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DEEP BRAIN STIMULATION IN TREATMENT-REFRACTORY ANOREXIA NERVOSA: CURRENT TARGETS, EMERGING TECHNIQUES, AND METHODOLOGICAL CHALLENGES

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ABSTRACT

Background: Anorexia nervosa (AN) is a severe psychiatric disorder associated with the highest mortality rate among mental illnesses. Up to 20% of patients develop Severe and Enduring Anorexia Nervosa (SE-AN), a life-threatening condition resistant to conventional psychotherapy and nutritional rehabilitation. In the absence of effective pharmacotherapy, Deep Brain Stimulation (DBS) has emerged as a potential neurosurgical intervention targeting dysfunctional circuits involved in cognitive control, reward processing, and emotion regulation.

Objectives: This review evaluates the current application of DBS in treatment-refractory AN, focusing on neuroanatomical targets, clinical efficacy, safety, and methodological, technological, and ethical challenges.

Methodology: A comprehensive literature search was conducted in PubMed, Scopus, ScienceDirect, Embase, and Google Scholar. Studies published between 2022 and 2026 were considered, with reference lists manually screened for additional relevant evidence.

Results: DBS may improve BMI, psychiatric symptoms, and quality of life in patients with SE-AN. Although the subcallosal cingulate cortex (SCC) and nucleus accumbens (NAcc) remain the principal targets, recent approaches increasingly emphasize phenotype-driven and connectome-guided neuromodulation. Emerging closed-loop, AI-assisted, and wireless technologies may further improve stimulation precision and reduce hardware-related complications.

Conclusions: DBS represents a promising harm-reduction approach for treatment-refractory SE-AN. However, limited evidence, surgical risks, and ethical concerns regarding informed consent in severely malnourished patients warrant its use only as a last-resort intervention. Robust randomized multicenter trials are needed to establish its long-term safety and target-specific efficacy.

KEYWORDS

Deep Brain Stimulation (DBS), Anorexia Nervosa, Severe and Enduring Anorexia Nervosa (SE-AN), Connectomics, Closed-loop Neuromodulation, Psychiatric Neurosurgery

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Introduction

Anorexia nervosa (AN), first described in 1873 and classified in the DSM-5 as one of six primary feeding and eating disorders, is a complex brain-based illness presenting in two main subtypes: the restricting type (AN-R) and the binge-eating/purging type (AN-BP). Its clinical presentation is characterized by a drastic and persistent restriction of energy intake relative to the body's requirements, leading to a critically low body weight, which is inextricably linked to an intense fear of gaining weight and a profoundly distorted perception of one's own body shape (Allam & Attia, 2026). This condition disproportionately affects women, with a lifetime risk reaching 4% (compared to 0.3% in men), and of particular concern is the steadily rising number of diagnoses among patients under 15 years of age (Kounatidis & Vallianou, 2025).

Extreme malnutrition leads to devastating medical complications, including cachexia, bradycardia, hypotension, hypothermia, as well as severe nutritional and hematological deficiencies. AN induces structural brain changes and alters cardiac function, causes a decline in sex hormones resulting in amenorrhea or delayed menarche, and destructively impacts the gastrointestinal tract, bones, and parenchymal organs, leading to conditions such as pancreatitis or transaminitis (Allam & Attia, 2026). Due to these life-threatening somatic complications and a drastically elevated risk of suicide, the mortality rate in AN stands at 5.9%, making it the most lethal of all psychiatric disorders (Hsu et al., 2022).

Although conventional treatments based on psychotherapy and nutritional rehabilitation yield improvement in approximately 79% of patients (Hsu et al., 2022), their long-term efficacy is frequently hindered by patients' strong resistance to weight gain and high relapse rates (Kounatidis & Vallianou, 2025). Consequently, in over 20% of individuals, the illness assumes a treatment-refractory, life-threatening course

known as Severe and Enduring Anorexia Nervosa (SE-AN) (Marcolini et al., 2024). While the exact criteria for this stage continue to evolve, it is generally characterized by extreme levels of distress and an illness duration of at least seven years (Marcolini et al., 2024). The complexity of SE-AN necessitates a shift in the clinical paradigm. Rather than focusing exclusively on symptom reduction, contemporary collaborative care models such as person-centered care prioritize improvements in quality of life and the achievement of individualized patient goals (Hay et al., 2025). The situation for these patients is further exacerbated by a complete lack of effective pharmacotherapy. Commonly used antidepressants offer minimal benefits, and to date, the FDA has not approved any medication specifically indicated for the treatment of AN (Kounatidis & Vallianou, 2025). This therapeutic gap has encouraged the development and investigation of innovative, often experimental treatment approaches, ranging from the use of psychedelics (psilocybin, ketamine) and fecal microbiota transplantation (FMT) to non-invasive brain stimulation, such as intermittent theta-burst stimulation (iTBS) (Hay et al., 2025; Kounatidis & Vallianou, 2025).

