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Deep Brain Stimulation in the Bed Nucleus of Stria Terminalis and Medial Forebrain Bundle in Two Patients With Treatment-Resistant Depression and Generalized Anxiety Disorder—A Long-Term Follow-Up

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ABSTRACT

This case report presents positive outcomes from deep brain stimulation (DBS) targeting the bed nucleus of the stria terminalis (BNST) in two patients with treatment-resistant depression and generalized anxiety disorder. DBS effects in the medial forebrain bundle (MFB) area were unclear. Further research into DBS's efficacy when comorbid anxiety is present is required.

1 | Introduction

In patients with severe depression who do not respond to conventional pharmacological or psychotherapeutic treatments, deep brain stimulation (DBS) has emerged as a treatment option [1, 2]. DBS is believed to modulate pathological brain activity through electrical stimulation [3]. However, the efficacy of DBS for depression remains inconclusive [4], and one possible reason for previous unsatisfactory results might be that earlier studies did not consider psychiatric comorbidities, such as anxiety disorders.

Generalized anxiety disorder (GAD) is characterized by persistent and excessive worry that interferes with daily life functioning. It is commonly co-occurring with depression [5], leading to reduced quality of life and increased suicide risk [6]. Until now, no DBS studies have been published targeting GAD as the primary diagnosis. However, there are case reports describing improvements in GAD and severe anxiety. One case report from our research group describes a patient with anorexia nervosa who also suffered from severe anxiety and depression [7]. Initially, the patient received DBS in the medial forebrain bundle (MFB) area with improved depressive and anxiety symptoms, but DBS was discontinued due to side effects (blurred vision). After changing the DBS target to the bed nucleus of stria terminalis (BNST), marked improvements in depression and anxiety symptoms were observed. A similar recovery was described by McLaughlin et al. who reported a positive outcome of DBS in the ventral capsule/ventral striatum (VC/VS) in a patient with anorexia nervosa, depression, and GAD [8].

Clinical studies on treatment-resistant obsessive-compulsive disorder (OCD) consistently show reductions in anxiety and depressive symptoms along with improvements in OCD symptoms; for example, in studies targeting the ventral anterior limb of the internal capsule (vALIC) [9], BNST [10], ALIC or BNST [11], and VC/VS [12]. In studies on treatment-resistant depression, reduced anxiety was reported in patients receiving DBS in the nucleus accumbens

(NAc) [13] and in BNST and NAc combined [14]. Also, DBS in the MFB area, including the superolateral branch (slMFB) showed improvements in anxiety symptoms [15–17].

Previous research has utilized data from neuromodulating treatments such as transcranial magnetic stimulation and DBS to investigate the role of brain circuits associated with anxiety symptoms in depression [18, 19]. In these studies, anxiety and depressive symptoms were theorized to respond to distinct neural networks, and dysphoric symptoms (sadness or anhedonia) were linked to the dorsolateral prefrontal cortex, and anxiety symptoms to the dorsomedial prefrontal cortex [18]. Using stimulation sites from these identified regions, they could then predict the treatment response to dysphoric and anxiety symptoms [19]. These findings emphasize the importance of personalized DBS strategies, utilizing functional connectivity mapping to optimize target selection and symptom-specific outcomes.

Given the relatively limited DBS research on patients with a primary diagnosis of treatment-resistant depression and comorbid severe anxiety or GAD, we here present two cases that were initially planned for DBS in the MFB area. Based on our previous results in reducing anxiety symptoms in OCD through DBS in BNST [10], we included BNST as an additional target. Both patients received electrodes in the MFB area and BNST bilaterally and were randomized to either target, followed by cross-over stimulation for 6 months. The patients were then followed for up to 5 years, with monitoring of depressive and anxiety symptoms and the global functioning level.

2 | Case History/Examination

2.1 | Patient 1

Patient 1 is a 57-year-old male who first came into contact with psychiatry at age 33, presenting with depressive symptoms including rumination and social withdrawal. He was diagnosed with major depressive disorder (MDD, Table 1). He also had a childhood onset of anxiety and was diagnosed with GAD in adulthood. Over time, the depressive symptoms worsened, leading to suicidal ideation, and he was hospitalized after a suicide attempt. He subsequently developed alcohol and benzodiazepine dependence, requiring treatment from an addiction psychiatry unit. Despite achieving 3 years of remission from alcohol and benzodiazepine use disorder, the depression and anxiety symptoms persisted, continuing to meet the criteria for MDD and GAD. Patient 1 also had a history of thyrotoxicosis and underwent a thyroidectomy at age 38. He later developed type II diabetes mellitus, sarcoidosis, and suffered from chronic lumbar pain.

