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Deep Brain Stimulation for the Treatment of Resistant Depression: Systematic Review of the Literature

Estimulação cerebral profunda para o tratamento de depressão resistente: revisão sistemática da literatura

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Abstract

Depression is the leading cause of disability worldwide, and it is related to high suicide rates. Furthermore, a great number of patients do not respond to any of the available treatments. Deep brain stimulation (DBS), a versatile technology with expanding indications, is considered a potential treatment for resistant depression. However, in over 10 years of clinical research, its efficacy has not been completely proven. Although new trials using DBS for treatment-resistant depression keep emerging, two of the three Level I evidence-based studies recently conducted have not provided conclusive data. Methodological limitations and major biases have compromised the obtention of clearer results. In this systematic review of the literature, we intend to critically assess the clinical trials performed in this field.

Keywords
- deep brain stimulation
- treatment-resistant depression
- refractory depression

Resumo

A depressão é a maior causa de incapacitação em nível mundial, e ela está relacionada com altos índices de suicídio. Ademais, um grande número de pacientes não responde a nenhum dos tratamentos disponíveis. A estimulação cerebral profunda (ECP), uma técnica versátil com indicações em expansão, é considerada um tratamento potencial para depressão refratária. Contudo, em mais de 10 anos de pesquisas clínicas, sua eficácia ainda não foi completamente comprovada. Embora novos estudos utilizando ECP para tratamento da depressão refratária venham sendo realizados, dois dos três ensaios recentemente conduzidos baseados em evidência com Nível 1 não forneceram dados conclusivos. Limitações metodológicas e vieses importantes comprometeram a obtenção de resultados mais claros. Nesta revisão sistemática da literatura, pretendemos avaliar criticamente as pesquisas clínicas executadas nesta área.

Palavras-chave
- estimulação cerebral profunda
- depressão resistente ao tratamento
- depressão refratária

Introduction

Depression is a severe psychiatric disorder, presently recognized as the most frequent mental illness and the leading cause of disability worldwide.[1] It currently affects 260 million people (3.6% of the global population) and is 1.5 to 2 times more common in women.[2] However, multimodal treatments have often failed in up to 30% of the patients,[3] a group considered to have treatment-resistant depression (TRD),[4] which exhibits a 2-fold suicide risk.[5] Globally, depression is the 2nd cause of death among 15 to 29-year-olds,[6]

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with alarming completed suicide rates of approximately 800 thousand per year, that is, 2,191 daily deaths.

Electroconvulsive therapy (ECT) is the most effective somatic treatment for depression, since it promotes remission rates $>$ 40%.[7,8] In spite of being effective, $\sim$ 52% of the patients resistant to antidepressants (ADs) do not respond to ECT either.[9]

Deep brain stimulation (DBS) consists in modulating deep brain structures through electrodes implanted using the stereotactic technique,[10] and it has also been used for the treatment of depression. It is reversible, adjustable, and can be applied in combination with ADs. Moreover, the simultaneous use of DBS and ADs allows titration of both methods. Nonetheless, efficacy, optimal targets, and stimulation parameters (frequency, amplitude, pulse width, duration) for TRD remain unclear.[11,12] The success of DBS for the treatment of Parkinson disease (PD), dystonia, obsessive compulsive disorder (OCD), and, more recently, epilepsy, points to the versatility of this surgical procedure in clinical settings, instigating laser-focused research for TRD. Therefore, the present systematic review of the literature aimed to critically assess clinical evidence of DBS for TRD.

Historical Remarks

Depression has long been known,[13] and so has neuromodulation through electricity and invasive brain procedures, inasmuch as Hippocrates (469–399 BCE) described trepanation for the management of intracranial hypertension.[14,15] Ancient Greek doctors modulated pain with electric eels.[16] The Greek word for these fish is *narka*, meaning "relief from pain", the root of the word *narkoun*, meaning "to benumb", which, in turn, is the root of the term "narcotics".[17]

Scribonius Largus (1–50 CE) described the use of the shocks of *Torpedo nobiliana*, a species of electric ray, for headaches and gout derived chronic pain. This therapy drew the attention of Galen (130–210 CE), and this started a "torpedonism" trend described in several medical documents, including the Canon of Medicine, written by Avicenna, where this treatment was proposed for melancholy.[18–20] This mental state is related to the melancholic depressive subtype and anhedonia, a core symptom of major depressive disorder (MDD)[21] associated with the reward circuitry.[22] Accessing the brain had further indications in other parts of the world, such as in Peru, where witch doctors (ca. 1000–1250 CE) employed this procedure to release bad spirits and treat mental illnesses.[14]

More recently, ablative surgery preceded in 30 years the advent of the first psychiatric drugs, that is, antipsychotics.[23] The stereotaxy apparatus brought minimally invasive procedures, allowing the access to subcortical, deep brain structures.[24] The term psychiatric neurosurgery,[25] fitting the idea of recognized dysfunctional circuits in the brain, emerged in the 20th century.[23] A pioneer trial targeting the subgenual anterior cingulate cortex (sACC) inaugurated the modern era of neurosurgery for TRD,[26] labelled later by the main investigator in the field as "keeping an eye on a moving target".[27]

Putative Neurocircuitry and Pathophysiology of Depression

Although the taxonomy of psychiatric disorders is still incipient, knowledge of the underlying biology of depression has expanded from the concept of a disease purely correlated to limbic structures[28] to a mental disorder involving several neural networks.[29] Cortical structures thought to be implicated in depression involve several Brodmann areas (BAs), such as the dorsomedial prefrontal cortex (DMPFC), the medial prefrontal cortex (mPFC), the dorsolateral prefrontal cortex (DLPFC), the dorsal anterior cingulate cortex (dACC), the anterior cingulate cortex (ACC), the ventromedial prefrontal cortex (vmPFC), and the globus pallidus pars interna (GPI).[14,29,30] The DLPFC and the orbitofrontal cortex (OFC)[31] are connected to subcortical structures, such as the hippocampus, the amygdala nuclei, and the nucleus accumbens (NAcc).[32] The cingulate gyrus and the hippocampus connect the vmPFC to the DLPFC. Furthermore, the hippocampus is intimately linked, both anatomically and physiologically, to the hypothalamus through the fornix, an axonal bundle that inhibits the hypothalamic pituitary adrenal (HPA) axis.[32]

Neoneurogenesis in the hippocampus is stimulated by monoaminergic agonists (e.g. selective serotonin reuptake inhibitors) and brain neurotrophins (e.g. brain derived neurotrophic factor [BDNF]), and negatively modulated by stress, corticosteroids, and glutamatergic agents.[32] In patients presenting with depression, the prefrontal cortex (PFC) would fail to inhibit overactive limbic structures implying cognitive, behavioral, mood, neuroendocrinal, pain modulation, and neurotransmitter activities due to its connection to the hypothalamus and the midbrain, notably the periaqueductal gray area.[33] Rumination, suicidality, and complex symptoms suggest dysfunction of neural networks, rather than targets,[34] outreaching the domain of anatomical/structural (overactive OFC/vmPFC, ACC, hippocampus, and amygdala, and hypoactive DLPFC), molecular (increased cortisol, corticotropin-releasing hormone, proinflammatory cytokines, decreased BDNF, serotonin, and noradrenalin), or cellular alterations (neurons, neural ensemble,[35] and glia).[32,36] It is believed that a major factor, yet to be unveiled, would trigger a cyclic "short-circuiting" in susceptible individuals,[32] relying on a substrate of genetic predisposition,[32] personal history, and affective temperament.[29] That would ultimately disrupt adequate neurotransmission, neuroendocrine response, autonomic response, and cognitive function.