This unmet clinical need underscores the potential utility of Deep Brain Stimulation (DBS) as a highly precise, modern alternative that directly targets dysfunctional brain circuits (Marcolini et al., 2024). Although psychiatric disorders can be effectively managed with pharmacological and behavioral therapies in most instances, stereotactic neurosurgical interventions provide a critical option for the most severe, treatment-refractory cases (El Jammal et al., 2026). DBS is currently regarded as a promising neuromodulation technique. Initially developed in the 1990s to treat movement disorders, the technique has evolved from early stereotactic procedures to precise targeting and adaptive stimulation (Soto Joven et al., 2026; Zhao et al., 2026). Over the past decades, the application of DBS has expanded to neuropsychiatric conditions such as treatment-resistant depression (TRD), post-traumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD) (Soto Joven et al., 2026), with the last being the only officially approved psychiatric indication for this type of therapy in the USA and Europe (Moleón-Ruiz et al., 2026).

The application of DBS in severe forms of anorexia nervosa finds strong neurobiological justification. Chronic malnutrition and profound dysregulation of eating behaviors lead to enduring changes in brain structure and function, making neuromodulation a highly promising therapeutic avenue for patients with SE-AN (Marcolini et al., 2024). AN shares common pathophysiological features with OCD and treatment-resistant depression, manifested by dysfunction in specific neural networks - including the prefrontal cortex and the nucleus accumbens. Because the success of DBS relies on its ability to disrupt and modulate pathological brain activity, precise electrical stimulation can modulate aberrant functional patterns within these impaired networks (Soto Joven et al., 2026).

Considering that approximately 20% of patients with anorexia nervosa fail to respond to any standard forms of therapy, innovative methods of nervous system stimulation often become a critical last-resort option for survival (Karaszewska et al., 2022). In response to this pressing clinical need, the aim of this review is to provide a comprehensive analysis of the application of DBS in treatment-refractory anorexia. Specifically, this article seeks to synthesize the current evidence base regarding established and emerging neuroanatomical targets, to critically appraise the clinical efficacy and safety profile of the method to date, and to examine the methodological, clinical, and ethical challenges inherent to implementing invasive neuromodulation within this rapidly evolving domain of precision psychiatry.

Results:

Mechanisms of action

In the DBS procedure, electrodes are implanted into specific brain regions, and stimulation protocols are configured to modulate neural activity in order to alleviate symptoms. The mechanism of action of this method is not yet fully understood. Current mechanistic frameworks indicate that the therapeutic effect of DBS may result simultaneously from depolarization block of certain neurons, an effect resembling an "informational lesion," and long-term reorganization of circuits via neuroplasticity (Zhao et al., 2026). In AN, the reward and compulsivity circuits encompassing the nucleus accumbens, insula, prefrontal cortex, and cortico-striato-limbic connections are of particular importance, and neuroimaging studies suggest that DBS may modulate the aberrant activity of these systems even when different anatomical targets are stimulated (Braeutigam et al., 2022; Oudijn et al., 2023). Furthermore, MEG and EEG studies demonstrate that the effects of DBS are spatially and temporally widespread, encompassing changes in oscillatory power, functional connectivity, and the organization of entire brain networks, which supports the view that this method reconfigures pathological

brain dynamics rather than acting purely locally (Braeutigam et al., 2022; Oudijn et al., 2025). Additionally, changes in white matter integrity observed after DBS, particularly in thalamo-frontal fibers and association bundles, suggest that secondary structural plasticity may contribute to sustaining the clinical effect (Abellana-Pérez et al., 2024).