Throughout his contact with specialized psychiatric care, he tried numerous medications for depression and GAD, including antidepressants (paroxetine, mirtazapine, citalopram, escitalopram, tranylcypromine, and venlafaxine),

TABLE 1 | Demographic information on Patient 1 and Patient 2 before DBS surgery.

	Patient 1	Patient 2
Age at DBS surgery, years	57	52
Sex	Male	Male
Education, years	13	11
Working status	Disability pension	Not employed
Age at depression onset, years	33	20
Primary diagnosis	MDD	MDD
Secondary diagnosis prior to intervention	GAD History of substance use disorder (alcohol and benzodiazepines)	GAD
MDD duration, years	24	32
History of suicide attempt	Yes	Yes
Somatic disorders	Diabetes mellitus type 2, sarcoidosis, thyrotoxicosis	Chronic pain
Treatments for depression before DBS surgery		
Antidepressants (classes)	SSRI, SNRI, NASSA, TCA, MAOI	SSRI, SNRI, NASSA, TCA, NDRI
Augmentation therapy/other medications	Lithium, lamotrigine, benzodiazepines, pregabalin, gabapentin	Lamotrigine, quetiapine, benzodiazepines, pregabalin
ECT	Three trials	One trial
Other treatments	Psychotherapy, physiotherapy	Psychotherapy

Abbreviations: DBS = deep brain stimulation, ECT = electroconvulsive treatment, GAD = generalized anxiety disorder, MAOI = monoamine oxidase inhibitors, MDD = major depressive disorder, NASSA = noradrenaline and specific serotonergic antidepressants, NDRI = norepinephrine–dopamine reuptake inhibitor, SNRI = serotonin-noradrenaline reuptake inhibitors, SSRI = selective serotonin reuptake inhibitors, TCA = tricyclic antidepressants.

lamotrigine, and lithium, all with insufficient antidepressant effect. Electroconvulsive therapy (ECT) was administered on three separate occasions, providing only temporary relief of symptoms lasting from a few hours to a few days. He also underwent several rounds of psychotherapy and physiotherapy treatments. Over the years, benzodiazepines (e.g., oxazepam, alprazolam), pregabalin, and gabapentin were prescribed for anxiety symptoms, but without long-lasting effects. Ultimately, due to the severity and treatment-resistant nature of his depressive and anxiety symptoms, he was referred for DBS.

2.2 | Patient 2

Patient 2 is a 52-year-old male with a childhood onset of anxiety who experienced his first MDD episode at age 20 (Table 1). Recurrent episodes of depression followed in the subsequent years. At the age of 24, he initiated contact with a specialized psychiatry clinic following a suicide attempt. From age 33, he maintained continuous contact with the psychiatric clinic due to recurrent depression and was diagnosed with GAD. During the months preceding DBS surgery, he had constant suicidal thoughts and was unable to take care of his home properly. He had a medical history of chronic pain in the shoulders and knee joints secondary to physical traumas. Due to the chronic pain, he was treated with dextropropoxyphene, tramadol, and finally methadone.

Before the DBS surgery, he had tried medications for MDD and GAD, including antidepressants (sertraline, paroxetine, mirtazapine, venlafaxine, amitriptyline, bupropion, mianserin), lamotrigine, and augmentation therapy with quetiapine. ECT was administered but resulted in increased anxiety, leading to premature termination. Over 10 years, he received at least three rounds of psychotherapy. He was treated with buspirone, alimemazine, and benzodiazepines (e.g., triazolam, clonazepam, oxazepam, and diazepam) and pregabalin for GAD without long-lasting effects.

2.3 | Study Enrollment

The patients were included in an ongoing study of DBS for treatment-resistant depression at the University Hospital of Northern Sweden in Umeå after signing an informed consent. MDD and GAD were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [20]. Treatment resistance was defined as four or more trials of standard treatments for depression, that is, psychotherapy, pharmacological, or ECT.

2.4 | Measures

Depression severity (primary outcome) was assessed with the clinical interview version of the Montgomery–Åsberg depression rating scale (MADRS) [21]. Depression treatment response was defined as a minimum of 50% reduction in MADRS scores compared to pre-surgery according to definitions used in previous studies [15, 16]. Anxiety was measured with the Hamilton Anxiety Rating scale (HAM-A) [22]. The Global Assessment of Functioning (GAF) scale was used to assess the level of function [23]. After DBS surgery, psychiatric symptoms were evaluated with MADRS, HAM-A, and GAF after three, six, and 12 months of active stimulation and then yearly until 4–5 years post-surgery. Due to missing data on pre-surgical GAF in Patient 2, a pre-operative GAF score was estimated retrospectively based on the clinical records before DBS surgery.

