, freezing, and naturalistic behavior. Chronic studies suggest that personalized adaptive stimulation can improve residual motor symptoms and quality of life, while gait-synchronized and activity-dependent paradigms may address axial disability. Major limitations include sensing artifacts, unstable biomarkers, heterogeneous programming, small samples, insufficient blinding, and limited evidence regarding cognition, speech, falls, and device burden. The proposed primary endpoint combines blinded motor-state improvement with reduced troublesome dyskinesia and off time. Secondary endpoints include falls, gait freezing, speech, cognition, quality of life, stimulation energy, programming time, adverse events, calibration, and subgroup performance.

Conclusion. Adaptive deep brain stimulation is transitioning from experimental physiology to regulated clinical therapy. Its durable value will depend on biomarker personalization, transparent algorithms, standardized outcomes, and independent multicenter validation.

Keywords: Parkinson's disease, adaptive deep brain stimulation, closed-loop neuromodulation, beta oscillations, local field potentials, gait freezing, neural biomarkers, personalized neurostimulation.

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АДАПТИВНАЯ ГЛУБОКАЯ СТИМУЛЯЦИЯ ГОЛОВНОГО МОЗГА ПРИ БОЛЕЗНИ ПАРКИНСОНА: НЕЙРОННЫЕ БИОМАРКЕРЫ, СИНХРОНИЗИРОВАННОЕ С

ХОДЬБОЙ УПРАВЛЕНИЕ И ПЕРСОНАЛИЗИРОВАННАЯ СЕТЕВАЯ НЕЙРОМОДУЛЯЦИЯ

Аннотация

Актуальность. Традиционная глубокая стимуляция головного мозга обеспечивает непрерывное лечение болезни Паркинсона, однако фиксированные параметры не учитывают лекарственные циклы, переходы сна и бодрствования, замирание ходьбы, дискинезию и дрейф биомаркеров. Адаптивная глубокая стимуляция реализует замкнутую нейромодуляцию, изменяя воздействие по регистрируемым нейронным или поведенческим сигналам.

Материалы и методы. Выполнен структурированный нарративный обзор рандомизированных и нерандомизированных исследований, проспективных когорт, документов, нейрофизиологических работ, опубликованных до июля 2026 года. Доказательства систематизированы по валидности биомаркеров, архитектуре управления, программируемости, эффективности, безопасности, энергосбережению, обобщаемости и учету человеческого фактора. Предложено многоцентровое перекрестное исследование взрослых пациентов с леводопа-чувствительной болезнью Паркинсона и моторными флуктуациями после оптимизации традиционной стимуляции.

Результаты. Амплитуда субталамической бета-активности и продолжительность бета-вспышек остаются изученными управляющими переменными. Индуцированная стимуляцией гамма-активность, корковые сигналы, события ходьбы, регистрируемые носимыми устройствами, и мультимодальные декодеры могут точнее отражать дискинезию, замирание и поведение в естественной среде. Хронические исследования показывают, что персонализированная адаптивная стимуляция способна уменьшать остаточные моторные симптомы и улучшать качество жизни, тогда как синхронизированные с ходьбой и активностью парадигмы воздействуют на аксиальные нарушения. Основными ограничениями являются артефакты регистрации, нестабильность биомаркеров, неоднородность программирования, малые выборки, недостаточное ослепление и ограниченные данные о когнитивных функциях, речи, падениях и нагрузке, связанной с устройством. Первичная конечная точка объединяет улучшение моторного состояния при слепой оценке с уменьшением мучительной дискинезии и времени выключения. Вторичные показатели включают падения, замирание ходьбы, речь, когнитивные функции, качество жизни, энергию стимуляции, время программирования, нежелательные явления, калибровку и результаты подгрупп.

Заключение. Адаптивная глубокая стимуляция переходит от экспериментальной нейрофизиологии к регулируемой клинической терапии. Ее долговременная ценность зависит от персонализации биомаркеров, прозрачности алгоритмов, стандартизированных исходов и независимой надежной многоцентровой валидации.

Ключевые слова: болезнь Паркинсона, адаптивная глубокая стимуляция мозга, замкнутая нейромодуляция, бета-осцилляции, локальные полевые потенциалы, замирание ходьбы, нейронные биомаркеры, персонализированная нейростимуляция.

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SamDTU huzuridagi neyroxirurgiya va neyroreabilitatsiya ixtisoslashtirilgan ilmiy-amaliy markazi

PARKINSON KASALLIGIDA ADAPTIV CHUQUR MIYA STIMULYATSIYASI: NEYRON BIOMARKERLAR, YURISH BILAN SINXRON BOSHQARUV VA BEMORGA XOS TARMOQ NEYROMODULYATSIYASI

Annotatsiya

Dolzarblik. An’anaviy chuqur miya stimulyatsiyasi Parkinson kasalligida davolashni ta’minlaydi, biroq o‘zgarmas parametrlar dori sikllari, uyqu va uyg‘oqlik almashinuvi, yurishning qotib qolishi, diskineziya hamda biomarkerlar dreyfini hisobga olmaydi. Adaptiv chuqur miya stimulyatsiyasi neyron yoki xulqiy signallarga muvofiq ta’sirni o‘zgartiruvchi yopiq konturli neyromodulyatsiyani amalga oshiradi.