Patient selection and classification criteria for DBS

As outlined by Moleón-Ruiz et al., DBS for anorexia nervosa remains investigational and is currently limited to clinical trials and specialized centers. In carefully selected, treatment-refractory patients, functional psychosurgery may reduce symptoms and improve quality of life but standardized preoperative assessment protocols are lacking. Candidacy consideration requires a structured, circuit-informed preoperative framework integrating diagnostic precision, psychopathological profiling, neuropsychological assessment, functional evaluation, and multidisciplinary ethical review.

Furthermore, the researchers highlight that eligibility criteria in published protocols reflect extreme disease duration and severe treatment refractoriness. Canonical inclusion parameters demand a confirmed DSM-5 diagnosis of anorexia nervosa, an illness duration often exceeding 5 to 10 years, and a sustained body mass index under 14 kg/m² for at least 12 months despite intensive specialized care. Candidates must show documented failure of multiple standard interventions, including specialized inpatient nutritional programs and structured psychotherapies, in the presence of severe comorbid affective or obsessive symptoms and high life-threatening risk. Conversely, absolute and relative exclusion criteria rule out progressive neurological diseases, major neurocognitive disorders, active psychotic episodes, and unmanageable somatic comorbidities. Beyond core diagnostic boundaries, comprehensive pre-surgical screening systematically evaluates several patient-level determinants such as patients' motivation and treatment adherence and expectations regarding potential procedural risks and limitations. Also, prior responsiveness to ECT or other neurostimulation strategies may signal a higher likelihood of clinical benefit (Moleón-Ruiz et al., 2026).

Established Anatomical targets

In anorexia nervosa, DBS has predominantly focused on three core anatomical targets: the subcallosal cingulate cortex (SCC), the nucleus accumbens (NAcc), and the ventral anterior limb of the internal capsule (vALIC). A 2023 meta-analysis highlighted this distribution, noting that the vast majority of participants received NAcc or SCC stimulation, rendering them the dominant empirical targets, while vALIC represents a smaller, yet significant, portion of the evidence base (Karaszewska et al., 2022). Additional structures, such as the ventral striatum and the BNST-related striatal circuitry, have also been explored, albeit to a much more limited extent (Aydin et al., 2024; Shaffer et al., 2022). Crucially, the field is transitioning away from the pursuit of a single, universally optimal gray-matter target. Recognizing the profound clinical heterogeneity of AN, contemporary approaches increasingly favor phenotype- and circuit-guided neuromodulation, where target selection is tailored to the patient's dominant symptoms, AN subtype, and specific psychiatric comorbidities (Abellana-Pérez et al., 2024; Karaszewska et al., 2022; Oudijn et al., 2023). The rationale for this targeted selection is deeply rooted in the distinct neurobiological functions of these regions.

The SCC is widely conceptualized in broader psychiatric DBS as a "top-down" entry point into limbic-motivational networks, acting as a central hub for emotional regulation and negative affect (Figue et al., 2022). In the context of AN, SCC targeting is justified by its robust connections to the anterior insula and its well-documented role in mediating anxiety and dysphoric mood (Karaszewska et al., 2022). Consequently, SCC-DBS has been extensively investigated across open-label cohorts (Elias et al., 2023), individual case reports (Bani Hamad et al., 2025), and functional follow-up studies examining network change (Oudijn et al., 2025).

Conversely, the NAcc is the most extensively rationalized target for addressing the aberrant reward valuation, motivational drive, and fronto-striatal control inherent to AN (Scaife et al., 2022; Tadayonnejad et al., 2022). Intricately connected to prefrontal, insular, limbic, and mesolimbic dopaminergic systems, the NAcc governs habit formation and reward processing (Duriez et al., 2025). This makes it a particularly compelling target for patients exhibiting restrictive persistence, pathological food choices, body image distortion, and prominent OCD-like symptom clusters (Braeutigam et al., 2022). Clinical evidence for NAcc-DBS is robust, spanning early pilot studies (Scaife et al., 2022) to advanced, protocol-driven multicenter trials (Duriez et al., 2025).

Expanding the neuromodulatory landscape, the vALIC has been integrated into AN research largely through translational borrowing from OCD and depression, where capsular stimulation modulates white-matter bundles of the affective and reward networks (Chan et al., 2024). Although clinical experience with vALIC in

AN is preliminary, primarily limited to highly severe binge-purging cases with complex comorbidities. Functional magnetic resonance imaging (fMRI) studies confirm its capacity to alter reward-related brain responsivity (Oudijn et al., 2023).

