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Reversible psychiatric adverse effects related to deep brain stimulation of the anterior thalamus in patients with refractory epilepsy

Soila Järvenpää [a,b,*], Jukka Peltola [a,b], Sirpa Rainesalo [b], Esa Leinonen [a,c], Kai Lehtimäki [a,b], Kaija Järventausta [a,c]

[a] University of Tampere, Faculty of Medicine and Biosciences, Tampere, Finland
[b] Tampere University Hospital, Department of Neurosciences, Neurology and Rehabilitation, Tampere, Finland
[c] Tampere University Hospital, Department of Psychiatry, Tampere, Finland

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ABSTRACT

Objective: Anterior nucleus of thalamus (ANT) deep brain stimulation (DBS) is becoming a more common treatment for drug-resistant epilepsy. Epilepsy and depression display a bidirectional association. Anterior nucleus of thalamus has connections to anterior cingulate cortex and orbitomedial prefrontal cortex, hence, a possible role in emotional and executive functions, and thus, ANT DBS might exert psychiatric adverse effects. Our aim was to evaluate previous and current psychiatric symptoms in patients with epilepsy undergoing ANT DBS surgery and assess the predictability of psychiatric adverse effects. Programming-related psychiatric adverse effects are also reported.

Method: Twenty-two patients with ANT DBS for retractable epilepsy were examined, and a psychiatric evaluation of depressive and other psychiatric symptoms was performed with Montgomery and Åsberg Depression Rating Scale (MADRS), Beck Depression Inventory (BDI), and Symptom Checklist prior to surgery, concentrating on former and current psychiatric symptoms and medications. The follow-up visit was one year after surgery.

Results: At the group level, no changes on mood were observed during ANT DBS treatment. Two patients with former histories of depression experienced sudden depressive symptoms related to DBS programming settings; these were quickly alleviated after changing the stimulation parameters. In addition, two patients with no previous histories of psychosis gradually developed clear paranoid and anxiety symptoms that also relieved slowly after changing the programming settings.

Conclusion: The majority of our ANT DBS patients did not experience psychiatric adverse effects. Certain DBS parameters might predispose to sudden depressive or slowly manifesting paranoid symptoms that are reversible via programming changes.

1. Introduction

One-third of patients with epilepsy do not respond adequately to antiepileptic drugs (AEDs) [1]. Epilepsy is defined as refractory when uncontrolled seizures continue after two or more appropriate AED treatments [2].

Deep brain stimulation (DBS) is a promising therapy for epilepsy. The bilateral anterior nucleus of thalamus (ANT) DBS has been studied previously [3–7]; in a double-blind randomized controlled trial, it was reported to reduce the frequency of seizures in patients with refractory epilepsy [8]. Since 2010, it has been CE (Conformité Européenne)-approved for epilepsy therapy in Europe, and it recently received approval from the Food and Drug Administration (FDA) in the USA. There is only limited knowledge of the basic mechanisms of DBS or of the optimal stimulation parameters. It has been suggested that DBS disrupts or inhibits epileptiform activity in epileptogenic thalamocortical networks [9].

The thalamus is connected and functionally related with the cortex and limbic structures. The ANT has a role in seizure activity in both absence and focal seizures; moreover, it is a part of the hippocampal system for episodic memory and has connections with the anterior cingulate and orbitomedial prefrontal cortex. Through its connections, it may contribute to both emotional and executive functions [10,11]. The ANT stimulation has been reported to activate the cingulate gyrus, insular cortex, and lateral neocortical temporal structures [12], which

Abbreviations: AED, antiepileptic drug; ANT, anterior nucleus of thalamus; AUDIT, Alcohol Use Disorders Identification Test; BDI, Beck Depression Inventory; DBS, deep brain stimulation; MADRS, Montgomery and Åsberg Depression Rating Scale; MRI, magnetic resonance imaging; NPI, Neuropsychiatric Inventory; SCL-90, The Symptom Checklist-90; SANTE, stimulation of the anterior nucleus of thalamus for epilepsy, trial; VNS, vagus nerve stimulation.

* Corresponding author at: Department of Neurology and Rehabilitation, Tampere University Hospital, PL 2000, 33521 Tampere, Finland.
E-mail addresses: soila.jarvenpaa@pshp.fi (S. Järvenpää), jukka.peltola@pshp.fi (J. Peltola), sirpa.rainesalo@pshp.fi (S. Rainesalo), esa.leinonen@pshp.fi (E. Leinonen), kai.lehtimaki@pshp.fi (K. Lehtimäki), kaija.jarventausta@pshp.fi (K. Järventausta).