Material va usullar. 2026-yil iyuligacha chop etilgan randomizatsiyalangan va randomizatsiyalanmagan tadqiqotlar, prospektiv kohortlar, hujjatlar, neyrofiziologik izlanishlar asosida strukturaviy narrativ sharh bajarildi. Dalillar biomarkerlar validligi, boshqaruv arxitekturasi, dasturlash imkoniyati, samaradorlik, xavfsizlik, energiya tejamkorligi, umumlashtirish va inson omiliga ko‘ra tizimlashtirildi. Levodopaga javob beruvchi Parkinson kasalligi va optimallashtirilgan an’anaviy stimulyatsiyaga qaramay motor fluktuatsiyalari saqlangan bemorlar uchun ko‘p markazli kesishma tadqiqot taklif etildi.

Natijalar. Subtalamik beta-faollik amplitudasi va beta-portlashlar davomiyligi asosiy boshqaruv o‘zgaruvchilari bo‘lib qolmoqda. Stimulyatsiya chaqirgan gamma-faollik, kortikal signallar, taqiladigan qurilmalar aniqlaydigan yurish hodisalari va multimodal dekoderlar diskineziya, qotib qolish hamda tabiiy xulqni aks ettirishi mumkin. Surunkali tadqiqotlar shaxsiylashtirilgan adaptiv stimulyatsiya qoldiq motor simptomlarini kamaytirishi va hayot sifatini yaxshilashi mumkinligini, yurish yoki faollik bilan sinxronlashtirilgan paradigmalar esa aksial buzilishlarga ta’sir qilishini ko‘rsatadi. Asosiy cheklovlar qayd artefaktlari, biomarkerlar beqarorligi, dasturlashdagi geterogenlik, kichik tanlanmalar, ko‘r qilinmaslik hamda kognitsiya, nutq, yiqilishlar va qurilma yuklamasi bo‘yicha dalillarning cheklanganligidir. Birlamchi yakuniy nuqta ko‘r baholangan motor holat yaxshilanishini diskineziya va “off” vaqtining kamayishi bilan birlashtiradi. Ikkilamchi ko‘rsatkichlar yiqilishlar, yurishning qotib qolishi, nutq, kognitsiya, hayot sifati, stimulyatsiya energiyasi, dasturlash vaqti, nojo‘ya hodisalar, kalibratsiya va kichik guruh natijalarini o‘z ichiga oladi.

Xulosa. Adaptiv chuqur miya stimulyatsiyasi eksperimental neyrofiziologiyadan tartibga solinadigan klinik terapiyaga o‘tmoqda. Uning qiymati biomarkerlarni shaxsiylashtirish, shaffof algoritmlar, standartlashtirilgan natijalar va mustaqil qat’iy ko‘p markazli validatsiyaga bog‘liq.

Kalit so‘zlar: Parkinson kasalligi, adaptiv chuqur miya stimulyatsiyasi, yopiq konturli neyromodulyatsiya, beta-ossillyatsiyalar, lokal maydon potensiallari, yurishning qotib qolishi, neyron biomarkerlar, shaxsiylashtirilgan neyrostimulyatsiya.

Introduction. Parkinson’s disease is a progressive multisystem neurodegenerative disorder characterized by degeneration of nigrostriatal dopaminergic projections, pathological α-synuclein accumulation, abnormal basal ganglia synchronization, and disruption of distributed motor, associative, limbic, and autonomic networks. Levodopa and dopamine-replacement strategies remain

central to symptomatic management, but long-term treatment is frequently complicated by wearing-off, delayed-on responses, unpredictable off episodes, peak-dose dyskinesia, nocturnal akinesia, neuropsychiatric manifestations, and progressive axial disability. For carefully selected patients with levodopa-responsive motor symptoms, deep brain stimulation of the subthalamic nucleus or internal globus pallidus can substantially reduce motor fluctuations and medication burden. Nevertheless, conventional deep brain stimulation delivers electrical pulses continuously according to parameters selected during intermittent programming sessions. This open-loop architecture assumes that therapeutic demand remains sufficiently stable between visits, although Parkinsonian physiology changes across medication cycles, voluntary movement, sleep, emotional state, cognitive load, and disease progression [1, 2, 3]. Continuous stimulation can therefore produce both undertreatment and overtreatment. During severe off periods, the programmed amplitude may be insufficient to suppress pathological network synchronization. During medication-associated on states, the same amplitude may contribute to dyskinesia, dysarthria, paresthesia, impaired postural control, or excessive energy consumption. The therapeutic window is particularly narrow when the electrode lies near the corticobulbar tract, medial lemniscus, oculomotor fibers, limbic subterritories, or nonmotor components of the subthalamic region. Conventional programming attempts to resolve these problems through contact selection, directional current steering, pulse-width modification, frequency adjustment, interleaving, and medication optimization. These strategies are clinically effective but remain episodic, labor-intensive, and dependent on observations made during relatively short clinic visits [3, 6, 10]. Adaptive deep brain stimulation represents a transition from fixed electrical delivery toward bidirectional neuromodulation. An adaptive system records a physiological or behavioral signal, extracts a candidate biomarker, compares the biomarker with one or more thresholds, and modifies stimulation according to a predefined control policy. Depending on the platform, the controller may alter amplitude, pulse width, frequency, contact configuration, temporal pattern, or stimulation timing. The system consequently acts as an implanted feedback loop rather than as an electrically active but physiologically blind pulse generator.