This diversity in anatomical targets underscores the growing adoption of symptom-matching strategies. For instance, recent cohorts assign SCC stimulation to patients with predominant affective comorbidities or restrictive AN, while NAcc targeting is reserved for those with anxiety disorders or binge-purging presentations (Abellana-Pérez et al., 2024; Gallop et al., 2022). This logic aligns seamlessly with broader psychiatric literature: the SCC modulates negative affect, while ventral striatal or capsular targets address compulsivity, anhedonia, and reward circuitry (Figuee et al., 2022). Ultimately, the lack of a single "best target" reflects a connectomic understanding of DBS. Despite utilizing different anatomical entry points, overall clinical outcomes in AN demonstrate surprisingly low heterogeneity (Karaszewska et al., 2022). This suggests that localized stimulation at distinct nodes converges on shared, disease-relevant circuits, normalizing broader aberrant network activity and culminating in comparable therapeutic effects across diverse clinical presentations (Oudijn et al., 2023).

Impact on Symptoms and Clinical Efficacy

Across all anatomical targets, DBS has demonstrated clinical efficacy in treatment-refractory AN. Recent meta-analyses report a large pooled effect size (Hedges' $g = 1.13$) for BMI restoration, alongside significant improvements in quality of life ($g = 0.86$) and reductions in psychiatric symptom burden ($g = 0.89$) among 56 evaluated patients, with minimal heterogeneity in BMI outcomes (Karaszewska et al., 2022). Furthermore, treatment network meta-analyses identify surgically invasive neuromodulation as one of the strongest interventions for weight restoration in AN, showing a pooled effect size of 1.43 (95% CI 1.00–1.86) and an estimated overall BMI increase of 24.82% over an average follow-up of 17.1 months (Khosravi, 2025).

For specific targets, stimulation of the SCC shows the most consistent concurrent improvements in weight, mood, anxiety, and affect regulation. In key SCC cohorts, mean BMI increased from 13.83 at implantation to 17.34 at 12 months. This physical improvement was accompanied by psychological changes, including a reduction in mean Hamilton Depression scores from 19 to 9 and Beck Anxiety Inventory scores from 38 to 27, along with improvements in affective dysregulation over the follow-up period (Costin et al., 2025; Khosravi, 2025). This consistent pattern explains why the SCC is often considered the optimal target for affective-dominant severe enduring AN. Patient-level network meta-analyses also rank the SCC as the most supported site for BMI changes at both 6- and 12-month intervals (Costin et al., 2025).

Clinical outcomes associated with the NAcc are broader but less consistent. A large longitudinal study showed that 43% (12 of 28) of patients receiving NAcc-DBS achieved a BMI > 18.5 kg/m² at 2 years. Significant weight restoration and reductions in obsessive-compulsive, depressive, and anxiety symptoms were evident by 6 months and maintained at 2 years (Khosravi, 2025). Similarly, a mixed-target cohort (SCC/NAcc) reported responder rates of 37.5% (3 of 8) at 6 months and 50% (4 of 8) at 12 months, based on BMI increase or stabilization criteria (Abellana-Pérez et al., 2024).

However, studies utilizing core eating-disorder psychopathology rather than BMI alone as the primary endpoint present a different perspective. In a NAcc/ALIC pilot study, 42.9% (3 of 7) of patients met responder criteria at 12 months, defined as a $>35\%$ reduction in Eating Disorder Examination (EDE) scores. Among these responders, EDE scores decreased by 70%, 44%, and 35.5%. Notably, two of these responders experienced a temporary recurrence of OCD symptoms, anhedonia, and depression during a blinded OFF phase, supporting the conclusion that symptom improvement was related to active stimulation. The remaining four patients were non-responders based on this psychopathological criterion. Analysis showed that all three responders had childhood-onset OCD predating their AN diagnosis, whereas non-responders generally had later-onset AN and less prominent OCD comorbidity (Scaife et al., 2022). This difference provides quantitative evidence that weight restoration and the reduction of core eating-disorder psychopathology do not always progress together, suggesting that NAcc/ALIC targeting may be most effective for patients with a compulsive, OCD-like AN phenotype.