2.5 | Surgical Procedure

A 1.5 T magnetic resonance image (MRI) scan was performed using a computerized navigational system to identify the target structure, and a trajectory was chosen. Two DBS electrodes were bilaterally implanted in the area of the MFB (Medtronic model 3389) in the posteromedial hypothalamic area just anterior to the red nucleus (RN), and two electrodes in the area of the BNST (Medtronic model 3387) [24]. After the procedure, the electrode positions were verified with a postoperative computed tomography scan fused with the preoperative stereotactic MRI (Figure 1).

2.6 | Treatment With Deep Brain Stimulation (DBS)

The participants were randomized to DBS in either MFB or BNST for the first 3 months, followed by a crossover to the opposite target area for 3 months, with patients and raters blinded to the DBS target. Following the blinded phase, the patients entered an open-label phase and received continuous stimulation in the most optimal targets. For the stimulation target and parameters, see Table S1.

3 | Outcome and Follow-Up

Before surgery, the patients had MADRS scores of 44 and 49 points, corresponding to severe depression [25], and HAM-A scores of 40 points, corresponding to severe anxiety [26] (Table 2).

Patient 1 received DBS in the BNST for the initial 3 months and experienced markedly reduced symptoms of depression and anxiety compared to pre-surgery (reductions: MADRS 77%, HAM-A 65%, Table 2). After switching to DBS in the MFB area, Patient 1 experienced an immediate worsening of symptoms. He continued to report severe anxiety and mild confusion and was offered to break the study protocol. However, the patient continued, and by the end of the three-month stimulation, the depression and anxiety symptoms were only slightly reduced compared to pre-surgery levels (reductions: MADRS 27%, HAM-A 30%, Table 2).

After the blinded randomization phase was completed, DBS was resumed in BNST and turned off in the MFB area. A week later, the patient reported anxiety relief. Over the next 6 months of BNST-DBS, the patient reported a marked reduction in anxiety and, therefore, continued to receive BNST stimulation during the four-year follow-up. Due to remaining depressive symptoms, mainly apathy, DBS in the MFB area was reactivated, but