Early adaptive DBS investigations demonstrated that subthalamic beta-band activity could be used to trigger stimulation and that intermittent biomarker-dependent stimulation could improve bradykinesia and rigidity while reducing delivered electrical energy. Subsequent bilateral, dual-threshold, proportional-control, and chronic home-use studies expanded the concept beyond short intraoperative or externalized-lead experiments [5, 11, 16]. Beta activity, however, is neither a universal nor symptom-complete biomarker. Tremor may occur without strong beta synchronization, dyskinesia may be better represented by narrow-band gamma activity, and freezing of gait involves distributed cortical, basal ganglia, brainstem, cerebellar, and spinal mechanisms. A single spectral feature recorded from one contact pair may therefore capture only a restricted fraction of the patient’s clinical state. The distinction between a biomarker and a control variable is important. A neural feature may correlate with disease severity at the group level but remain unsuitable for real-time control because it is unstable, contaminated by stimulation artifacts, altered by movement, or unavailable in an individual patient. Conversely, a feature with modest mechanistic specificity may still be clinically valuable when it can be recorded reliably and used to discriminate states that require different stimulation intensities. Beta amplitude, beta-burst duration, stimulation-entrained gamma activity,

cortical electrocorticography, tremor measured by inertial sensors, gait-phase detection, wearable-derived bradykinesia scores, electromyography, and multimodal decoders represent different positions along this spectrum [4, 7, 14]. The clinical relevance of adaptive stimulation changed substantially when chronic sensing-capable devices enabled home use and when adaptive functionality entered regulated clinical practice. The pivotal ADAPT-PD program enrolled 68 participants receiving stable continuous DBS and medication. Forty participants were evaluated with dual-threshold adaptive stimulation and 35 with single-threshold stimulation. Most participants maintained acceptable on time without troublesome dyskinesia, and single-threshold therapy reduced total electrical energy delivered relative to continuous stimulation. However, signal artifacts or insufficient α–β peak amplitude contributed to screening failures, illustrating that adaptive therapy is not automatically available to every implanted patient [8, 9, 25].

More recent investigations have moved beyond conventional beta-threshold control. Personalized gamma-based stimulation has been tested in patients with residual motor fluctuations despite optimized conventional DBS. Activity-dependent controllers have used decoded mobility states to adapt stimulation during sitting, standing, walking, and obstacle avoidance. Gait-phase-synchronized stimulation has explored rapid bilateral modulation linked to the swing phase of each leg. These studies suggest that future adaptive systems may combine continuous neural sensing with wearable kinematics and symptom-specific network models rather than rely on a single threshold derived during an office visit [10, 13, 23]. The present article evaluates the biological rationale, technical architecture, clinical evidence, limitations, and future research requirements of adaptive DBS in Parkinson’s disease. It also proposes a multicenter comparative protocol designed to link neurophysiological control accuracy with outcomes that are meaningful to patients, including functional mobility, falls, speech, cognition, dyskinesia, off time, quality of life, and treatment burden.

Materials and Methods. A structured narrative review framework was used to integrate evidence available through July 2026. Eligible evidence included randomized crossover trials, prospective clinical studies, nonrandomized chronic home-use investigations, diagnostic and neurophysiological studies, device-development reports, consensus publications, regulatory documentation, and clinically relevant technical research. Priority was given to studies involving implanted sensing-capable systems and real-world or home-based adaptive stimulation. Acute studies using externalized leads were retained when they provided foundational evidence regarding biomarkers, controller latency, stimulation-induced artifacts, or physiological mechanisms. The evidence was organized into seven domains: biological validity of the control signal, within-patient discriminative performance, temporal stability, technical compatibility with simultaneous sensing and stimulation, clinical efficacy, safety, and implementation feasibility. Biomarker validity was evaluated according to association with motor state, responsiveness to dopaminergic therapy or DBS, reproducibility across sessions, and susceptibility to behavioral or electrical confounding. Controller performance was assessed according to threshold strategy, update rate, ramping behavior, state-transition latency, total electrical energy delivered, and protection against unintended stimulation changes. Clinical outcomes of interest included the Movement Disorder Society–Unified Parkinson’s Disease Rating Scale part III, patient motor diaries, on time without troublesome dyskinesia, off time, Unified Dyskinesia Rating Scale scores, freezing-of-gait measures, fall frequency, gait speed, stride

