

TITLE: Deep Brain Stimulation for Post-traumatic Stress Disorder or Treatment-resistant Depression: A Review of the Clinical Effectiveness

DATE: 06 October 2014

CONTEXT AND POLICY ISSUES

Major depressive disorder (MDD) and post-traumatic stress disorder (PTSD) are common debilitating disorders with a lifetime prevalence rate around 12% and 8% of Canadians, respectively.^{1,2} Despite advances in the understanding of the psychopharmacology and the introduction of novel antidepressants, 30%-40% of MD and PTSD patients do not respond to antidepressant therapy,³ in response to which different treatment modalities such as psychotherapy, electroconvulsive therapy, transcranial magnetic stimulation, vagus nerve stimulation, and deep brain stimulation (DBS) have been suggested.^{3,4}

Deep brain stimulation (DBS) is a neurological procedure in which a medical device called a brain pacemaker is implanted subcutaneously. The device sends electrical impulses through implanted electrodes to provide electrical stimulation to targeted parts of the brain.^{5,6} It is believed that DBS in select brain regions can provide therapeutic benefits for treatment-resistant movement and affective disorders such as Parkinson's disease, essential tremor, dystonia, chronic pain, major depression, Tourette syndrome, and obsessive-compulsive disorder.^{7,8} DBS has recently been proposed for use in the treatment of post-traumatic stress disorder (PTSD).^{9,10} A number of neuroanatomical targets have been utilized for DBS for severe forms of treatment-resistant depression (TRD) (depression that does not have an adequate response to at least one antidepressant trial of adequate dose and duration³) including the subgenual/subcallosal cingulate cortex, nucleus accumbens, ventral capsule/ventral striatum, inferior thalamic nucleus, lateral habenula and medial forebrain bundle.¹¹⁻¹³

This Rapid Response report aims to review the clinical evidence of DBS for treatment-resistant depression (TRD) or PTSD.

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RESEARCH QUESTIONS

1. What is the clinical effectiveness of deep brain stimulation for adults with treatment-resistance depression?
2. What is the clinical effectiveness of deep brain stimulation for adults with post-traumatic stress disorder?

KEY FINDINGS

In general, data from a systematic review that included mostly observational studies with small sample sizes found that between 40% and 70% of TRD patients treated with DBS showed at least 50% reduction in Hamilton Depression Rating Scale scores (HDRS) or Montgomery-Asberg Depression Rating Scale scores (MADRS). Response rates to DBS therapy and percentage of changes in depression scores after limited long-term follow-up did not vary significantly between anatomical targets. Meta-analyses of four pre-post observational studies on DBS therapy targeted to the SCC of TRD patients showed remission rate of 26% and drop-out rate of 11% after 12 months of treatment. In terms of safety, there were no serious complications reported except one case of temporary hemiparesis in one study. There were completed or attempted suicides, but the causality of DBS therapy to suicides cannot be proven due to the high risk of suicide in patients with severe depression.

The low quality of the study designs (pre-post observational designs) limit the ability to prove causality between intervention (DBS) and outcomes (reduction of depression) in patients with TRD. The heterogeneity in patients' characteristics and measurement tools among the included trials reduced the robustness and generalizability of findings of the evidence.

There is lack of evidence on the clinical effectiveness of DBS on post-traumatic stress disorder.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 9), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and September 8, 2014.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed for relevance. Full texts of any relevant titles or abstracts were retrieved, and assessed for inclusion. The final article selection was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults with treatment-resistant depression Adults with PTSD
Intervention	Deep brain stimulation
Comparator	Usual care, pharmacological interventions, psychotherapy interventions
Outcomes	Clinical effectiveness (e.g. symptom reduction, remission rate, duration of effectiveness, quality of life), safety
Study Designs	Health technology assessments (HTAs), systematic reviews (SRs), meta-analyses (MAs), randomized controlled trials (RCTs), and non RCTs.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria in Table 1, if they were published prior to January 2009, if they were duplicate publications of the same study, or if they were referenced in a selected systematic review.