To date, putative DBS targets for the treatment of TRD include:

1. Subcallosal cingulate gyrus (SCg): also called subgenual cingulate gyrus, subcallosal cingulum, or SCg25 in the context of DBS TRD trials, it is the portion of the ACC lying ventrally to the corpus callosum, below its genu.[37] It corresponds primarily to BA 25, as well as to the caudal portions of BA 32 and of the inferior BA 24.[26,29,38] The converging region in the SCg implicated in the response to fluoxetine[39] was chosen as the first DBS experimental target.[35]

2. Ventral capsule/ventral striatum (VC/VS)/ventral anterior limb of the internal capsule (vALIC)/NAcc: The VC/VS comprehends a target region considered related to the pathophysiology of OCD and depression.[40] The vALIC contains the prefrontal corticopontine tract and the anterior thalamic radiation (ATR), interconnecting mPFC and cingulate gyrus with the anterior and dorsomedial thalamic nuclei,[41] both extensively connected with the cortical and subcortical limbic areas,[29,41] a functional link between the frontal lobe and the thalamus. The NAcc is a component of the VS linked to the ventral tegmental area (VTA), the amygdala, the hippocampus, the OFC, the mPFC, the motor territories of the caudate nucleus, and the GPI.[42] Moreover, the NAcc is indirectly connected to the SCg and to the mPFC, and acts as "hub", amplifying or decreasing the signals from emotion centers.[43]
3. Bed nucleus of the stria terminalis (BNST): located in the adjacencies of the VC/VS and NAcc regions, partially overlapping the VC/VS but distinct from it, it is an output pathway of the amygdala, and it regulates anxiety and threat vigilance,[44] with projections to the medial forebrain bundle (MFB) and to the NAcc.[45] The rationale for borrowing this target from OCD is that strong antidepressant effects appeared, particularly if the contacts were situated in or near the BNST.[45]
4. MFB: a white matter tract that mediates connectivity to the VTA and the NAcc, the hypothalamus (medial and lateral), the preoptic regions (lateral and medial), and the BNST. Its anatomical and functional connectivities have been described in diffusion tensor imaging studies.[46,47] The MFB hypothetically mediates positive emotions,[48] particularly through the superolateral branch of the medial forebrain bundle (slMFB), and opposes the negative emotion modulation of ATR. The VTA is a key node of the reward circuit, mostly through dopamine. Rat models for optogenetics evidenced dopamine cell firing from the VTA.[49]
5. Inferior thalamic peduncle (ITP): a fiber bundle connecting the nonspecific thalamic nuclei/dorsomedial thalamus (midline, intralaminar, and paralaminar) to the OFC. Subcaudate tractotomy includes the ITP and is classically described to treat TRD. Hypothetically, metabolic abnormalities in the frontal cortical regions are associated with depression, which could be modulated by employing DBS of the ITP.[50]
6. Lateral habenula (LHb): is a brain structure projecting to several monoaminergic brainstem nuclei, involved in the metabolism of dopamine (substantia nigra pars compacta and VTA), serotonin (dorsal and medial raphe),[51] and noradrenalin (locus coeruleus).[52–54] Augmented activation in the nucleus of the LHb has been reported in depressed patients,[55] and shown to downregulate neurotransmitters and stimulation of the HPA axis.[56]

Methods

A systematic review of the literature was carried out aiming to identify the efficacy of DBS for the treatment of TRD by two independent investigators, following the protocols of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA). The databases searched for this review were: Australian New Zealand Clinical Trials Registry (ANZCTR), ClinicalTrials.gov, Cochrane Central Register of Controlled Trials (CENTRAL), Deutschen Register Klinischer Studien (DRKS), Instituto Brasileiro de Informação em Ciência e Tecnologia (IBICT), Latin American and Caribbean Health Sciences Literature (LILACS), Medical Literature, Analysis, and Retrieval System Online (MEDLINE), Netherlands Trial Registry (NTR), Portal de Periódicos da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior do Ministério da Educação (CAPES/MEC), The Digital Library of Theses and Dissertations of the University of São Paulo (Digital Library USP), and World Health Organization International Clinical Trials Registry Platform (WHO ICTRP).

The following descriptors were used alone and with Boolean operators: *depression*, *treatment-resistant depression*, *treatment-refractory depression*, *deep brain stimulation*,

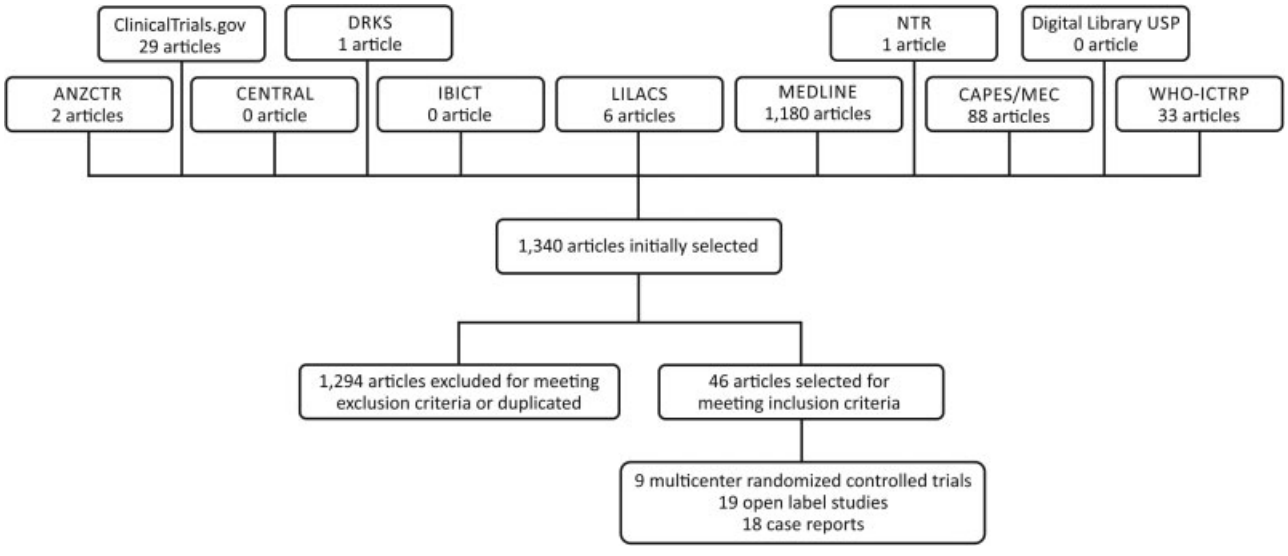

Fig. 1 Data collected during this systematic literature review.