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all have projections to amygdala, a structure involved in the initiation of emotional responses [13].

There is a bidirectional association between epilepsy and depression, and there could be some common pathophysiological mechanisms underlying the onset of epilepsy and psychiatric disorders including depression and anxiety [14,15]. Therefore, ANT DBS might impact psychiatric signs and symptoms. There are a few reports of psychiatric adverse effects related to ANT stimulation. In the stimulation of the anterior nucleus of thalamus for epilepsy, trial (SANTE) study [8], the patients in the active stimulation group reported more depressive symptoms compared with the control group (sham). One depression event in the active stimulation group was serious (suicide). Some, but not all patients, who experienced depression had also a prior history of depression. Subjective reports of depression and memory impairments have also been reported [16].

The aim of the present study was to evaluate previous or present psychiatric symptoms in patients intending to undergo an ANT DBS operation and to evaluate if these can predict possible psychiatric adverse effects that they might experience after the operation. The types of psychiatric adverse effects and also their management are described and also reported here.

2. Materials and methods

Twenty-two patients (14 males and 8 females; 36 ± 11.5 years old) with bilateral ANT DBS for refractory epilepsy participated in this study. The age of onset of epilepsy was 14 ± 8.6 years. The patients were severely ill; the mean frequency of their seizures was 42/month. The group was heterogenic with respect to epilepsy type, age of onset, medications, and burden of disease.

The patients had their ongoing AED treatments, and the possible psychiatric medications were also continued at the time of operation.

All patients gave written informed consent. The study protocol was approved by Tampere University Hospital Ethics Committee.

The DBS devices were implanted by a neurosurgeon in Tampere University Hospital during February 2010 to March 2016. The DBS electrodes (3389, Medtronic, Inc.) were implanted under general anesthesia using a Leksell Stereotactic Frame (Elekta). The initial stereotactic target was 5–6 mm lateral, 0–2 mm anterior, and 12 mm superior respective to the midcommissural point (MCP). The target was then adjusted according to each individual's anatomy in the 3-T magnetic resonance imaging (MRI) (Siemens) short tau inversion recovery (STIR) images by visualizing the mammillothalamic tract.

When the operation was being planned, a psychiatric interview was performed at baseline by an experienced psychiatrist concentrating on former and current psychiatric symptoms and medications. The follow-up visit was conducted at one year after the surgery. The Symptom Checklist-90 [17] (SCL-90) was performed to evaluate the subjective psychiatric symptoms. Beck Depression Inventory [18] (BDI) and Montgomery and Åsberg Depression Rating Scale [19] (MADRS) were used to assess the presence and severity of depressive symptoms. The Alcohol Use Disorders Identification Test (AUDIT) [20] was used to evaluate the risks associated with alcohol use. Neuropsychiatric symptoms were inquired by using the Neuropsychiatric Inventory [21] (NPI). Increase in score indicates increased severity in symptoms in all of the tests used.

The stimulation was initiated using the optimal contacts with a voltage of 5 V, 90 μs pulse width, and 140 Hz frequency. The cycling was 1 min on and 5 min off. The contacts or parameters were changed according to clinical judgment to improve the stimulation response in relieving epileptic seizures or due to psychiatric adverse effects.

Three-dimensional (3D) models of DBS electrodes, ANT, and volume of activated tissue were constructed with Medtronic SureTune II software using preoperative 3-Tesla MRI and postoperative computer tomography (CT) scan fusion images.

3. Results

There was no significant psychiatric morbidity in the whole study group. At baseline, the mean BDI score was 6.3 (range: 0–19), and MADRS was 2.7 (range: 0–8) in 18 patients (missing data in four patients). After one year, the corresponding values were BDI: 7.8 (range: 0–24, 20 patients, missing data in two patients) and MADRS: 5.1 (range: 0–11, 18 patients, missing data in four patients). Five patients were being prescribed with psychiatric medication before the operation: antidepressants, antipsychotics, and diazepam (DZP). Clobazam (CLB) and clonazepam (CLN) were used for epileptic seizures. One patient had a history of severe transient psychotic episodes of aggression and paranoid delusions and mental confusion one year before the DBS operation but did not experience DBS-related psychiatric adverse effects later. Some AED changes were made during the follow-up (Tables 1 & 2), but these did not cause the improvement in seizure control or mood changes in any of our patients.