variability, speech intelligibility, neuropsychological performance, Parkinson's Disease Questionnaire scores, medication burden, programming time, and device-related adverse events. Technical outcomes included biomarker availability, sensing failure, artifact burden, classification accuracy, calibration error, battery consumption, telemetry reliability, and the proportion of time spent at minimum, intermediate, and maximum stimulation. A prospective, multicenter, randomized, assessor-blinded crossover trial is proposed as the original clinical component of this article. Adults with idiopathic, levodopa-responsive Parkinson's disease would be eligible when they have bilateral sensing-capable subthalamic or pallidal DBS, stable lead localization, optimized continuous stimulation for at least three months, and residual motor fluctuations, troublesome dyskinesia, freezing, or stimulation-related adverse effects. Exclusion criteria would include severe dementia, uncontrolled psychosis, unstable depression with suicidality, inability to complete motor diaries, frequent syncope, major untreated sleep disorder, structurally damaged leads, clinically significant impedance abnormalities, and absence of any technically usable neural or behavioral control signal.

Following baseline characterization, each participant would undergo biomarker mapping during medication-off, medication-on, rest, repetitive movement, speech, dual-task walking, turning, obstacle negotiation, and sleep. Candidate control features would include subthalamic or pallidal alpha–beta power, beta-burst duration, stimulation-entrained gamma activity, cortical signals when available, and wearable-derived motor states. A predefined algorithm would rank candidate features by separability, temporal stability, artifact resistance, and clinical relevance. Participants would then receive optimized continuous DBS and personalized adaptive DBS in randomized order, with each treatment period lasting twelve weeks and separated by a two-week reoptimization interval when necessary. The proposed primary endpoint is a hierarchical composite consisting of change in blinded MDS-UPDRS III score, daily off time, and on time with troublesome dyskinesia. The adaptive strategy would be considered superior only if it improved the composite without increasing persistent dysarthria, falls, cognitive decline, or serious device-related events. Secondary endpoints would include freezing-of-gait frequency, objectively measured falls, gait variability, speech intelligibility, executive function, quality of life, total electrical energy delivered, programming time, caregiver burden, and participant preference.

Mixed-effects models would include treatment, period, sequence, target, medication state, and study center as fixed effects, with participant as a random effect. Carryover would be assessed explicitly. Calibration of adaptive state detection would be evaluated using reliability curves, Brier scores, sensitivity, specificity, false-trigger rate, and time-weighted classification error. Prespecified subgroup analyses would examine sex, age, disease duration, DBS target, baseline beta-peak amplitude, phenotype, cognitive status, and lead type. Because subgroup analyses are vulnerable to false-positive findings, interaction estimates and confidence intervals would be emphasized rather than isolated within-group significance.

Table 1. Conceptual differences between conventional and adaptive deep brain stimulation

Domain	Conventional DBS	Adaptive DBS	Proposed clinical implication

Stimulation delivery	Continuous or scheduled fixed parameters	Parameters vary according to sensed state	Better matching of stimulation to fluctuating therapeutic demand
Physiological sensing	Usually absent from active control	Continuous or intermittent neural or behavioral sensing	Enables bidirectional neuromodulation
Programming basis	Clinic examination and clinician experience	Clinic examination plus biomarker calibration	Potentially more individualized but technically complex
Medication interaction	Indirectly managed through manual adjustment	Controller may respond to medication-related neural changes	Potential reduction of off periods and dyskinesia
Gait control	Fixed stimulation across gait phases	Activity- or gait-phase-dependent stimulation	Potential treatment of freezing, instability, and falls
Energy delivery	Often constant despite changing need	Can decrease or increase according to state	Battery benefit is possible but not guaranteed
Failure mode	Persistent under- or overstimulation	Misclassification, artifact-driven adaptation, biomarker loss	Requires safety limits and fallback programming
Transparency	Parameters are directly inspectable	Algorithmic decisions may be less obvious	Requires interpretable logs and clinician oversight
Evidence base	Extensive randomized and long-term evidence	Expanding but still heterogeneous	Multicenter comparative validation remains necessary

Results. Excessive synchronization within the beta range is associated with bradykinesia and rigidity in Parkinson's disease. Dopaminergic medication and therapeutically effective DBS suppress beta activity, while prolonged beta bursts correlate more closely with motor impairment than averaged spectral power alone. Adaptive stimulation can truncate prolonged pathological bursts, shifting the distribution toward shorter and lower-amplitude events. This observation provides a mechanistic rationale for using beta amplitude or burst duration as a feedback variable [2, 3, 18]. Beta-controlled stimulation has several practical advantages. Local field potentials can be recorded from the same implanted leads used for stimulation, avoiding additional cortical hardware. Beta peaks are identifiable in many patients with subthalamic electrodes, and amplitude thresholds can be implemented with relatively low computational complexity. Dual-threshold control allows stimulation to increase when the signal exceeds an upper threshold and decrease when it falls below a lower threshold, reducing rapid oscillation between states. Ramping parameters can prevent abrupt paresthesia or motor deterioration. However, averaged beta power is influenced by voluntary movement, posture, medication, sleep, electrode position, contact selection, and stimulation artifact. Physiological beta desynchronization during movement could be misinterpreted as reduced therapeutic need even when the patient is entering a gait state that requires additional stimulation. Conversely, nonmotor cognitive

or postural demands may change beta activity without corresponding to bradykinesia severity. Biomarker drift can also occur as medication is adjusted, disease progresses, or tissue–electrode interfaces evolve. These limitations explain why some patients lack a stable sensing configuration despite technically satisfactory DBS leads [6, 13, 28].