Table 1 Articles selected in this systematic review

Target structure	Design	n	Follow-up	Stimulation parameters				Response/remission rates		Comment	Reference
				Electrode type	Amplitude	Frequency (Hz)	Pulse width (μs)	Response (%)	Remission (%)		
SCg	OLS	6	6 months	BL, MP	4.0 V	130	60	66	50	Reduction in local cerebral blood flow and changes in downstream limbic and cortical sites; 35% improvement in the Clinical Global Impressions Scale	Mayberg et al[26]
SCg	OLS	20	6 months	BL, MP	3.5–5.0 V	130	90	55	33	Mood improvements within 1 month lasting for at least 1 year in TRD patients	Lozano et al[57]
SCg	OLS	6	12 months	MP	3.0–4.0 V	130	60	66	NA	Improves cognitive functions with time without producing positive effects on mood behavior	McNeely et al[58]
SCg	CR	1	16 months	BL, BP	5.0 V	150	210	NA	NA	Reduced amygdalar-thalamic and amygdalar-SCg connections could be a contraindication to DBS for depression	McNab et al[59]
SCg	CR	1	12 months	BL, BP	3.6 V	135	90	100	0	Decrease in relapse rate and maintenance therapy of electroconvulsive therapy	Puigdemont et al[60]
SCg	CR	1	18 months	UL, MP	4.5 V	120	90	NA	NA	Suggests the preeminence of right hemisphere in regulation of depression	Guinjoan et al[61]
SCg	CR	1	6 months	BL, MP	6.0 mA	130	91	NA	NA	Report a marked and sustained antidepressant response	Holtzheimer et al[62]
SCg	OLS	20	36–72 months	BL, MP	3.5–5.0 V	130	90	64.3	42.9–50	Follow-up for long run DBS remains a safe and effective treatment for TRD patients	Kennedy et al[63]
SCg	OLS	17	24 months	BL, MP	4.0-8.0 mA	130	91	92	58	No patient achieving remission experienced a spontaneous depressive relapse and supported the long-term safety	Holtzheimer et al[64]
SCg	OLS	12	4–24 weeks	BL, MP	6.0–8.0 V	130	90	67.8	NA	FTC can serve as early biomarker for screening DBS effect on depression severity	Broadway et al[65]
SCg	OLS	8	12 months	BL, BP	3.6 V	135	90	62.5	50	Potential utility of this target to treat TRD patients	Puigdemont et al[66]
SCg	CR	1	6 months	BL, MP	2.5 V	130	90	NA	NA	Monoamine oxidase inhibitor potentiates the effects of DBS	Hamani et al[67]
SCg	OLS	21	12 months	BL, MP	3.5–5.0 V	110–140	65–182	29	NA	Reduction in depressive symptomatology and disease severity in patients	Lozano et al[68]
SCg	OLS	6	24–36 weeks	BL, MP	2.5–10.0 V	130	90	33.3	33.3	Exerts moderate acute and chronic antidepressant effects	Merkl et al[69]
SCg	OLS	4	36 weeks	BL, MP	0–10.5 V	2–185	60–450	50	50	Demonstrates association between longer pulse widths (270–450 μs) and reductions in HDRS scores	Ramasubbu et al[70]
SCg	OLS	7	1 months after 6 months of DBS	BL, MP	4.0–8.0 mA	130	91	92	NA	Reduction in negative words endorsed as self-descriptive associated with a reduction in depression severity	Hilimire et al[71]
SCg	OLS	7	9 months	BL, MP	3.5–5.0 V	135	120–210	NA	NA	Inactive stimulation decreases metabolism in Brodmann area 24/6 and putamen with respect to active stimulation	Martín-Blanco et a.[72]

Table 1 (*Continued*)

Target structure	Design	n	Follow-up	Stimulation parameters				Response/remission rates		Comment	Reference
				Electrode type	Amplitude	Frequency (Hz)	Pulse width (μs)	Response (%)	Remission (%)		
SCg	RCT	5	6 months	BL, MP	3.5–5.0 V	130–135	120–240	NA	NA	Continuous electrical stimulation is required to maintain therapeutic effects in TRD patients	Puigdemont et al[73]
SCg	OLS	8	12 months	BL, BP	3.6 V	135	90	NA	NA	Improvement in memory performance without worsening of cognitive function after chronic stimulation	Serra-Blasco et al[74]
SCg	OLS	4	12 months	BL, MP	2.0–5.0 V	130	90–450	50	NA	SCg-DBS for TRD may be associated with decreased levels of serum brain derived neutrophic factor	Ramasubbu et al[75]
SCg	OLS	5	24 months	BL, MP	5.0 V	130	90	79	20	DBS of the bilateral posterior gyrus rectus found effective in one patient as compared with SCg-DBS	Accolla et al[76]
SCg	CR	1	6 months	BL, MP	4.2 V	130	90	NA	NA	DBS targeting the limbic system may increase the risk of seizure in depressive patient	Richieri et al[77]
SCg	RCT	90	24 months	BL, MP	4.0–8.0 mA	130	91	20% (active) 17% (control)	5% (active) 7% (control)	No statistically significant antidepressant effects after 6 months of active versus sham stimulation in randomized, double-blind, sham-controlled trial	Holtzheimer et al[78]
SCg	OLS	11	12 months	BL, MP	6.0–8.0 mA	130	91	81.8	54	Tractography-based surgical targeting to reduce variability and increases number of responders	Riva-Posse et al[79]
SCg	RCT	9	13 months	BL, MP	4.0–8.0 mA	20 or 130	91	23.1	NA	High-frequency stimulation exhibits superior antidepressant effects in long-term study	Eitan et al[80]
SCg	RCT	8	28 months	BL, MP	2.5–10.0 V	130	90	33.3	33	Double-blind assessment fails to show significant antidepressant effect between sham and active	Merkl et al[81]
NAcc	CR	1	12 months	BL, MP	3.0–4.5 V	130	90	NA	NA	Extremely effective treatment of alcohol dependency using DBS of NAcc and improvement of depression	Kuhn et al[82]
NAcc/caudate nucleus VC/VS	OLS	15	12 months	BL, MP	6.7 V	127	113	53.3	40	Significant improvements in depressive symptoms	Malone et al[83]
NAcc/caudate nucleus VC/VS	OLS	17	14–67 months	BL, MP	2.5–8.0 V	100–130	NA	71	35	Sustain improvements across multiple scales of depression, anxiety and global function in TRD patients	Malone et al[84]
NAcc/caudate nucleus VC/VS	CR	1	48 months	MP	6.0 V	130	120	NA	NA	DBS might compensate for reward deficits and reduce smoking	Strong et al[85]
NAcc/caudate nucleus VC/VS	OLS	6	12 months	BL, MP	4.0–8.0 V	130	60	NA	NA	NAcc is a key structure within the cortico striatal loop in the pathophysiology of TRD	Millet et al[86]
NAcc/caudate nucleus VC/VS	RCT	30	16 weeks	BL, MP	8.0 V	NA	90–210	23.3 (active) 20 (control)	200	Double-blind RCT VC/VS-DBS is not an efficacious therapy for TRD patients	Dougherty et al[15]
NAcc/caudate nucleus	CR	1	30 months	BL, MP	4.0–6.0 V	130	90	NA	NA	Acute and reproducible improvements of mood, related to DBS of the NAcc	Giordana et al[87]
vALIC	RCT	25	52 weeks	BL	2.5–6.0 V	130–180	90	40.0	20.0	Double-blind RCT, a significant decrease of depressive symptoms in 10 of 25 patients	Bergfeld et al[88]