Emerging Techniques, Connectomics, and Advanced Neuroimaging in DBS for AN

Contemporary approaches to deep brain stimulation (DBS) in the treatment of anorexia nervosa (AN) are undergoing a dynamic evolution. The classical model, which relied on the continuous and static inhibition of single anatomical targets, is giving way to highly precise, network-based interventions tailored to the individual clinical profile of the patient. The future of psychiatric neuromodulation hinges on the integration of advanced imaging, connectomic analysis, and closed-loop feedback systems, unlocking unprecedented potential for treatment personalization.

The Role of Connectomics, Tractography, and Surgical Innovations

A core component of this transformation is the departure from universal atlas coordinates toward preoperative planning driven by patient-specific tractography and diffusion tensor imaging (DTI) (Abellaneda-Pérez et al., 2024; Loh et al., 2022). This shift enables the identification of optimal stimulation sites relative to critical white-matter pathways, such as the uncinate fasciculus, cingulum, or forceps minor. Stimulation of structures like the SCC or the NAcc has been shown to induce measurable plastic changes in white matter integrity, including an increase in fractional anisotropy (FA) within the anterior thalamic radiation (ATR) and the superior longitudinal fasciculus-parietal bundle (SLFP) (Abellaneda-Pérez et al., 2024). This reinforces the connectomic paradigm that therapeutic efficacy depends on engaging relevant white-matter tracts and reconstructing cognitive control networks, rather than simply placing a contact inside a specific nucleus (Oudijn et al., 2023). Furthermore, the precision and safety of the implantation procedure are drastically enhanced by robotic assistance (e.g., ROSA or Neuromate systems) combined with intraoperative 3D imaging (O-Arm). Fusing MR images (3T and 7T) with intraoperative computed tomography provides frameless navigation with millimeter accuracy, which eliminates the need for time-consuming intraoperative microelectrode recording (MER) and minimizes complication risks while maintaining the highest neurosurgical standards (Defrance et al., 2025).

fMRI, VBM, and Reward Processing Mapping

In vivo neuroimaging techniques are proving instrumental in verifying the mechanisms of DBS. fMRI studies employing reward anticipation paradigms have demonstrated that stimulating areas like the NAcc or vALIC effectively normalizes activity within cognitive control and reward processing circuits (Loh et al., 2022; Oudijn et al., 2023). Patients exhibit a reduction in the pathological hyperactivation of the striatum and precuneus, alongside a simultaneous increase in medial orbitofrontal cortex (mOFC) activity. These activation shifts reflect a clinical return to goal-directed behaviors, breaking the pathological avoidance patterns consolidated by the illness (Oudijn et al., 2023). Moreover, unique "fMRI signatures" elicited by stimulation can serve as objective biomarkers of long-term improvement, facilitating the optimal programming of the pulse generator (Loh et al., 2022). These findings are complemented by voxel-based morphometry (VBM), which reveals that baseline gray matter volume, particularly in the left caudate and the right middle frontal gyrus, may act as a valuable predictor of treatment success regarding postoperative BMI restoration (Wang et al., 2025).

Adaptive Systems (Closed-Loop), AI, and Wireless Technologies

The future of the field lies in a shift from static, open-loop systems toward adaptive, closed-loop DBS, in which stimulation parameters are dynamically adjusted based on the patient's real-time neural activity. Modern protocols increasingly rely on the continuous recording of local field potentials (LFP) to identify pathological biomarkers and trigger stimulation only during their occurrence. This approach prevents habituation and optimizes energy consumption. Artificial intelligence (AI) and machine learning (ML) will be vital in decoding these complex brain states. However, clinical implementation requires "explainable AI" to ensure the transparency, auditability, and safety of automated therapeutic decisions (Costin et al., 2025). In parallel, radically innovative, wireless neuromodulation systems are currently under investigation. Experimental devices utilizing ultrasonic wideband (UsWB) waves to power and communicate with miniature implants may soon revolutionize DBS surgery entirely by removing the need for subcutaneous wires and bulky implantable pulse generators (IPGs), thereby drastically reducing hardware-related complications (Neimat et al., 2025).

Collectively, these emerging innovations affirm that the efficacy of AN treatment does not rely on stimulating a rigid atlas coordinate, but rather on highly personalized, biomarker-driven network interventions.