Stimulation-entrained gamma oscillations represent an alternative control signal. Finely tuned gamma activity may track hyperkinetic states, medication effects, and residual motor symptoms differently from beta power. Personalized gamma-based adaptive DBS was superior to optimized continuous stimulation in a blinded randomized feasibility study involving a small number of participants, supporting the concept that the optimal biomarker may differ across patients. Nevertheless, gamma sensing can be technically challenging because the relevant frequency may lie near stimulation harmonics or be contaminated by electrical artifacts. The clinical meaning of gamma activity may also depend on whether the oscillation is physiological, medication-induced, stimulation-entrained, or associated with dyskinesia [11, 12, 20]. Cortical sensing offers access to signals that may reflect movement intention, speech, dyskinesia, and network state more directly than subcortical beta activity. Chronic electrocorticography can provide high-amplitude signals and may improve detection of behavioral transitions. The disadvantage is the need for additional implanted hardware, with associated operative time, infection risk, lead migration risk, and regulatory complexity. Future systems may instead combine subcortical local field potentials with noninvasive wearable information, thereby increasing state resolution without requiring another intracranial electrode.

Table 2. Candidate feedback signals for adaptive DBS

Feedback signal	Principal clinical association	Main strength	Main limitation
Alpha–beta power	Bradykinesia, rigidity, medication state	Available from standard sensing DBS leads	May be absent, unstable, or movement-sensitive
Beta-burst duration	Severity of pathological synchronization	Greater temporal specificity than averaged power	Threshold definition varies across patients
Stimulation-entrained gamma	Dyskinesia and individualized motor state	May identify states poorly represented by beta	Susceptible to stimulation harmonics and artifacts
Tremor-band activity	Rest or action tremor	Direct symptom-related signal in selected patients	Does not represent akinesia, gait, or nonmotor symptoms
Cortical electrocorticography	Movement intention, dyskinesia, speech	High signal amplitude and network-level information	Requires additional intracranial hardware
Inertial sensors	Tremor, gait, turning, falls, bradykinesia	Measures real-world behavior directly	Motion artifacts and limited access to internal state

Electromyography	Muscle activation and gait phase	Rapid peripheral detection of movement	Sensors must be worn and maintained
Multimodal decoder	Combined neural and behavioral state	Potentially captures complex symptoms	Greater computational and validation burden

Control architectures and programming. Adaptive control can be implemented through single-threshold, dual-threshold, proportional, state-machine, phase-locked, or machine-learning-based policies. Single-threshold systems typically switch between lower and higher stimulation states. Dual-threshold controllers create a hysteresis zone that stabilizes transitions. Proportional controllers adjust amplitude continuously according to biomarker magnitude. State-machine approaches classify the patient into discrete states such as rest, walking, dyskinesia, tremor, sleep, or medication off, after which a state-specific stimulation program is selected. The pivotal chronic experience demonstrates that both single- and dual-threshold strategies can preserve clinically acceptable on time in patients previously stable on continuous stimulation. In ADAPT-PD, 68 participants were enrolled, 45 entered the principal adaptive evaluation, and 44 elected to continue adaptive therapy into long-term follow-up. The predefined performance goal was achieved by a high proportion of participants. Single-threshold stimulation reduced total electrical energy delivered by approximately 15% relative to continuous stimulation, while most stimulation-related adverse effects resolved during setup and adjustment [15, 17, 27].

These findings should not be interpreted as proof that adaptive stimulation is universally superior. Participants were already responsive to conventional DBS, required a suitable sensing configuration, and underwent structured programming by experienced teams. The trial primarily established tolerability, maintenance of therapeutic effectiveness, and practical long-term operation. It did not resolve whether adaptive stimulation provides superior control of gait, cognition, speech, or disease-specific quality of life across broad clinical populations. Programming remains a major implementation barrier. Conventional DBS programming is already multidimensional, involving target selection, contact geometry, current amplitude, frequency, pulse width, medication state, and symptom prioritization. Adaptive programming adds sensing contact selection, frequency-band selection, upper and lower thresholds, ramp rates, update intervals, minimum and maximum amplitudes, blanking periods, artifact mitigation, and fallback rules. An apparently logical controller may fail if the sensed biomarker is contaminated, if the stimulation contact suppresses the biomarker needed for control, or if the chosen threshold was calibrated during a state unrepresentative of daily life. Automated anatomical programming may reduce the search space by estimating the volume of tissue activated and its relationship with symptom-specific pathways. Multicenter connectomic analyses indicate that tremor, bradykinesia, rigidity, and axial symptoms are associated with partially distinct white-matter networks. Tremor improvement has been related to pathways connected with primary motor and cerebellar systems, whereas axial responses involve supplementary motor and brainstem connectivity. Combining connectomic targeting with adaptive temporal control could therefore personalize both where and when stimulation is delivered [7, 14, 19].