(*Continued*)

Table 1 (*Continued*)

Target structure	Design	n	Follow-up	Stimulation parameters				Response/remission rates		Comment	Reference
				Electrode type	Amplitude	Frequency (Hz)	Pulse width (μs)	Response (%)	Remission (%)		
vALIC	RCT	25	52 weeks	BL	2.5–6.0 V	130–180	90	40.0	20.0	No lasting positive or negative impact on cognition in TRD patients	Bergfeld et al[89]
vALIC/BNST and ITP	OLS	7	3–8 years	BL	NA	NA	NA	71.4	28.5	Stimulation of both targets decreases depressive symptoms, but six out of seven patients preferred vALIC/BNST stimulation versus ITP-DBS	Raymaekers et al[90]
MFB	OLS	7	12–33 weeks	BL, BP	2.0–3.0 V	130	60	86	57.1	Rapid onset of antidepressant efficacy and a higher proportion of the population responded	Schlaepfer et al[91]
MFB	OLS	8	12–48 months	BL, BP	2.0–3.0 V	130	60	75	50	Long-term results suggest acute and sustained antidepressant effect	Bewernick et al[92]
MFB/BNST	CR	1	24 months	BL, BP	2.8–3.0 V	130	60	NA	NA	Blurred vision problem occurred after 10 months of DBS; therefore, patient reoperated for other brain region after 2 years	Blomstedt et al[44]
LHb	CR	1	15 months	NA	10.5 V	NA	NA	NA	NA	Shows a sustained full remission of depressive symptoms in TRD patients	Sartorius et al[56]
ITP	CR	1	18 months	BP	3.0–5.0 V	130	450	NA	100	Produces antidepressant response as reflected by decrease in HDRS scores, without any potential side effects	Jiménez et al[93]
ITP	CR	1	3 years	BP	3.0–5.0 V	130	450	85.71	100	HDRS score changed from 42 to 6	Jiménez et al[50]
VCN	CR	1	15 months	BL	2.0–4.0 V	130	90–120	NA	NA	Deep brain stimulation of the ventral caudate nucleus markedly reduced this patient's symptoms of OCD and major depression and produced delayed onset of the alleviation of obsessional effects	Aouizerate et al[94]
GPI	CR	1	18 months	BL, MP	3.5–3.8 V	130	90	NA	NA	DBS at different targets located within this network, including GPI, could lead to a modulation of mood	Kosel et al[95]
BNST	OLS	5	Between 18 and 24 months	BL, MP	1.0–7.0 V	130	120–240	NA	NA	DBS applied to the BNST as therapeutic potential in patients with highly refractory depression	Fitzgerald et al[96]
slMFB	OLS	24	Between 12 and 33 weeks	BL	NA	NA	NA	85	57	The medial forebrain bundle is an important structure of reward and motivation. The slMFB emerges as a potential region for the treatment of major depression with DBS	Coenen et al[97]

Abbreviations: BL, bilateral; BNST, bed nucleus of the stria terminalis; BP, bipolar; CR, case report; DBS, deep brain stimulation; FTC, frontal theta cordance; GPI, globus pallidus pars interna; HDRS, Hamilton Depression Rating Scale; ITP, Inferior thalamic peduncle; LHb, lateral habenula; MP, monopolar; NA, not available; NAcc, nucleus accumbens; MFB, medial forebrain bundle; mo, month/s; OLS, open label study; RCT, multicenter randomized controlled trial; SCg, subcallosal cingulate gyrus; slMFB, superolateral branch of the medial forebrain bundle; TRD, treatment-resistant depression; UL, unilateral; vALIC, ventral anterior limb of the internal capsule; VCN, ventral caudate nucleus; VC/VS, ventral capsule/ventral striatum.

DBS, *neurofunctional surgery*, *electrode implantation*, *neurostimulation*, *neuromodulation*, and *psychiatric surgery*, and their equivalents in Portuguese, Spanish, German, French, Dutch, and Czech. The terms were searched in all fields of the databases.

For the selection of the studies, the following inclusion criteria were adopted: 1. studies correlating TRD and DBS as a treatment strategy; 2. studies published until September 2018; 3. publications in English, Portuguese, Spanish, German, French, Dutch, and Czech. 4. human experimental trials.

The exclusion criteria chosen for the present review were: 1. duplicate publications; 2. studies involving animals; 3. studies involving the ethical and existential implications of DBS; 4. editorials, comments of the authors, and debates; 5. studies addressing depression secondary to any other diseases; 6. studies reporting any neurosurgical interventions other than DBS.

Articles with short- and long-term outcomes of the same trial published separately were both included, because some featured new patients and/or novel stimulation strategies. Official documents released by relevant societies and references used in experimental articles were also examined. Subsequently, the results were manually reviewed and selected for analysis.

Results

A total of 46 papers were selected for the present systematic review, including 9 multicenter randomized controlled trials (RCTs), 19 open label studies, and 18 case reports (►**Fig. 1**, ►**Table 1**). The targets employed were the BNST, the GPI, the ITP, the LHb, the MFB, the NAcc, the SCg, the slMFB, the vALIC, the ventral caudate nucleus (VCN), and the VC/VS.

A double-blind multisite RCT (20 institutions), known as the Brodmann Area 25 Deep Brain Neuromodulation (BROADEN) trial, targeting the SCg and involving 90 participants, has been the largest psychiatric DBS study so far. Response to treatment was defined as a decrease $\geq$ 40% in the Montgomery-Åsberg Depression Rating Scale (MADRS) score from baseline and no worsening in the Global Assessment of Functioning (GAF) score. The DBS parameters were adjusted using an algorithm, and the concomitant use of ADs was allowed as long as the doses remained steady. Patients with chronic, unremitting depression were implanted and randomly assigned to 6 months of active or sham DBS, followed by 6 months of open-label SCg DBS. Both groups exhibited overall improvement on daily function (average of 132.2%), 92% of the patients reached a MADRS decrease from baseline of at least 50%, and 58% of them had complete remission.[78]

However, during the double-blind sham-controlled phase (12 patients with active versus 5 with sham DBS), the sham response rate was 17%, but no statistically significant difference was found in the responses of both groups. No psychiatric or neuropsychological adverse events (AEs) were reported at the 6- or 12-month follow-ups. Major AEs included suicidality (3/17), with 2 suicides in the control group during the 6-month open-label phase, anxiety (5/17), infection (5/17), system malfunction (3/17), and worsening of the depression (2/17).[78]

During the long-term open-label follow-up at 12, 18, and 24 months, the responses were 29%, 53%, and 49%, respectively. Of the 30 subjects in this phase, 26 decided to continue with DBS stimulation. A futility analysis was performed when approximately half of the patients received active DBS, completing the double-blind phase, indicating that the study had a 17% chance of success if continued. Although at the given timepoint this number did not meet the definition for futility ($\geq$ 10% chance of success), the study was halted.[78]

The rationale of targeting the SCg started in a pioneer study that included six patients aiming to access the feasibility and safety of DBS modulation of the SCg and of the adjacent white matter. A decrease $\geq$ 50% in the 17-item Hamilton Depression Rating Scale (HDRS-17) was considered a response to treatment. Response and remission rates at the 1- and 6-month follow-ups were 35%, 10%, 60%, and 35%, respectively.[26]

