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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jabbrv-ltwa-all.ldf jabbrv-ltwa-en.ldf**KEY CLINICAL MESSAGE**

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

Keywords: Deep brain stimulation, bed nucleus of the stria terminalis, medial forebrain bundle, depression, generalized anxiety disorder, clinical trial, neurosurgery

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 network brain activity through electrical stimulation (3). However, the efficacy of DBS for depression remains inconclusive (4) and one possible reason for these unsatisfactory results is that previous 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). To date, only case reports have described the treatment outcomes of DBS for severe anxiety or GAD. One case report from our research group describes improvements in a patient with anorexia nervosa, severe anxiety, and depression symptoms from DBS in the bed nucleus of stria terminalis (BNST) (7). Initially, the patient received DBS in the medial forebrain bundle (MFB) area which effectively reduced depressive and anxiety symptoms but was discontinued due to side-effects (blurred vision). Two years later, the DBS target was switched to BNST resulting in improvements in depression and anxiety symptoms. A similar recovery was described by McLaughlin et al. who reported a positive outcome after DBS in the ventral capsule/ventral striatum (VC/VS) in a patient with anorexia nervosa, depression, and GAD (8).

The above reports describe DBS delivered into BNST or VC/VS which are brain targets in close anatomical proximity to one another, believed to be part of the anxiety network (9,10). Other DBS anxiety network targets include the ventral anterior limb of the internal capsule (vALIC), and nucleus accumbens (NAc). DBS targeting this network has shown promise in treating obsessive-compulsive disorder (OCD), see Meyer et al. for review (11), with some studies showing reduced symptoms of depression and anxiety which indicate that the anxiety network may also influence mood regulation (12,13).

However, DBS studies on patients with treatment-resistant depression, targeting the anxiety network, have

yielded mixed results. For example, Dougherty et al. found no significant differences in depressive symptoms between patients randomized to active or sham stimulation in VC/VS after twelve weeks (14) and after two years, only seven of the 30 patients showed a treatment response. In contrast, Van der Wal et al. found that active vs. sham DBS in vALIC significantly reduced depressive symptoms, although differences in study design complicate direct comparisons to other studies (15). Open-label studies targeting BNST (16), NAc (17), or BNST and NAc simultaneously (18) showed treatment response of depression in a majority of the patients after one year or longer.

Given the limited research on DBS for patients with treatment-resistant depression and comorbid 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, we included BNST as an additional target (13). Both patients received bilateral dual electrodes in the MFB and BNST, randomized to either target, followed by cross-over stimulation for six months. The patients were then followed for up to five years, with monitoring of depressive and anxiety symptoms and overall functioning.

Case history / examination

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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 three 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, \soutand 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), 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.

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 age 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 ten 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.

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) (19). Treatment resistance was defined as four or more trials of standard treatments for depression, i.e. psychotherapy, pharmacological, or ECT.

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Depression severity (primary outcome) was assessed with the clinical interview version of the Montgomery-Åsberg depression rating scale (MADRS) (20). Depression treatment response was defined as a minimum of 50% reduction of MADRS scores compared to pre-surgery. Anxiety was measured with the Hamilton Anxiety Rating scale (HAM-A) (21). The Global Assessment of Functioning (GAF) scale was used to assess the level of function. (22). After DBS surgery, psychiatric symptoms were evaluated with MADRS, HAM-A, and GAF after three, six, and twelve months of active stimulation and then yearly until four- or five 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.

Surgical procedure

A 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 of the red nucleus, and two electrodes in the area of the BNST (Medtronic model 3387). After the procedure, the electrode positions were verified with a postoperative computed tomography scan fused with the preoperative stereotactic MRI (Figure 1).

Treatment with deep brain stimulation (DBS)

The participants were randomized to DBS in either MFB or BNST for the first three months, followed by a crossover to the opposite target area for three 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 Supplement Table 1.

Outcome and follow-up

Before surgery, both patients had MADRS scores of 44 and 49 points and HAM-A scores of 40 points, corresponding to severe depressive and anxiety symptoms (Table 2).