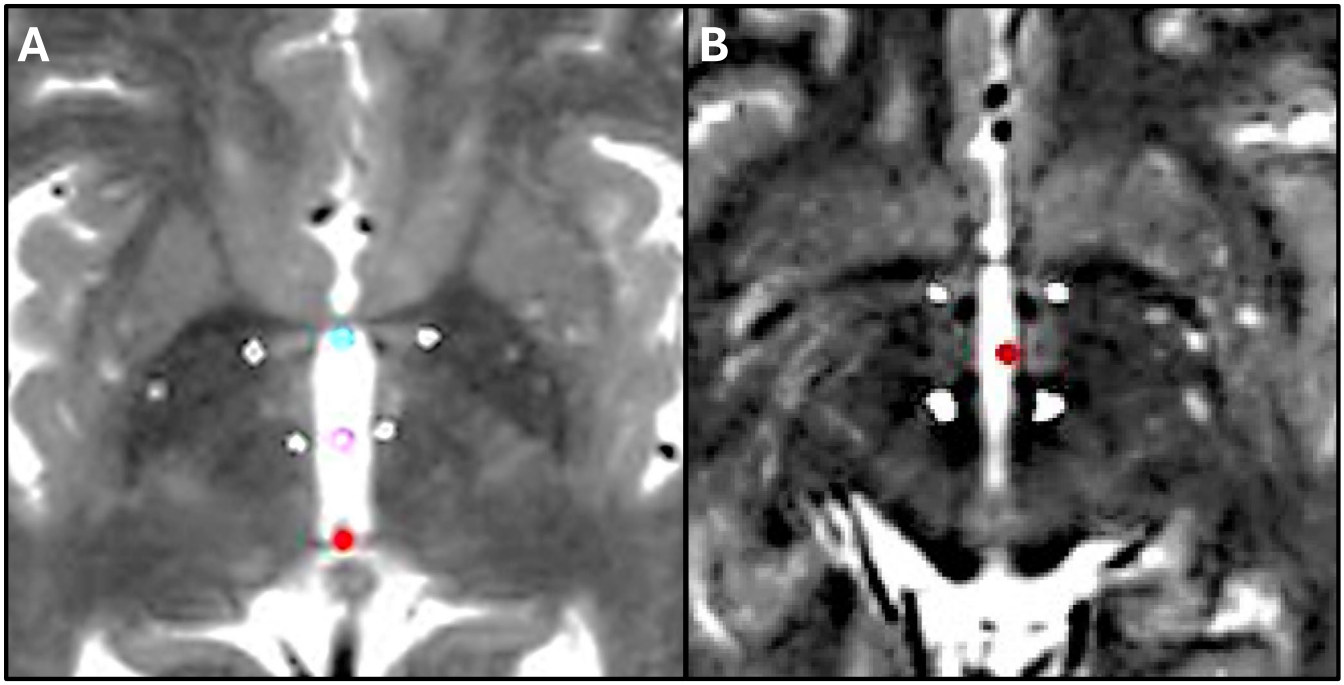

FIGURE 1 | Intraoperative computer tomography (CT) scans fused with pre-operative T2-weighted magnetic resonance imaging (MRI) scans, displaying the electrode locations. The colored circles mark the commissures and their mid-point. (A) Electrode location as seen at the AC-PC level in Patient 1. (B) Electrode location as seen 3 mm deeper in Patient 2.

the current level was lowered to avoid a worsening of symptoms (from 3.6–4.4 V during the blinded phase to 2.5 V; see Table S1 for details). During the following months of simultaneous stimulation in the MFB and BNST areas, there were no suspected side effects, but the patient's depressive symptoms were, however, unchanged. When the current strength was increased, he experienced fatigue and MFB-DBS was again inactivated. In year four, MFB-DBS was reactivated at a low current level (0.5 V), with the intention to gradually increase the current to avoid triggering additional side effects. Four years after surgery, stable improvements were observed, especially regarding anxiety symptoms, but also depression, although the patient still reported feelings of apathy (reductions: MADRS 48%, HAM-A 70%, Table 2).

Patient 2 received DBS in the MFB area for 3 months, and minor reductions in depression and anxiety symptoms were recorded compared to pre-surgery (reductions: MADRS 10%, HAM-A 25%, Table 2). After switching to BNST-DBS, depressive symptoms were markedly reduced (reductions: MADRS 51%, HAM-A 13%). In the open-label phase, BNST-DBS was delivered, and there was a gradual reduction of depression symptoms fulfilling the criteria of remission and for anxiety symptoms 5 years after surgery (reductions MADRS 55%, HAM-A 65%, Table 2). Attempts at combined stimulation in both targets (BNST and MFB area) were performed, but without any clear beneficial effects, and isolated BNST-DBS was used for chronic stimulation.

3.1 | Assessment of Global Functioning Pre- and Post-DBS Surgery

Patient 1 had a GAF score of 40 before DBS, indicating significant impairments regarding work/daily activities and family relations. Four years after DBS surgery, the GAF had increased to 55, corresponding to moderate symptoms or impairments in work- or family relations. Patient 2 was estimated to have a GAF score of 30 before surgery. Five years after DBS surgery, the GAF score had increased to 55 (Table 3).

3.2 | Adverse Events

Patient 1 reported increased anxiety, mild confusion, and fatigue during DBS in the MFB area, but the side effects ceased after terminating DBS. Patient 2 reported visual side effects during DBS in the MFB area and sleep disturbances and fatigue during DBS in BNST that were all transient.

4 | Discussion

In this case report, we describe the short- and long-term treatment responses from DBS in the BNST and MFB areas in two patients with treatment-resistant depression and severe and disabling anxiety manifested as GAD. Both patients reached treatment response in depression following short-term DBS in the BNST, and one of the patients had a major reduction in anxiety symptoms. However, DBS in the MFB area showed no clear short-term effects on depressive or anxiety symptoms. During the long-term follow-up, both patients continued to receive DBS in the BNST. One of the patients also had several trials of DBS in the MFB area due to persistent depressive symptoms but did not experience any clear additive anti-depressive effect in addition to the BNST stimulation. After 4–5 years, stable reductions in depressive and anxiety symptoms were recorded in both patients, and the global functioning level was slightly improved.

TABLE 2 | Depression and anxiety scores pre- and post-surgery until the end of follow-up.