Neuropsychological analyses revealed that DBS was also effective to improve self-negative bias.[71] Neuroimaging evidenced metabolic changes, and a neurocognitive assessment in six patients proved the procedure to be safe.[58]

A 12-month follow-up incorporated an additional 14 patients to this cohort, and adjustable stimulation parameters were based on the presence of acute behavioral effects. The benefits were maintained and no permanent AEs occurred.[57] The extended follow-up showed average response rates of 62.5%, 46.2%, 75%, and 64.3% after 1, 2, 3, and 3 to 6 years, respectively. Overall, AEs were transient, and the most frequent was suicidality (3/20), with a confirmed suicide at 35 months and an attempted suicide at 75 months. Also, worsening of the depression (3/20), infection (3/20), and 1 case of perioperative seizure were registered.[63] Despite the initial good response, 1 patient from this series relapsed 4 years later; nonetheless, the use of tranylcypromine, a monoamine oxidase inhibitor (MAOI), along with DBS decreased the MADRS score by 60% after 4 months.[67]

Another case study from this series presented transient oscillation of response and important depressive episodes, one of them related to battery depletion. However, the patient was responsive to medication adjustments and obtained an overall sustained response.[62]

Investigators replicated the design of SCg DBS in a multicenter approach involving 21 patients during 12 months, but employing a different stimulation device. Setting the response criterium at $\geq$ 50% decrease in the HDRS-17, the results were 57%, 48%, and 29% at the 1-, 6-, and 12-month follow-ups, respectively. After 12 months of DBS, establishing the response criterium at $\geq$ 40%, total responders increased to 62%, which was attributed to amelioration in disease severity. Major AEs were nausea/vomiting and suicidality (2/21).[68]

The same system was also investigated in a cohort study with a sham-controlled design including 10 unipolar TRD individuals and 7 bipolar subtype II treatment-resistant

patients. At the 2-year endpoint, the response was 92%, whereas the remission was 58%. Two suicide attempts were reported, an MDD remitter at 2 years, and a bipolar patient at 54 months of follow-up.[64]

In a pilot study, baseline frontal theta cordance (FTC) appeared as a biomarker for predicting 6-month clinical response to SCg DBS for TRD. In addition to that, lower FTC at baseline and higher FTC after 4 weeks were predictors of lower depression severity scores at the 24-week follow-up.[65]

A multicenter double-blind randomized crossover of 13 months was carried out with 9 MDD patients resistant to treatment to evaluate the effects of high (130 Hz) vs low (20 Hz) frequency BA 25 DBS. Response ($\geq$ 40% MADRS) was achieved by 4/9 patients, with similar improvements in high and low frequency stimulation groups after 6 months. In the second period of the trial, the high frequency group showed higher improvement regarding the response criteria.[80]

An uncontrolled double-blind (delayed versus non-delayed stimulation onset) study included five patients with TRD and one with bipolar affective disorder type I who underwent SCg DBS. Two attained remission (HDRS-24 $\geq$ 10) at 24 and 36 months, with no AEs due to acute high intensity stimulation ($>$ 10 V). The main outcome was depression severity assessed using the HDRS-24, and the secondary outcome parameters were MADRS and Beck Depression Inventory (BDI) scores. Acute 24-hour stimulation caused moderate decreases in all the scales. Between 24 and 36 weeks, 2 patients were remitters and 4 were non-responders.[69]

Another report by the same group included participants in the aforementioned cohort, encompassing seven patients with TRD and one with bipolar affective disorder type I. The response rate was 51%, and 2 patients achieved remission (33.3%) at the 28-month and 4-year follow-ups. No statistical differences were found between different onset groups.[81]

A diffusion tensor imaging study on this same series found that the only responder had the contacts located bilaterally in the posterior gyrus rectus (BA 14). This displayed strong connectivity between the stimulated regions and the mPFC.[76]

A Spanish group initiated a study in 2008 performing SCg DBS in 8 TRD patients following an open-label design.[66] In a preliminary result, 1 patient from this series relapsed at 4 months and presented with psychotic symptoms. The DBS system was turned off and, after nine sessions of frontal ECT, when DBS was turned on again, the patient successfully reached remission.[60]

After 1 year of stimulation, they obtained a response of 62.5% in the HDRS-17 and remission in 50% of the cases, with improvement in social function and neurocognitive safety, as well as benefit for the memory.[74] Except for a suicide attempt in the group of nonresponder patients, no other serious AEs occurred.

Subsequently, stimulation was ceased in the 5 previous responders under a double-blind randomized design, resulting in sustained remission (2/5), relapse (2/5), and progressive worsening without relapse (1/5) in their 3-month sham protocol.[73] Simultaneously, remitters underwent double-blind sham stimulation.[72] Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) scans evidenced metabolism decreases in the dACC (BA 24), in the premotor region (BA 6), and in the putamen, not followed by changes in HDRS-17 scores.

In a pilot cohort, four patients with TRD underwent SCg DBS surgical procedure. After that, the frequency and pulse widths were randomly changed weekly. Evaluations of changes in mood and depression were performed using a visual analogue scale (VAS) and the HDRS-17. Longer pulse widths (270–450 µs) were related to short-term clinical improvement (HDRS-17) in 3 participants and to positive mood response (according to results indicated in the VAS) in all of the patients. No associations between DBS frequency and mood or clinical response were found. After 6 months of the open-label postoptimization phase, 2 patients (50%) showed clinical response, and 1 showed partial response.[70]

The same group of researchers carried out a double-blind trial including the same patients. They found that the stimulation was related to decreases in serum BDNF concentration compared to pre-DBS baseline.[75]

In an open-label cohort of 11 patients, the fibers activated were proven to be more related to the response than the site of the implanting (mainly projections to BA 10), using whole brain activation volume tractography. At 6 months, 8 patients had an increase in current from 6 to 8 mA. Response, considered as $\geq$ 50% decrease in the HDRS-17, was reached by 72.7% of the sample at 6 months, and by 81.8% at 12 months. Remission criterium (HDRS-17 $\geq$ 7) was attained by 6 patients, and 2 never met it. One of them had minimal variation in the HDRS-17, whereas the other achieved 40% decrease in this score at 12 months. A whole brain activation volume tractography and the common probabilistic tract map generated for all subjects (responders and nonresponders) at 6 months featured the inclusion of the forceps minor, the uncinate fasciculus, the frontostriatal fibers, and of the cingulum bundle.[79]

In an Argentinian case report, patient-blind unilateral stimulation produced rapid mood worsening on the left hemisphere. Most electrodes placed in the SCg and in the adjacent white matter produced stimulation related to acute onset of orthostatic hypotension, both at the postoperative testing and at a the 6-month assessment (the contacts were permanently kept turned off). No alterations were observed in the opposite hemisphere.[61]

In a French case report, a patient with long-term MDD and TRD, who had undergone extensive unilateral ECT that led to cognitive deficits, presented with late postoperative seizures as a possible side effect, displayed at standard stimulation parameters (90 µs, 130 Hz, 4.2 V). Most likely, DBS has revealed a previously existing temporal lobe epilepsy, although the participant had no individual or family history of convulsions. The patient was responsive to treatment.[77]