Critical Appraisal of Individual Studies

The quality of the included systematic reviews was assessed using the AMSTAR checklist.¹⁴ Numeric scores were not calculated. Instead, the strengths and limitations of the studies are summarized and presented.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 481 citations. After screening of abstracts from the literature search and from other sources, 38 potentially relevant studies were selected for full-text review. Two systematic reviews with literature search up to December 2013 were included in this review.

The PRISMA flowchart in Appendix 1 details the process of the study selection.

Summary of Study Characteristics

A detailed summary of the included study is provided in Appendix 2.

Study design

Two systematic reviews published in 2014 met the inclusion criteria.^{15,16} One systematic review¹⁵ provided a narrative review of the included studies. The second review¹⁶ included a meta-analysis.

Population

The systematic reviews included studies on patients with treatment-resistant depression, including both MDD and bipolar disorder.^{15,16}

Interventions and comparators

The intervention was DBS in the one systematic review¹⁵ and one systematic review/meta-analysis¹⁶ identified. Targets included the nucleus accumbens, ventral striatum/ventral capsule, subgenual cingulate cortex, lateral habenula, inferior thalamic nucleus, and medial forebrain bundle in the systematic review,¹⁵ and the subgenual cingulate cortex in the systematic review/meta-analysis.¹⁶

There was no comparator in the included systematic reviews.

Outcomes

Outcomes of interest in the included systematic reviews were response rates, remission rates and change in depression scores.

Summary of Critical Appraisal

One included systematic review was qualitative review,¹⁵ one systematic review was quantitative with meta-analyses.¹⁶ Both provided an a priori design, list of included studies and studies characteristics, and stated no conflict of interest. The qualitative review only searched Medline, included case reports and personal communications, did not include the list of excluded studies and did not perform an analysis of publication bias,¹⁵ while the quantitative review performed a more comprehensive search, included the list of excluded studies, and performed an evaluation of publication bias, which did not identify bias.¹⁶ With the exception of three included RCTs, the majority of studies in both reviews were observational with uncontrolled pre-post designs. Neither review had an independent study selection and data extraction process in place, and did not assess the quality of the included studies. The meta-analysis provided pooled estimates of outcomes of interest, however the findings for depression scores did not specify which scale (three different scales were used in the included studies) and it is therefore unclear whether pooling of these outcomes was appropriate. The low quality of the study designs (pre-post designs of observational studies) limit the ability to prove causality between intervention (DBS) and outcomes (reduction of depression). The heterogeneity in patients' characteristics and measurement tools among the included trials reduced the robustness and generalizability of findings of the evidence.

Details of the strengths and limitations of the included studies are summarized in Appendix 3.

Summary of Findings

Main findings of included studies are summarized in detail in Appendix 4.

1. What is the clinical effectiveness of deep brain stimulation for adults with treatment-resistance depression?

The literature search identified two systematic reviews on the clinical effectiveness of DBS for the treatment of TRD.^{15,16} In general, data from mostly observational studies with populations smaller than 21 patients showed a statistically significant decrease in depression scores in 40 to 70% of TRD patients treated with DBS.

The qualitative systematic review¹⁵ included 22 studies, comprising of three RCTs, one review with follow-up outcomes to an included study, and 18 observational studies, on patients undertaking DBS for TRD, with anatomical targets including nucleus accumbens, ventral striatum/ventral capsule, subgenual cingulate cortex (SCC), lateral habenula, inferior thalamic nucleus, and medial forebrain bundle. Follow-up times ranged from 1.5 months to 72 months. There was no indication on which studies had a comparator to DBS therapy. Reported outcomes included response rates to DBS therapy [defined as patients with at least 50% reduction in Hamilton Depression Rating Scale scores (HDRS) or Montgomery-Asberg Depression Rating Scale scores (MADRS)], reduction in depression scores, and complications.