Patient 1 received DBS in the BNST for the initial three 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.

After completion of the randomization phase, DBS was resumed in BNST and turned off in the MFB area. A week later the patient reported anxiety relief. Over the next six 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 the patient did not experience any positive effect on depression during the following months. 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 volts), 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 three 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 five years after surgery (reductions MADRS 55%, HAM-A 65%, Table 2). Attempts of 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.

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 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).

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 sleeping disturbances and fatigue during DBS in BNST that were all transient.

jabbrv-ltwa-all.ldf jabbrv-ltwa-en.ldf**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 achieved remission from 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 open-label phase, both patients continued to receive BNST-DBS. One of the patients had several trials of DBS in the MFB area but did not experience any additive effect on depression, in addition to the anxiolytic effect of DBS in BNST. After four to five years, stable reductions in depressive and anxiety symptoms were recorded in both patients and the level of global functioning had increased.

In line with our findings, reduced anxiety or depressive symptoms have been previously reported in DBS studies on treatment-resistant depression (16,18,23), in OCD (12,13,24,25), and in two case reports on patients with comorbid anorexia nervosa, depression, and GAD (7,8). In the studies mentioned above, brain targets in the anxiety regulation network were stimulated (9). Thus, we speculate that DBS in areas believed to affect the anxiety regulation network might be more effective in treatment-resistant depression with a clear anxiety component.

The absence of a short-term antidepressant effect from DBS in the MFB area in the two cases could be due to several factors, such as a suboptimal placement of the electrodes, or a too-short stimulation period to achieve a sufficient antidepressant effect as previously discussed (26). In this report, the target area of the MFB was identified on a T2 MRI, based on the visualization of the subthalamic nucleus, red nucleus, and corpora mammillaria. However, it has been suggested that tractography (27,28) or intracranial electrophysiology recordings (29) are more precise methods to determine the electrode position.

jabbrv-ltwa-all.ldf jabbrv-ltwa-en.ldf*Conclusion*

This case report describes positive short- and long-term outcomes on anxiety and depressive symptoms and GAF from BNST-DBS in two patients severely disabled from treatment-resistant depression and GAD. The short-term effect of MFB-DBS in these particular 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.

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Author contributions

Matilda Naesström: Conceptualization, Data curation, Investigation, Methodology, Project administration, Validation, and Writing - review & editing. Patric Blomstedt: Conceptualization, Funding acquisition, Investigation, Methodology, Supervision and Writing - review & editing. Viktoria Johansson: Formal analysis, Writing - original draft and review & editing.

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 have no conflicts of interests to declare.

Ethical statement

The study was approved by the regional ethics committee in Umeå (Dnr 08-090M). 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.

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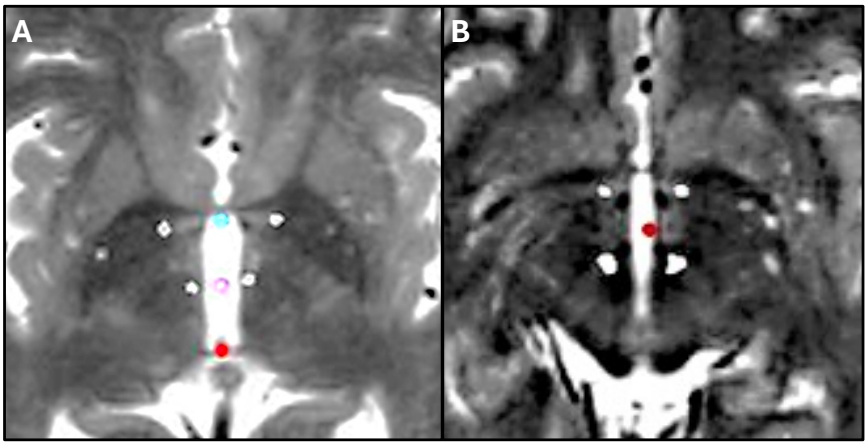
Figure legend

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.



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