A study from England reported a patient with bipolar disorder and treatment resistance, with an infarct in the right thalamus (dorsomedial nucleus) that produced severe depressive symptoms within hours and TRD at 9 months

(BDI-II: 41; Beck Anxiety Inventory: 26). DBS of sACC at high frequency (> 150 Hz) did not produce any clinical effects, probably due to the reduction in structural connectivity from the sACC back to the amygdala on the right side. Projection to frontal areas was not clearly differentially disrupted. The patient was followed-up 1 year after the procedure, when the battery of the DBS was running low, but cessation of stimulation had no effect. This patient died in his sleep 16 months after the DBS surgery.[59]

In a randomized clinical trial, 25 patients in the Netherlands underwent DBS of the vALIC for TRD. An open-label optimization trial was conducted for 52 weeks followed by a sham-controlled double-blind multisite crossover RCT. The response criterium was $\geq$ 50% decrease in the MADRS from baseline to the 16th week of the blind phase, while the remission criterium was HDRS-17 $\geq$ 7 at the 2nd assessment. At the end of the optimization phase, 10 patients were responders and 15, non-responders. In the crossover phase, 16 of these patients – 9 responders and 7 non-responders – participated. During active DBS, the HDRS-17 scores were significantly lower (13.6). Adverse events included: suicide attempts (5), increased suicidal ideation (2), suicide (1), euthanasia (1), and surgery-related extreme nausea (1) that interrupted the operation, which was performed 2 weeks later with success. Battery depletion was suspected in two patients. Active DBS had significant antidepressant effect in 10 out of 25 TRD patients compared with sham DBS, classified as responders ($\geq$ 50% decrease) and partial responders ($\geq$ 25 but < 50% decrease).[88] No permanent impact (either positive or negative) on cognition was observed in a posterior study with the same sample.[89]

A double-blind crossover trial with seven TRD patients investigated the stimulation in either the anterior limb of the internal capsule/BNST or in the ITP. All of the patients participated in the follow-ups for at least 3 years, but some were followed-up up to 8 years after the procedure. A significant average decrease in the HDRS-17 score (61%) was attained by 5 responders and 2 remitters. Only one participant preferred ITP stimulation. Most patients reported fluctuant worsening of depressive symptoms and suicide ideation, and the patient that preferred ITP stimulation presented with transient extrapyramidal-like AEs (hypomimia, micrographia, hesitant walking, and less fluent movement). Two patients had a suicide attempt history prior to implanting and committed suicide at 39 and 80 months after the procedure, respectively.[90]

A 16-week randomized blind sham-controlled trial of DBS, known as RECLAIMTM, targeted the VC/VS in 30 patients with TRD, with a subsequent open-label phase. The response, set as a decrease $\geq$ 50% in the MADRS score, was 20%, 26.7%, and 23.3% at the 12-, 18-, and 24-month follow-ups, respectively. However, no significant differences in response rates were found between the active and sham treatments, or changes in the MADRS scores at the end of the 16-week controlled phase. A total of 71 serious AEs were recorded for 22 patients, and the most frequent were worsening of the depression (8), suicidal ideation (5 in the active and 3 in the sham group), suicide attempts (4), and a completed suicide of a nonresponder who ceased stimulation while preparing for explanting. During the blind phase, the most frequent psychiatric AEs in the active group were worsening depression and insomnia.[10]

In a multisite open-label investigation, 14 MDD patients and 1 bipolar (subtype not specified), 13 of which had failed both AD and ECT, and 2 who were also resistant to vagus nerve stimulation, were treated with DBS of the VC/VS. The response rates were 40% and 53.3% in the HDRS, and 46.7% and 53.3% in the MADRS, and the remission rates were 20% and 40% in the HDRS, and 26.6% and 33.3% in the MADRS at the 6-month and last follow-ups, respectively.[83]

A following study enrolled two additional patients, both AD- and ECT-resistant, who also underwent DBS of the VC/VS. Response was attained by 53 and 71% of the sample ($n = 17$) at the 3-month and last follow-ups, respectively. Interestingly, 35% of the patients continued in remission (MADRS score $\leq$ 10) at the last follow-up, and a remarkable reduction in suicidality occurred at 1 month and persisted in the next 12 months ($p \geq 0.001$). Serious AEs related to DBS included: anxiety, autonomic effects, mood changes, and paresthesia. However, they were transient and, after adjusting the stimulation parameters, all of them disappeared.[84]

One of the patients of the aforementioned multisite open-label investigation,[83] who had been a remitter for 4 years, experienced increase in smoking (50–200%) and concurrent worsening depressive symptoms in 3 different occasions, all related to interruption of DBS caused by battery depletion. Nevertheless, once DBS stimulation was restarted, the smoking pattern reverted to baseline and the depressive symptoms decreased.[85]

A patient with TRD, comorbid bulimia, and borderline personality disorder showed improvement in depression (as per results in the HDRS score) after initial placement of electrodes in the ITP without electrical stimulation, probably because of a microlesion effect. After a phase of stimulation (130 Hz, 0.45 µs, 2.5 V), it was discontinued in a double-blind fashion, and the HDRS score did not return to preoperative levels, remaining between 2 and 8. This patient was later explanted and remained in remission up to 7 years.[93]

A patient with a history of treatment-resistant OCD, recurrent MDD, and unsuccessful cognitive-behavioral therapy was referred to DBS of the VCN. Nonetheless, several AD strategies improved the depressive symptoms prior to the procedure. In the first 3 months of stimulation, depressive symptoms progressively worsened, but at the 6-month follow-up, the patient achieved MDD remission (HDRS = 7; Hamilton Anxiety Rating Scale = 10), which was sustained until the end point, 15 months after the surgery. The patient also attained OCD remission, but more slowly, markedly between the 12- and 15-month follow-up, with progressive increase in Global Assessment of Functioning (GAF) scores. No negative neuropsychological effects were noted.[94]

A group of 10 patients presenting with very severe forms of TRD, refractory to ADs, psychotherapy, and ECT, underwent DBS of the NAcc. Response (50% decrease in the HDRS-28) was reached by 50% of the patients at the 12-month

follow-up, and 3 participants achieved remission (HDRS-28 $\leq$ 10) for a period of 1 month.[98]

The long-term effects of DBS of the NAcc were assessed in the same group of participants described above[98,99] and in an additional patient enrolled posteriorly. Follow-ups were carried out 12 months, 24 months, and 4 years after the procedure with 11, 10, and 5 patients, respectively. Adverse events related to DBS were transient. By the 12-month follow-up, 1 patient had committed suicide and 1 had attempted suicide, both nonresponders to the surgery. After 12 months, 45% of the participants were considered responders, and did not show worsening symptoms at the 4-year follow-up.[100]

In a double-blind placebo-controlled trial, three patients with extreme forms of TRD (resistant to psychotherapy, ADs, and ECT) received DBS implantation in the NAcc. The voltage ranged from 0 to 4 V in 1-V steps, in a double-blind manner. At each step, HDRS-24 and MADRS were reapplied, and a negative correlation was observed for both scores in all of the patients. No relevant AEs occurred. Single items of both scales, often used to assess aspects of anhedonia, were verified, but no significant changes were found, in spite of clear clinical changes in anhedonia. Metabolic imaging displayed activations in bilateral VS (including NAcc), bilateral DLPFC and DMPFC, bilateral cingulate cortex, and bilateral amygdala, simultaneously with deactivations in the vmPFC, the ventrolateral PFC, the dorsal caudate nucleus, and in the thalamus.[43]