Gait-synchronized and activity-dependent stimulation. Gait impairment is one of the most clinically important limitations of conventional DBS. Freezing, postural instability, reduced stride

length, impaired turning, and falls may respond incompletely to dopaminergic therapy and fixed high-frequency stimulation. In some patients, stimulation improves appendicular symptoms while axial disability continues to progress. In others, specific frequencies or stimulation distributions may worsen speech, balance, or freezing. Recent activity-dependent studies demonstrate that subthalamic signals contain information about sitting, standing, walking, and obstacle negotiation. Machine-learning models can use these signals to identify mobility states and alter stimulation in real time. This approach differs conceptually from conventional beta-threshold control: rather than estimating a scalar degree of Parkinsonian impairment, the controller identifies the activity currently being performed and applies stimulation optimized for that activity [16, 23, 30]. Gait-phase-synchronized stimulation introduces an even faster control timescale. Neural or peripheral signals are used to identify the swing or stance phase of each leg, after which stimulation is modulated independently across hemispheres. A 2026 randomized feasibility study showed that rapid gait-phase-dependent adjustments were tolerated and could improve several gait metrics while preserving general control of Parkinsonian symptoms. The study involved only a small number of participants, so efficacy, durability, and external generalizability remain uncertain. Nevertheless, it establishes that DBS need not be limited to slow amplitude changes driven by medication-related beta fluctuations. The emerging challenge is multiscale control. Medication-related changes evolve over minutes or hours; beta bursts evolve over hundreds of milliseconds; gait phases change within approximately one second; tremor cycles may require still faster detection; and disease progression unfolds over months or years. A single controller must either operate across these timescales or coordinate several nested controllers. Safety constraints are essential because rapid adaptation could produce abrupt disequilibrium, paresthesia, speech disruption, or rebound symptoms.

Clinical effectiveness and patient-centered outcomes. Motor scores obtained in standardized medication-off conditions remain useful but are insufficient as the sole endpoint for adaptive therapy. The central clinical promise of aDBS is continuous personalization during everyday life. Evaluation must therefore include home mobility, falls, turning, dual-task performance, speech, sleep, dyskinesia, off time, medication use, occupational participation, caregiver burden, and patient preference. Motor diaries remain valuable because they characterize daily on and off states, but they are vulnerable to recall error and incomplete adherence. Wearable sensors can complement diaries by measuring tremor, step count, turning speed, stride variability, freezing episodes, and falls. However, algorithmic performance must be validated against clinically adjudicated events. A wearable classifier developed in one laboratory or device ecosystem may not perform equally across different ages, gait aids, cultural environments, home layouts, or comorbid musculoskeletal conditions. Speech and cognition require particular attention. Continuous stimulation can impair verbal fluency, articulation, response inhibition, or affective processing in susceptible patients. Adaptive reduction of unnecessary stimulation could theoretically mitigate these effects, but a poorly selected biomarker might instead cause unstable stimulation during conversation or cognitive tasks. Trials should include blinded speech recordings, semantic and phonemic fluency, executive testing, mood scales, apathy assessment, and ecological measures of communication.

Energy reduction is a useful technical outcome but should not be treated as an automatic surrogate for clinical superiority. Adaptive stimulation may reduce average amplitude when low

stimulation is sufficient, but more sophisticated controllers can also increase energy delivery during high-demand states. Rechargeable systems reduce the importance of battery longevity but add charging burden. Nonrechargeable systems may benefit more directly from reduced energy, although battery replacement timing depends on pulse width, frequency, impedance, and telemetry use as well as amplitude.

Safety and failure analysis. Adaptive DBS retains the surgical risks of conventional DBS, including intracranial hemorrhage, infection, seizure, lead malposition, hardware erosion, and anesthetic complications. It also introduces algorithm-specific hazards. False-negative state detection may result in undertreatment, whereas false-positive detection may trigger unnecessary stimulation. Artifact-driven adaptation may create repetitive oscillation between amplitudes. Loss of a previously stable biomarker may cause chronic bias toward the minimum or maximum permitted stimulation state. Safety architecture should therefore include hard clinician-defined amplitude limits, maximum rates of change, artifact rejection, sensing-quality monitoring, fallback to a validated continuous program, event logging, and patient-accessible emergency controls. Changes to the controller should be versioned, auditable, and reversible. Clinicians must be able to determine why stimulation changed at a particular time rather than receiving only a summary score from an opaque model. Cybersecurity is also a clinical safety issue. Wireless telemetry and remote programming increase convenience but create potential vulnerabilities involving unauthorized access, corrupted updates, data interception, or denial of service. Device manufacturers and clinical centers require secure authentication, encrypted communication, update verification, access logs, and procedures for responding to software failure.