		Randomization phase					Open-label phase					
		Pre-surgery	3 months post-surgery	Reduction pre- versus 3 months	6 months post-surgery	Reduction pre- versus 6 months	12 months post-surgery	2 years post-surgery	3 years post-surgery	4 years post-surgery	5 years post-surgery	Reduction pre- versus 4- or 5-years
DBS brain target			BNST		MFB		BNST & MFB	BNST & MFB	BNST	BNST & MFB[a]		
Patient 1	MADRS	44	10	77%	32	27%	27	32	24	23	—	48%
	HAM-A	40	14	65%	28	30%	16	16	20	12	—	70%
DBS brain target			MFB		BNST				BNST			
Patient 2	MADRS	49	44	10%	24	51%	34	24	24	19	22	55%
	HAM-A	40	30	25%	35	13%	30	25	26	12	14	65%

Note: Presented as the total score of the Montgomery–Åsberg Depression Rating Scale (MADRS) for depression and the Hamilton Anxiety Rating scale (HAM-A) for anxiety symptoms. Changes in scores compared to baseline are presented as percentages (%).
Abbreviations: BNST = bed nucleus of stria terminalis, DBS = deep brain stimulation, HAM-A = Hamilton anxiety rating scale, MADRS = Montgomery–Åsberg depression rating scale, MFB = medial forebrain bundle.
[a]Amplitude 0.5 volt.

TABLE 3 | Results from assessments with the global assessment of functioning (GAF) pre-surgery and after deep brain stimulation (DBS).

		Pre-surgery	3 months	6 months	12 months	2 years	3 years	4 years	5 years
Patient 1	GAF	40	55	52	48	51	55	55	55
Patient 2	GAF	30[a]	48	48	50	50	50	50	55

[a]Retrospectively assessed value using information from the clinical records before DBS surgery due to missing data.

Reduced anxiety and depressive symptoms were previously reported in DBS studies on treatment-resistant depression and OCD, targeting areas in proximity to BNST, for example, ALIC/vALIC, VC/VS, or NAc [9–14], which also agrees with previously reported overlapping effects from DBS in the BNST and the ALIC and NAc areas, as was shown in an electric field study by our research group [27]. Our results also align with an electric field study based on data from multiple DBS studies that identified BNST as one of the optimal stimulation sites for reducing anxiety [28]. In contrast to our results, eight patients with treatment-resistant depression, of which several had comorbid GAD or other anxiety disorders, had no short-term antidepressant effect from the BNST stimulation [29]. However, the follow-up period was shorter in this particular study, and anxiety parameters were not specifically reported.

We could not detect any clear short-term effect on anxiety symptoms from DBS in the MFB area in the two presented cases. However, we cannot exclude that the worsened effect experienced by Patient 1 during the blinded phase was due to extended stimulation effects towards the hypothalamic area [30, 31]. Moreover, it is not possible to rule out that the on-and-off stimulation in the MFB area during the open-label phase had an additive positive effect along with the continuous BNST stimulation. Indeed, previous studies on treatment-resistant depression reported improved anxiety when targeting the MFB area, although the anxiety data presented was limited to year in these studies [15, 17].

The absence of a short-term antidepressant effect from DBS in the MFB area could be due to several factors. The stimulation period of 3 months during the blinded phase may have been too short to achieve a sufficient antidepressant effect, as previously discussed [32]. As seen on MRI, the electrodes were placed in a more medial aspect of the target area in relation to RN, the subthalamic nucleus (STN), and corpora mammillaria (CM), which differs from a previous study by Schlaepfer et al. on DBS in slMFB [33]. The target area of the MFB was identified on a T2 MRI, based on the visualization of the STN, RN, and CM. However, it has been suggested that tractography [34, 35] or intracranial electrophysiology recordings [36] are more precise methods to determine the electrode position.

5 | Conclusion

This case report describes positive short- and long-term outcomes on anxiety and depressive symptoms and global functioning from DBS in BNST in two patients severely disabled from treatment-resistant depression and GAD. The short-term effect of DBS in the MFB area in these specific cases was unclear. Further studies are needed to clarify the role of DBS in BNST for patients with treatment-resistant depression and comorbid severe anxiety, including GAD.

Author Contributions

Matilda Naesström: conceptualization, data curation, funding acquisition, investigation, methodology, project administration, writing – review and editing. **Patric Blomstedt:** conceptualization, funding acquisition, investigation, methodology, resources, supervision, writing – review and editing. **Viktoria Johansson:** formal analysis, writing – original draft, writing – review and editing.

Ethics Statement

The study was approved by the regional ethics committee in Umeå (Dnr 08-090 M). DBS for treatment-resistant depression is considered an experimental therapy, and the patients underwent thorough examinations, received detailed information orally and in writing, and signed an informed consent before participation.

Conflicts of Interest

Professor Patric Blomstedt has served as a consultant for Abbott and Boston Scientific and is a shareholder in Mtithridaticum AB. Matilda Naesström and Viktoria Johansson declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.