In a case report of a patient with a 20-year history of MDD, agoraphobia, and alcohol dependence for the previous 10 years, DBS of the NAcc produced acute pleasure. In 12 months, the patient became an occasional drinker. However, decreases in depression or anxiety were minimal.[82]

A depressed woman, with a 46-year history of severe MDD and 9 years of TRD, failed to respond to ADs and ECT. Her depressive episode at the intervention included delusions of guilt, mutism, and pronounced anxiety, with HDRS-21 rates around 45. Deep brain stimulation of the LHb produced full remission of depressive symptoms within a period of 4 months. The patient relapsed, and the voltage was increased, leading to stable remission. One accidental switch off caused an additional relapse, but it was transient.[56]

The superolateral branch of the medial forebrain bundle (slMFB) was targeted based on a neuroanatomical and functional hypothesis using new fiber tracking techniques: two opposing systems, the ATR and the slMFB, were anatomically described and assumed to mediate negative (ATR) and positive (slMFB) emotions.[48]

A decrease $\geq$ 50% in the HDRS was achieved by 6 patients, and 4 reached remission 12 months after DBS of the slMFB. Moreover, long-stable effects were reported up to 4 years after the procedure. The main AEs were oculomotor effects (blurred and double vision), responsive to reduction of amplitude of stimulation. Discontinuation of a nonresponder at 18 months decreased the score, but not exceeding baseline, and explantation kept remission until 12 months.[92]

The same design used above was replicated by the Houston group using deterministic tractography. After 52 weeks, 4 out of the 5 remaining patients that ended the trial had a decrease $>$ 70% in the MADRS scores compared to baseline. The modulated fiber tracts revealed significant common orbitofrontal connectivity in all of the responders. Neuropsychological testing verified safety, and ^{18}F-FDG-PET cerebral metabolism evaluations at baseline and at 52 weeks showed minimal changes. Increased depression was associated with battery depletion in four patients, and accidental deactivation in three.[101]

Evaluation of the tractographies showed that responders typically have their active contacts exclusively situated in the center of the triangle, with no contact with the nuclear environment. Thus, every treatment should be based on individual slMFB (tractography) geometry.[97]

A case report presented a patient with TRD and nervous anorexia who was treated with DBS and showed great response. However, after 10 months, she presented blurred vision and was reoperated with electrodes placed on the BNST. At 12 months, the results were: MADRS = 13; HDRS = 6; HAM-A = 5.[44]

A pilot open-label series included five female patients resistant to AD and ECT, who underwent DBS of BNST. Clinical response was observed by means of various assessments rather than by a stated definition. Stimulation induced: 1 remission at 6 months; 1 response and 1 remission at 12 months; 3 remissions at the last follow-up, 2 of them stable (MDRS of 1 and 3) up to 6 years; and an eventual reoccurrence and restoring of remission after battery replacement. One patient had explantation of DBS, which was reimplanted in the sACC, but, by the end of the second treatment, she committed suicide. A significant increase in quality of life and depression scores, as well as neurocognitive stability, were attained. Two suicide attempts, apparently not related to stimulation, occurred during the trial, and one of these patients reached remission later. Transient insomnia was the most common AE related to increase in stimulation.[96]

An anecdotal case report targeted the GPI for TRD and severe tardive dyskinesia (TD) in a patient with a history of failing to over 60 psychotropic drugs, who had been treated with typical and atypical neuroleptics, and developed severe neuroleptic-induced TD. The patient attained a $\geq$ 50% decrease in the HDRS 18 months after DBS implantation. The HDRS score dropped from 26 at baseline preoperatively to 13 at the 18-month follow-up, whereas the Burke-Fahn-Marsden Dystonia Rating Scale score decreased from 27 to 17.5 (35%).[95]

A preliminary study of four patients targeted the NAcc and, in the event of failure, the caudate nucleus, in a limbic vs cognitive fashion. The primary and secondary outcomes were $\geq$ 50% HDRS and remission, defined as HDRS = 7 after 4 months, respectively. Stimulation of the NAcc was performed from the 1st to the 5th month. At month 5, nonresponders underwent stimulation of the caudate target until month 9, followed by a 6-month extension phase (up to month 15), with adaptable parameters and concomitant treatments. A significant improvement in mood was achieved by 3 patients, with lower HDRS scores at the end

of the 15 months. Following the start of stimulation, benefit was obtained at the extension phase, with open parameters. One patient did not meet response criteria at month 5, but NAcc stimulation was kept due to clinical perception of improvement. Furthermore, aripiprazole was added at month 11, leading the patient to a stable improvement until reaching response.[86]

A case report featured amplitude and dynamics of the mood changes, systematically quantified using the HDRS-17, in a nonresponder after DBS of the Nacc. The patient rapidly achieved and sustained remission 11 months after increasing the voltage of the most distal contact of each electrode located in the NAcc to 5V. Some worsening due to battery depletion was also reported.[87]

Discussion

Deep brain stimulation research for the treatment of patients with TRD has been marked by amelioration[102] contrasting with inconsistent results of the three largest multicenter RCTs.[10,78,88] Therefore, it could be inferred that DBS is not effective for TRD, at least in the way it has been currently performed and assessed. Aiming to understand these controversial outcomes, we tried and dissected factors that may be impacting trials and leading to fails.

On the one hand, little can be said about the efficacy of SCg as a DBS target based exclusively on the interrupted BROADEN trial.[78] On the other hand, open-label studies focused on optimizing targets, as well as on mapping response patterns, patient subtypes, and connectomics, obtaining exceptional results.[79]

The largest study followed the standard paradigm focusing on the Food and Drug Administration (FDA) validation at 6 months, with restricted parameters, that is, the surgical intervention was adequately isolated by not allowing post-surgical support, psychological or pharmacological treatment before the trial, and potentially reduced the chance of patient recovery at the short endpoint of the futility analysis.[78]

A significant increase in response after SCg DBS was observed in the open-label original series from the 1st to the 3rd year, since the average response rose from 62.5 to 75%.[62,63] In sum, BROADEN could have been more thorough in terms of duration, adjustment of parameters, and optimization phase.

Considering open-label studies and case reports, the SCg remains promising, although BA 24 is probably the key area underlying the effects.[61] In addition to this, unilateral vs bilateral hemisphere stimulation matters persist.[49]

The blind-treatment phase of the RECLAIM™ trial was probably too short and avoided high stimulation parameters to preserve blinding and prevent AEs. No significant differences were found during the sham phase, contrasting with the findings of a previous phase of the trial, in which 36% of the patients achieved response in 1 year and 92% in 2 years.[64]

The solely good performance of the vALIC large RCT highlights some particular characteristics, such as: a smaller sample; a 52-week open-label parameter optimization phase; stratification of response (partial response if 25–50% decrease in symptoms); and the intent-to-treat analyses to discriminate response from non-response.[88]

The case reports corroborated the severity of TRD in highly resistant patients and related complications such as TD[95] and cognitive deficit after years of ECT.[77] They also described strategies biased by the small casuistic, which were nevertheless life-changing in the context they were proposed, that is, contraindication to ECT,[60] MAOI restoring DBS response,[67] and substance dependance.[82] After all, these are common exclusion criteria in studies, but in the case reports selected, the patients presenting with them were treated using DBS.