Findings showed that the response rate to DBS therapy and percentage of changes in depression scores did not vary much between anatomical targets. Overall, response rate across studies was between 40% and 70% of patients undergoing DBS therapy, with a 41% to 89% reduction in HDRS, and 44% to 79% in MADRS. In terms of safety, there were no serious complications reported except one case of temporary hemiparesis in one study. There were completed or attempted suicides, but the causality of DBS therapy to suicides cannot be proven due to high risk of suicide in patients with severe depression.

The systematic review/meta-analysis¹⁶ included four pre-post observational studies on 66 TRD patients undergoing DBS targeting the SCC, with follow-up times from 3 to 24 months. Reported outcomes included response rate to DBS therapy [(defined as patients with at least 50% reduction in Hamilton Depression Rating Scale scores (HDRS), Montgomery-Asberg Depression Rating Scale scores (MADRS)], reduction in depression scores, remission rates, and drop-out rates after 12 months.

Findings showed that, at 12 months of therapy, the response rate was 39.9% (95% CI 28.4% to 52.8%), remission rate was 26.3% (95% CI 13% to 45.9%), percentage changes in depression scores (scale not specified) was -1.89 (95% CI -2.64 to -1.15, $P < 0.0001$), and drop-out rate was 10.8% (95% CI 4.3% to 24.4%), though reasons for drop-out were not provided.

2. What is the clinical effectiveness of deep brain stimulation for adults with post-traumatic stress disorder?

The literature search did not find clinical evidence on deep brain stimulation for adults with post-traumatic stress disorder

Limitations

Data were from mostly observational studies with populations smaller than 21 patients. Pre-post designs of the observational studies limit the ability to prove causality between intervention (DBS) and outcomes (reduction of depression). The high drop-out rate described in one systematic review also limits the interpretation of the findings. No reasons for drop-out were provided and it is uncertain how missing data from drop-outs was handled. If the large proportion of drop-outs was treatment related and these patients were excluded from the analysis, this may result in an overestimation in treatment effect. Significant heterogeneity among the included studies in designs, patients' characteristics and measurement tools, as well as relatively short follow-up periods lead to lack of robustness and generalizability of the findings.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

In general, data from a systematic review that included mostly observational studies with populations smaller than 21 patients found that from 40% to 70% of TRD patients treated with DBS showed at least 50% reduction in Hamilton Depression Rating Scale scores (HDRS) or Montgomery-Asberg Depression Rating Scale scores (MADRS). Response rate to DBS therapy and percentage of changes in depression scores after limited long-term follow-up did not vary much between anatomical targets. Meta-analyses from four pre-post observational studies on DBS therapy targeted to the SCC of TRD patients showed remission rate of 26% and drop-out rate of 11% after 12 months of treatment. In terms of safety, there were no serious complications reported except one case of temporary hemiparesis in one study. There were completed or attempted suicides, but the causality of DBS therapy to suicides cannot be proven due to high risk of suicides in patients with severe depression. Findings from our review agree with a preliminary evidence review done by Health Quality Ontario in 2013 that found that low quality of evidence showed that DBS improved depression severity in patients with TRD and that future investigations of the clinical effectiveness and safety of DBS are warranted.¹⁷ There is lack of evidence on the clinical effectiveness of DBS on post-traumatic stress disorder.

Since improvement in depression symptoms can be related to the natural course of the disease, differences in individual care, or to a placebo effect of the intervention, lack of a comparator intervention in most of the included observational studies and their pre-post design limit the ability to prove causality between intervention (DBS) and outcomes (reduction of depression).