Equity requires examination at both the surgical and algorithmic levels. DBS access is already influenced by geography, socioeconomic status, referral patterns, specialist availability, sex, age, ethnicity, and insurance coverage. Adaptive systems may widen these disparities if they require prolonged programming at highly specialized centers. Algorithms trained predominantly on selected patients with strong beta peaks may perform less reliably in tremor-dominant phenotypes, atypical electrophysiological profiles, older adults, women, or patients using mobility aids. Performance should therefore be reported across clinically relevant subgroups rather than only as an overall mean [21, 24, 31].

Table 3. Proposed prospective multicenter crossover study

Component	Proposed specification
Study population	Adults with levodopa-responsive Parkinson’s disease, sensing-capable bilateral DBS, and residual motor fluctuations or stimulation-related adverse effects
Study design	Randomized, assessor-blinded, two-period crossover comparison
Intervention	Personalized adaptive DBS based on the best validated neural or multimodal biomarker
Comparator	Clinically optimized continuous DBS
Duration	Twelve weeks per treatment period with structured calibration and reoptimization
Primary endpoint	Hierarchical composite of blinded MDS-UPDRS III, off time, and on time with troublesome dyskinesia
Key safety condition	No increase in persistent dysarthria, falls, cognitive decline, or serious device-related adverse events

Secondary endpoints	Freezing, objective falls, gait variability, speech, cognition, quality of life, energy, programming time, caregiver burden
Technical endpoints	Biomarker availability, calibration, false-trigger rate, signal loss, artifact burden, controller latency
Statistical framework	Mixed-effects crossover analysis with period, sequence, target, center, and medication state
External validity	Prespecified subgroup analysis and testing across manufacturers, centers, targets, and lead types
Originality	Direct linkage of controller performance with functional mobility, communication, cognition, safety, and treatment burden

Discussion. Adaptive deep brain stimulation is best understood not as a single treatment but as a family of feedback-controlled therapies. The therapeutic effect depends on four interacting components: the anatomical location of stimulation, the physiological signal used for feedback, the algorithm translating that signal into action, and the clinical outcome selected as the optimization target. Failure in any component can limit the entire system. The strongest current evidence supports chronic adaptive stimulation based on alpha–beta local field potential activity in appropriately selected patients with sensing-capable subthalamic or pallidal systems. The ADAPT-PD experience established that long-term home use is feasible, that most evaluated participants maintained clinically acceptable motor control, and that many elected to continue adaptive therapy. The study also revealed practical limitations: not every implanted patient had a usable signal, substantial setup and adjustment were required, and the main efficacy framework emphasized maintenance of good on time rather than broad superiority across all motor and nonmotor domains [23, 30, 32]. Smaller personalized studies have suggested that adaptive stimulation can improve residual symptoms beyond optimized continuous DBS. These investigations are scientifically important because they test within-patient biomarker selection rather than assuming that one spectral band applies to everyone. Their small sample sizes, specialized hardware, intensive programming, and single-center expertise limit immediate generalization. The field should resist replacing evidence-based programming with algorithmic enthusiasm before independent replication is available. Beta activity will probably remain important because it is mechanistically relevant, chronically recordable, and technically compatible with commercial systems. However, the future is unlikely to consist of beta-only stimulation. Parkinson's disease is not a unitary beta oscillopathy. Tremor, dyskinesia, freezing, speech impairment, impulsivity, apathy, sleep disturbance, and autonomic dysfunction emerge from partly distinct circuits and timescales. Multimodal adaptive therapy may combine a slowly varying medication-state estimator with rapid detection of tremor or gait phase. A state machine could select a symptom-specific control policy, while hard safety constraints prevent abrupt or excessive stimulation.

This architecture raises a fundamental question: should the controller optimize a neural biomarker or a clinical state? Suppressing beta activity does not necessarily guarantee improved function, particularly when beta desynchronization occurs during physiological movement. A purely biomarker-driven controller may optimize the signal while overlooking speech, balance, or cognition. Clinical development should therefore use biomarker normalization as an intermediate endpoint, not as a substitute for patient-centered outcomes. Activity-dependent and gait-synchronized approaches

are especially promising because they address disability that often remains resistant to conventional stimulation. Their clinical translation will require robust performance in homes and community environments, where patients encounter uneven surfaces, fatigue, distraction, narrow passages, crowds, medication variability, and anxiety. Laboratory gait tasks cannot reproduce all triggers of freezing. Longitudinal validation should therefore combine controlled assessments with wearable monitoring and adjudicated fall events. Connectomic information may improve both electrode programming and adaptive control. Symptom-specific network models can identify which contacts are most likely to influence tremor, rigidity, bradykinesia, or axial function. Adaptive algorithms could then modulate stimulation within a personalized anatomical search space rather than adjusting amplitude on a contact selected only by trial and error. This convergence of connectomics and closed-loop physiology has been termed adaptive circuit targeting and represents a logical direction for precision functional neurosurgery [16, 17, 21].