Heterogeneity inherent to psychiatric neurosurgery occurs within trials in multiple domains: selected patients, pretrial treatments, trial designs (open label, crossover, and parallel), optimization of parameters (if allowed and duration), surgical technique, individual variability due to structural and functional connectivity,[102] scales to define and monitor response and remission.

Major depressive disorder is a bureaucratic diagnosis, based on clinically-derived, however, arbitrary criteria. A mathematical analysis showed that 227 different combinations of depressive symptoms[103] can fulfill the DSM-5 diagnostic criteria for MDD.[21] Given that some items are multiple or alternative symptoms (i.e., insomnia or hypersomnia), if each component symptom is considered separately, 14,528 combinations are possible.[103]

Lack of a global definition of TRD potentially adds a second level of phenotype heterogeneity labelled together with the population of interest; therefore, the inclusion criteria consistently diverge between studies. It is possible that by targeting DBS for TRD, distinct phenotypes/subtypes of this mental condition fall under the same label. This way, they have probably been addressed using the same circuits and the effects vary according to the deficits. Stage 5 treatment-resistant depression (irresponsiveness to three ADs and ECT)[104] seems the most adequate definition of TRD for trial purposes.

The definition of response varies, but it is frequently set as a decrease by 50% in depressive symptoms assessed using HDRS and MADRS.[105] Even though the former has different versions and numbers of items (i.e. HDRS-17, -21, -24, and -28), the exact scale is not always mentioned in the studies.[44]

The fallacy of thresholds, a methodological bias explored for AD trials with TRD patients, showed that scales lose statistical power when used to compare treatment against placebo.[106] By doing so, researchers assume that sensibility and specificity are the same in both groups, responders in the placebo group might fit "intuitive definitions" of response less well than patients under treatment, and patients in the adjacencies of cutoff scores of scales are often clinically indistinguishable.[107]

For Parkinson disease (PD), the Unified Parkinson's Disease Rating Scale[108] was necessary to validate the evident impact DBS had on symptom control. Given that modeling mood disorders is even more complex, research on TRD should possibly follow the same path by developing a specific scale.[35]

The MFB study showed exceptionally good immediate and sustained efficacy (~ 80%). This makes this target the most promising of the open-label trials selected.[97]

The MFB is the most rapid to produce response, most probably because it lies at the center of the reward pathway,[14,91,109] with acute effects also more pronounced on the NAcc.[87] Nonetheless, whenever acute responses are present, the insertional effect (possibly related to acute inflammatory mediators[11] or glial released neurotransmitters[12,32] in early time-points must be considered. Sustained and low progressive improvement in the blind stimulation cohorts and acute mood changes related to alterations in parameters months after surgery[87] tend to indicate efficacy of the surgical procedure.[110]

Although sham designs mitigate placebo effect, especially if longer shams are employed, this effect is still relevant (five times stronger than medications in DBS for PD). It possibly happens due to expectation per se following the instructions of the doctor, follow-up visits, and high-frequency stimulation potentially rising subtle AEs and affecting patient blinding. Yet, placebo effect and spontaneous remissions are not usual in patients with very severe TRD.[7,26] Worsening symptoms because of unintended "shams" such as battery depletion were frequently highlighted in the present systematic review, corroborating the efficacy of DBS. Strategies to overcome placebo effect include longer shams and optimization phases. Nevertheless, the latter may imply selection bias in the randomization phase. The counterpart effects, nocebo and lessebo,[66,110] cannot be rejected whenever patients are aware of the possibility of being in the sham arm, which the inform consent provides.

The suicides reported appear to be dissociated from system malfunction or from changes in parameters, and were comparable to mortality rates in naturalistic studies.[111,112] Whether suicide after DBS occurs due to lack of efficacy and disease progression or because stimulation lowers the suicide threshold remains unanswered.

Overall, other stimulation AEs are transient and responsive to parameter adjustment. Visual disturbances are particularly common in patients undergoing high stimulation parameters at some targets, especially the slMFB. Therefore, this AE is a relative limitation to slMFB DBS.[44] Emphasis should be given to investigational studies, as this target reportedly exhibits the most rapid and a sustained response. Additionally, high oculomotor-stimulating frequencies are likely associated with DBS efficacy.[64]

Optimal DBS parameter settings are still under debate.[31,34,53,75] Evidence points that short pulse width–low intensity, short pulse width–high intensity, as well as long pulse width–low intensity stimulation are the possible combinations. The high- versus low-frequency debate arises,[31] with some strong evidences[34,53] indicating that high-frequency stimulation promotes better AD response.[73,80]

The fact that the commercial value of being first to market is undoubtedly appealing[25] might have contributed to the prematureness of the three pivotal researches.[10,78,88] Whereas the trials herein presented have used open-loop systems, alternatively closed-loop or adaptive DBS systems, in dynamic stimulation settings based on a patient-control variable, in a feedback-like manner, tend to play a significant role in a near future.[113] This dynamic model seems coherent with the most common symptoms of the disease and with the idea that different phenotypes fall under the umbrella of TRD.

Since in standard magnetic resonance imaging sequences the slMFB is not visualized, tractography generates the hypothesis of a target, culminating in response above 80%. Therefore, tractographies are mandatory for this target.[97]

Outcome predictors of efficacy of DBS for TRD appear to be related to symptoms rather than to the syndromic diagnosis, as underpinned by evidence of symptom-target relationship such as the connection of negative mood[26] to the SCg25, the MFB, and the NAcc.[91] This brings psychiatrists to the operating room, where the presence of this professional enhances patient trust,[28] and the functional neurosurgeon to a clinical interdisciplinary health care team.[114]

Evidently, treatment options for MDD have never been so diverse, and, yet, suicide and depression rates have been increasing.[115] Deep brain stimulation is promising; however, it is restricted to specialized centers and highly selected patients, the market is dominated by a few companies,[116] and the procedure is costly.[117] This illustrates the long way ahead before DBS for TRD achieves efficacy and effectiveness.

Based on our exploratory exercise prior to the present systematic review of the literature, we conveniently conveyed inclusion criteria to allow psychiatric comorbidities, obtaining highly heterogeneous populations, closer to the reality of resistant populations. However, the theoretical modeling of DBS for TRD was compromised, posing a limitation to the present study. Furthermore, statistical analyses were not performed, since the trials selected are substantially different and, thus, not statistically comparable. Consequently, the successful and failing outcomes presented must be interpreted with caution, as these limiting factors potentially impair generalizations.

Conclusion

The current DBS research for TRD shed some light on the understanding of the most prevalent mental disorder. The studies here examined are among the most sophisticated to date. Nonetheless, they were not sufficient to reject or confirm the clinical pertinence of DBS. Despite the expansion of the therapeutic range of somatic therapies for depression, contemporary concerns on the repercussions of TRD and its lethality make DBS key to engross the list of treatment modalities. Thus, DBS remains one of the most promising and versatile strategies of this potential toolkit.

Conflicts of Interests
The authors have no conflicts of interests to declare.

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