Despite promising results on DBS for psychiatric conditions in general, and for TRD in particular, ethical concerns have been raised about the decisional ability of severely depressed patients and their potential misconceptions about the intervention such as benefits, risks and individualization.¹⁸⁻²² Patients' high expectations for the new technology and their competence to consent due to disturbances of mental functions are challenges to informed consent.²³⁻²⁵

Despite optimism and interest in neurosurgery for psychiatric disorders,²⁶ the inherent risk that neurosurgery may cause, the unknown efficacy, and unclear mechanism of action of DBS are some of the reasons that DBS remains an investigational treatment of TRD as mentioned by the Canadian guidelines for the treatment of depressive disorders.²⁷

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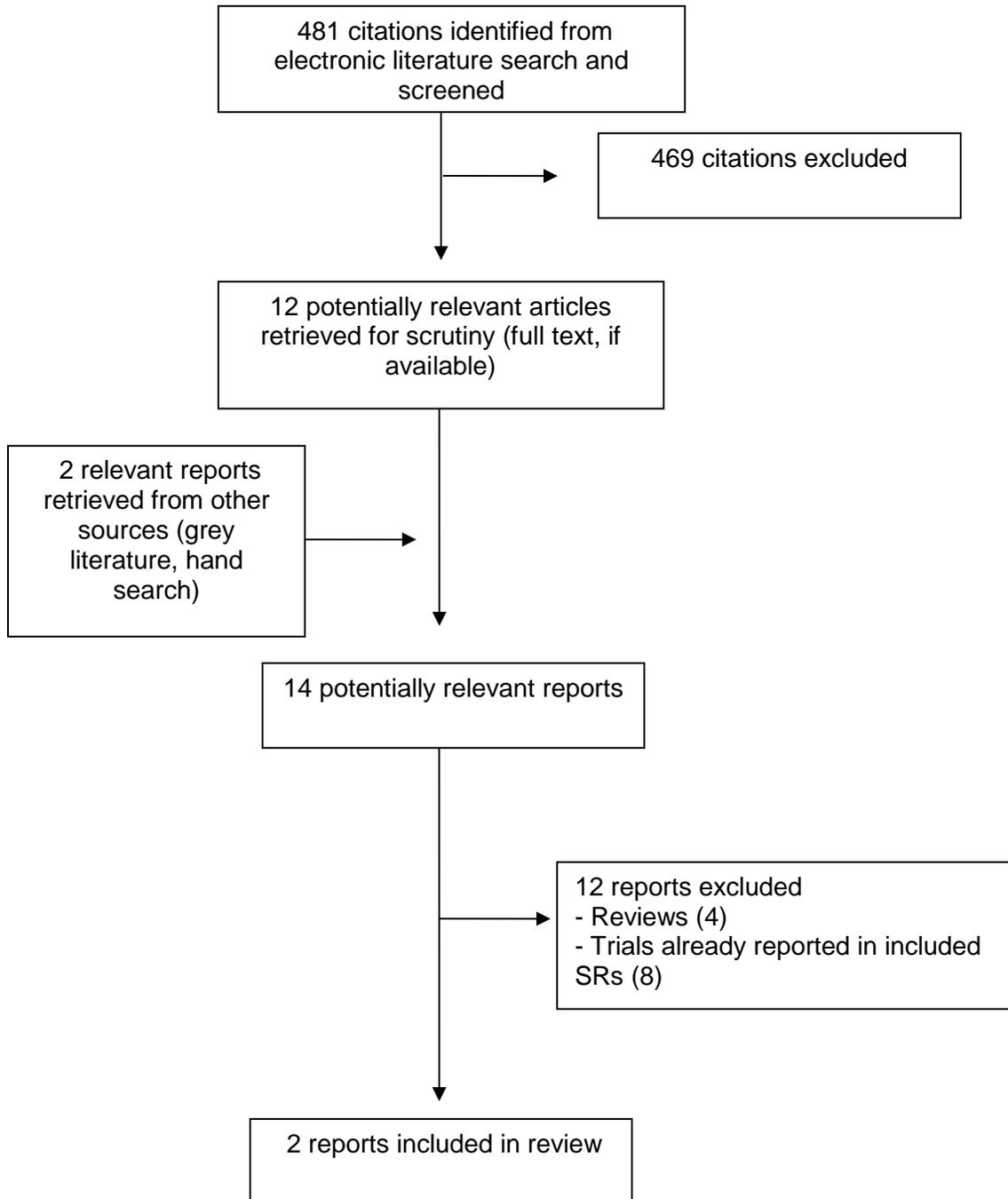
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Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Studies