Machine learning can increase classification accuracy but also creates methodological risks. Flexible models may overfit small datasets, especially when many signal features are tested repeatedly. Randomly dividing data from the same patient into training and test sets can produce optimistic estimates because adjacent recordings are temporally correlated. Stronger validation requires separation by session, medication state, day, and ultimately patient and center. External validation should preserve the locked feature-processing pipeline, thresholds, and model weights.

Calibration must also be reported. A classifier that correctly ranks high- and low-symptom periods may still provide poorly calibrated probabilities. In a closed-loop device, calibration matters because threshold crossing directly changes therapy. Investigators should report false-trigger rates, missed-state duration, transition latency, time spent at safety limits, and behavior during signal dropout. Accuracy alone does not capture the clinical consequences of errors. Human factors are equally important. Programming should be understandable to movement-disorder neurologists, neurosurgeons, nurses, engineers, patients, and caregivers. Excessively complex interfaces may increase setup errors and restrict treatment to a few expert centers. A clinically successful system should automate signal-quality assessment, identify candidate frequency bands, visualize biomarker–symptom relationships, recommend safe thresholds, and display interpretable summaries of controller behavior. Automation must support rather than replace expert judgment.

The proposed multicenter crossover study addresses several weaknesses of the existing literature. First, it compares adaptive therapy against genuinely optimized continuous stimulation rather than against a suboptimal historical program. Second, it links technical accuracy with motor diaries, blinded examination, gait, falls, speech, cognition, quality of life, and treatment burden. Third, it requires safety noninferiority before superiority can be claimed. Fourth, it includes calibration, artifact burden, and false-trigger rates as formal outcomes. Finally, it prespecifies subgroup and external-validation analyses.

The crossover design increases efficiency because each participant serves as their own control, which is valuable in a heterogeneous disease. Nevertheless, carryover and period effects must be considered. Adaptation to new stimulation may take days or weeks, and participants may recognize treatment periods from symptom changes despite nominal blinding. Washout to no stimulation would be unethical for many patients. The protocol therefore uses reoptimization intervals and statistical

assessment of sequence effects rather than complete washout. Several limitations of the present synthesis should be acknowledged. The evidence base includes heterogeneous targets, biomarkers, devices, algorithms, follow-up durations, and endpoints. Many studies involve small cohorts treated at highly specialized centers. Publication bias may favor technically successful adaptive paradigms, while failed biomarker-selection or programming attempts may remain underreported. Direct comparisons between beta-, gamma-, cortical-, wearable-, and gait-driven controllers are scarce. Evidence regarding long-term cognition, speech, falls, neuropsychiatric outcomes, hardware longevity, and cost-effectiveness remains incomplete.

The regulatory transition of adaptive DBS does not eliminate the need for independent research. Commercial approval establishes that a defined system can be marketed for specified use; it does not demonstrate that every algorithm, biomarker, or future software update improves outcomes. Post-market registries should track programming burden, adverse events, reasons for discontinuation, battery performance, and patient-reported benefit. Software modifications that materially change controller behavior require transparent evaluation and version-specific reporting.

Cost-effectiveness will depend on more than device price. Adaptive DBS may reduce medication burden, unscheduled visits, battery replacement, falls, hospitalization, and caregiver demands. Conversely, it may increase programming time, telemetry requirements, software maintenance, and specialist dependence. Economic analyses should measure cost per quality-adjusted life-year and cost per additional hour of functional on time, while accounting for long-term hardware and clinical-service costs. Patient autonomy should remain central. Individuals should understand which signals are recorded, how stimulation decisions are generated, what data are stored or transmitted, and how the system behaves during failure. Some patients may prefer the predictability of fixed stimulation even when adaptive therapy offers potential advantages. Others may value fewer fluctuations or reduced need for manual adjustment. Shared decision-making should include realistic discussion of uncertainty rather than describing adaptive DBS as an autonomous cure.

Conclusion. Adaptive deep brain stimulation marks a major evolution in functional neurosurgery by transforming DBS from continuous open-loop stimulation into responsive, physiology-informed therapy. Subthalamic alpha–beta activity and beta-burst dynamics currently provide the most mature feedback signals, while gamma activity, cortical recordings, wearable sensors, gait-phase detection, and multimodal decoders expand the range of treatable clinical states. Current chronic studies support feasibility, tolerability, preservation of therapeutic effectiveness, and potential improvements in residual motor symptoms or electrical-energy use. Activity-dependent and gait-synchronized approaches indicate that adaptive stimulation may eventually address freezing, postural instability, and falls more precisely than fixed stimulation. Nevertheless, biomarker instability, sensing artifacts, programming complexity, small study populations, limited blinding, and insufficient long-term functional evidence remain substantial barriers. Future trials must compare personalized adaptive therapy with optimized conventional DBS using standardized, patient-centered endpoints. Technical performance should be linked directly with mobility, dyskinesia, off time, speech, cognition, falls, quality of life, caregiver burden, safety, and device burden. Transparent control algorithms, interpretable programming interfaces, robust fallback mechanisms, subgroup analysis, cybersecurity,

and independent multicenter external validation are essential before adaptive DBS can be regarded as a universally preferable standard.

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