Discussion

The application of DBS in the treatment of AN requires an initial, complete shift in the current paradigm and the establishment of a coherent consensus regarding patient classification criteria (Hay et al., 2025; Marcolini et al., 2024). SE-AN requires precise definition, which most frequently should encompass a disorder duration, a body mass index, and documented resistance to standard forms of psychotherapy and multidisciplinary rehabilitation (Moleón-Ruiz et al., 2026). Furthermore, evaluating treatment efficacy in this group cannot rely exclusively on weight gain, as forcing it upon patients at all costs frequently provokes strong resistance or even increases the risk of suicide (Marcolini et al., 2024). The paradigm shift therefore involves moving toward a harm-reduction approach, in which improving quality of life and the targeted reduction of core psychopathology become equal or superior priorities (Duriez et al., 2025; Marcolini et al., 2024).

The advancement of neurosurgical methods means that the classification of anatomical targets is also evolving, because the modern approach moves away from stimulating single, isolated nuclei toward modulating entire pathways and tracts connecting these targets (J. & S., 2026). The success of neuromodulation does not depend on rigid atlas coordinates, but rather on the individual mapping of key white matter tracts using tractography (DTI) and matching interventions to the patient's phenotype (symptom-matching) (Abellaneda-Pérez et al., 2024). Stimulation of the SCC or the NAcc is no longer perceived as simple structural inhibition, but as a mechanism disrupting pathological synchronization (disruption hypothesis) in cognitive control circuits and the reward system (Zhao et al., 2026). This is supported by neuroimaging studies, such as fMRI and VBM, which illustrate how DBS induces the remodeling of neural networks through neuroplasticity (Oudijn et al., 2023; Wang et al., 2025).

Despite the extremely dynamic development of DBS technology, including the introduction of innovative methods such as closed-loop systems responding in real time to electrophysiological biomarkers, or miniature wireless devices powered by ultrasonic waves (UsWB), our knowledge still relies on very limited literature (Costin et al., 2025; Neimat et al., 2025). This field struggles with fundamental methodological problems: relatively small and heterogeneous study samples, a lack of standardization of stimulation parameters, and an insufficient number of randomized trials (Khosravi, 2025; Soto Joven et al., 2026). Even the most advanced techniques and machine learning algorithms will not replace the urgent need to conduct rigorous clinical trials, including the use of blinded ON/OFF phases, and to establish multicenter registries, without which full confirmation of the long-term efficacy of this form of treatment remains impossible (Braeutigam et al., 2022; Karaszewska et al., 2022).

The implementation of these novel methods is inextricably linked to difficult ethical dilemmas arising from the invasive nature of the procedure itself and the risk of adverse events (Aydin et al., 2024; Giordano et al., 2023). Brain stimulation carries not only the risk of acute surgical complications, such as intracranial hemorrhages or severe infections, but also side effects associated with the neurostimulation itself, encompassing sudden mood fluctuations, hypomanic states, apathy, or transient cognitive impairments. A severe ethical burden is also the objective assessment of an extremely malnourished patient's capacity to provide fully informed consent for such an intrusive procedure (Aydin et al., 2024; Khosravi, 2025). Although the latest technologies (such as wireless systems eliminating the risk of failure and infections of subcutaneous IPG generators) significantly limit certain complications, physical and psychological risks still exist (Neimat et al., 2025). This is precisely why DBS must unremittingly remain a last-resort procedure, utilized strictly as a life-saving intervention of last chance in patients in whom all other available treatment methods have been exhausted (Karaszewska et al., 2022; Moleón-Ruiz et al., 2026).

Conclusions

DBS represents a promising, precision-oriented intervention for SE-AN refractory to standard therapies. Current evidence demonstrates meaningful benefits extending beyond weight restoration to include significant improvements in affective symptomatology and psychosocial functioning. Current paradigms are shifting away from a single universal target toward phenotype-driven and circuit-guided strategies, using connectomics to individualize stimulation sites based on distinct clinical profiles. While emerging technologies like closed-loop systems, biomarker-driven programming, and wireless devices hold great potential to enhance therapeutic precision and safety, they still require rigorous clinical validation. Furthermore, the current literature remains constrained by small, heterogeneous cohorts and a notable scarcity of blinded, randomized controlled trials. Given its invasive nature and complex ethical dilemmas, particularly regarding surgical risks and informed consent in critically malnourished patients, DBS must strictly remain a last-resort intervention within highly

specialized settings. Ultimately, advancing DBS from an experimental approach to an established treatment will depend on clear patient classification, comprehensive outcome measures, and robust multicenter trials to confirm its long-term safety and target-specific efficacy.

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