Table A1: Characteristics of Included studies				
First Author, Year, Country,	Literature Search Strategy	Inclusion Criteria	Exclusion Criteria	Studies included Main outcomes
Systematic reviews				
Morishita, ¹⁵ 2014, USA	"We performed a Medline search from January 1999 to December 2013" (p 477)	"In an exhaustive literature review, we included English language, clinical research articles pertaining to DBS for treatment-resistant depression, including both MDD and bipolar disorder. Papers that contained clear descriptions of clinical outcomes utilizing validated outcome measures, such as the Hamilton Depression Rating Scale scores (HDRS), were included. We included all available case reports and personal communications, as the number of useful studies in the literature was limited." (p 477)	"We excluded studies primarily treating other disorders (e.g., OCD, Parkinson disease, dystonia, etc.)" (p 477)	22 studies included (including 3 RCTs, 18 observational studies and 1 review with follow-up data) Response rate to DBS therapy (responders defined as patients with at least 50% reduction in HDRS or MADRS) % changes in depression scores Adverse events
Berlim, ¹⁶ 2014, Canada	"We identified articles for inclusion in this meta-analysis by searching MEDLINE, EMBASE, PsycINFO, the Cochrane Central Register of Controlled Trials (CENTRAL) and SCOPUS from January 1, 1999 until December 25, 2012." (p 33)	"Candidate studies (judged on the basis of their title and abstract) had to meet the following criteria (Higgins and Green, 2008): Study validity: PROSPECTIVE design with clinical assessments at baseline, 3, 6, 12, and/or 24 months, and inclusion of Z5 subjects with MD; Sample characteristics: Subjects aged 18–75 years with a diagnosis of primary major depressive episode (unipolar or bipolar) according to the Diagnostic and Statistical Manual of Mental Disorders – 4th edition or later (APA, 1994) or the International Classification of Diseases criteria (WHO, 1992); Treatment characteristics:	"Studies were excluded if they: Presented results on "duplicated" samples; _ Enrolled subjects with secondary MD (e.g., vascular depression); _ Started DBS at the same time as a new antidepressant medication; Did not report depression scores, and/or rates of response/ remission at follow-up." (p 33)	Four observational studies included. Response rate to DBS therapy (responders defined as patients with at least 50% reduction in HDRS or MADRS) Remission rate % changes in depression scores Drop-out rate at 12 months

Table A1: Characteristics of Included studies				
First Author, Year, Country,	Literature Search Strategy	Inclusion Criteria	Exclusion Criteria	Studies included Main outcomes
		<i>DBS applied to the SCC as a treatment for TRD; Publication related: Articles written in English” (p 33)</i>		

DBS: deep brain stimulation; HDRS: Hamilton Depression Rating Scale scores; MADRS: Montgomery-Asberg Depression Rating Scale scores; MDD: major depressive disorder

Appendix 3: Summary of Critical Appraisal of Included Studies

Table A2: Summary of Critical Appraisal of Included Study		
First Author, Publication Year	Strengths	Limitations
Critical appraisal of included systematic reviews (AMSTAR ¹⁴)		
Morishita, ¹⁵ 2014	<ul style="list-style-type: none"> • a priori design provided • list of included studies, study characteristics provided • conflict of interest stated 	<ul style="list-style-type: none"> • comprehensive literature search not performed • unclear whether independent study selection and data extraction procedure are in place • majority of included studies are observational. Case reports were also included. • list of excluded studies, study characteristics not provided • heterogeneity in study designs, patients characteristics and measurement tools among the included trials • quality assessment of included studies not provided • no assessment of publication bias performed
Berlim, ¹⁶ 2014	<ul style="list-style-type: none"> • a priori design provided • comprehensive literature search performed • list of included studies, study characteristics provided • list of excluded studies, study characteristics provided • assessment of publication bias performed • conflict of interest stated 	<ul style="list-style-type: none"> • unclear whether independent study selection and data extraction procedure are in place • all included studies are observational studies • heterogeneity in study designs, patients characteristics and measurement tools among the included trials • quality assessment of included studies not provided

Appendix 4: Main Study Findings and Authors' Conclusions

Table A3: Main Study Findings and Authors' Conclusions		
First Author, Publication Year	Main Study Findings	Authors' Conclusions
Research question 1 (clinical effectiveness of deep brain stimulation for adults with treatment-resistance depression)		
Morishita, ¹⁵ 2014	<p><u>Response rate to DBS therapy (responders defined as patients with at least 50% reduction in HDRS or MADRS)</u></p> <p>For NAcc : 41.7% to 45.5% For VC/VS and SSC: 29% to 71% For Habenula: NA For ITP: NA For sIMFB: NA</p> <p><u>% changes in depression scores</u> (range from lowest % to highest %)</p> <p>For NAcc : 31.3% to 42.0% in HDRS; 31% to 34% in MADRS For VC/VS: 41.4% to 89.0% in HDRS; 44% to 79% in MADRS For Habenula: 100% in HDRS; NA in MADRS For ITP: 83% in HDRS; NA in MADRS For sIMFB: NA in HDRS; 63% in MADRS</p> <p><u>Adverse events</u></p> <p><i>"Most complications were minor surgery-related issues such as superficial infection. There were no serious complications reported except for 1 case of temporary hemiparesis due to intracerebral hemorrhage reported in a sIMFB DBS study [55]. Stimulation-induced side effects such as mood changes were temporary and adjustable. However, it should be noted that there were patients who attempted and completed suicide after DBS [31, 32, 42, 49, 50]. Completed suicide and suicide attempts were the most significant adverse events following DBS surgery and happened both with and without stimulation... All patients included in these studies had severe, treatment refractory depression and were at higher risk of suicide owing to the nature and severity of their illness."</i> (p 481)</p>	<p><i>"We conclude that DBS for MDD shows promise, but remains experimental and further accumulation of data is warranted."</i> (p 475)</p>
Berlim, ¹⁶ 2014	<p><u>Response rate to DBS therapy after 12 months (responders defined as patients with at least 50% reduction in HDRS or MADRS)</u></p> <p>39.9% (95% CI 28.4% to 52.8%)</p> <p><u>Remission rate after 12 months</u></p> <p>26.3% (95% CI 13% to 45.9%)</p> <p><u>% changes in depression scores after 12 months (in HDRS)</u></p> <p>-1.89 [95% CI -2.64 to -1.15, P < 0.0001]</p> <p><u>Drop-out rate at 12 months</u></p> <p>10.8% (95% CI 4.3% to 24.4%)</p>	<p><i>"DBS applied to the SCC seems to be associated with relatively large response and remission rates in the short- and medium- to long-term in patients with severe TRD. Also, its maximal anti- depressant effects are mostly observed within the first 6 months after device implantation. Nevertheless, these findings are clearly preliminary and future controlled trials should include larger and more representative samples, and focus on the identification of optimal neuroanatomical sites and stimulation parameters."</i> (p 31)</p>

Table A3: Main Study Findings and Authors' Conclusions		
First Author, Publication Year	Main Study Findings	Authors' Conclusions
Research question 2 (clinical effectiveness of deep brain stimulation for adults with post-traumatic stress disorder)		
The literature search did not find clinical evidence on deep brain stimulation for adults with post-traumatic stress disorder		

HDRS: Hamilton Depression Rating Scale scores; ITP: inferior thalamic peduncle; MADRS: Montgomery-Asberg Depression Rating Scale scores; NA: data not available; NAcc: nucleus accumbens; sIMFB: superolateral branch of the medial forebrain bundle; SCC: subgenual cingulate cortex; VC/VS: ventral capsule/ventral striatum