Two patients experienced sudden-onset depressive and melancholic symptoms that were associated with programming. These symptoms appeared within a few days after adjusting the initial stimulation parameters; these were managed by either reducing the stimulation current or changing the contacts. In one of the patients (patient 2, Fig. 2), this took place at 1 month after the operation, and in the other patient, at 1.5 years after the implantation (patient 4, Fig. 4). Moreover, other kinds of psychiatric symptoms were detected in two patients; these included irritation, sleep disturbances, anxiety, fear, and paranoid symptoms. These symptoms developed slowly, over months, and were successfully managed also by adjusting the stimulation parameters and changing the active contacts (Figs. 1 & 3). The patients with these adverse effects and their management are described below (four case examples). Both patients with depressive adverse effects had former histories of depression, but none of them had previously experienced paranoid or anxiety symptoms.

3.1. Patient 1 (Fig. 1)

A woman in her late 40s had experienced focal epilepsy since 33 years. She was working as an assistant, and she lived alone. Her epilepsy was refractory despite several AED trials. Her seizure frequency ranged from 14 to 34/month. This patient was not a candidate for resective surgery. Vagus nerve stimulation (VNS) had been tried without any response. She had no former psychiatric history. Levetiracetam (LEV) had induced some depressive thoughts that vanished after discontinuation of the medication. Immediately after ANT DBS, she felt more active but was not diagnosed as being hypomanic. Monopolar stimulation was initiated with active contacts 2/10 (voltage: 4/4 V, therapeutic current: 4/6.6 mA current, 90 μs pulse width, and 140 Hz frequency). After six months, her seizure frequency was halved. Unfortunately, after 10 months of stimulation, the patient reported sleep disturbances and feeling depressive, and soon afterwards, she began to feel paranoid and annoyed. The change was insidious and happened without any clear triggering factors. Her initial psychiatric symptoms were mild but worsened gradually to an outright psychotic state including delusions and erotomanic thoughts. There were no signs of delirium, and the patient remained conscious and oriented throughout. She also began to experience psychogenic nonepileptic seizures along with anxiety and low mood. The patient had experienced similar nonepileptic seizures 8 years before, and these were confirmed at that time by video-electroencephalography (VEEG) as psychogenic nonepileptic seizures. Citalopram (CIT) 20 mg was provided to treat her depression and anxiety. The stimulation contacts were also changed to more cranial, active contacts were moved to 3 and 11, and the current was decreased to 5.9 mA/6.3 mA (right/left). After this reprogramming, the patient felt better, and gradually, her psychotic symptoms disappeared. Citalopram was continued 40 mg/day, patient also had her ongoing AEDs: zonisamide (ZNS) 400 mg, pregabalin (PGB) 600 mg, and lacosamide (LCM) 400 mg, quetiapine 25 mg was administered in the evening for sleep disturbances, when

Table 1
Responders (n = 15). Age, years with epilepsy, and medication are defined at the time of implantation. Only AEDs and psychiatric medication are detailed. Responder status is defined by at least a 50% seizure reduction in the dominant seizure type at 1 year after the surgery [22]. The case histories of the patients 1–3 are described in more detail in the text.
Abbreviations: CBZ, carbamazepine; CD, cortical dysplasia; CIT, citalopram; CLB, clobazam; CLN, clonazepam; DZP, diazepam; ESL, eslicarbazepine acetate; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; MZP, mirtazapine; NA, not available; OXC, oxcarbazepine; PGB, pregabalin; PHT, phenytoin; PSY, psychiatric; RIS, risperidone; TPR, topiramate; VPA, valproic acid; ZNS, zonisamide.

Patient	Sex	Age	Years with epilepsy	AED/PSY medication (mg) baseline → at 1 year	BDI baseline→ at 1 year	MARDS baseline→ at 1 year	Etiology	Epileptic zone
1	F	48	33	ESL 1600 → 0, LCM 0 → 400, PGB 600, ZNS 400	0 → 0	2 → 5	Unknown	Left occipital
2	F	24	7	CLB 20, CIT 20, OXC 1500, TPR 400	7 → 12	3 → 5	Encephalitis	Multifocal
3	M	29	9	CBZ 100, CLB 10 → 20, MZP 0 → 30	0 → 2	0 → 5	CD	Multifocal
5	F	32	31	CLN 8 → 6, PHT 200	1 → 3	4 → 9	CD	Left frontal
6	M	30	18	CBZ 1200, CLB 30, CIT 10 → 15	NA → 13	NA	CD	Multifocal
7	F	26	19	OXC 1500 → 1800, CLB 15, ZNS 400 → 300	NA → 4	NA → 0	CD	Multifocal
8	F	36	10	CBZ 800, CIT 40 → 30, DZP 0 → 20, KTP 0 → 600, LCM 200, LEV 1000, RIS 2 → 1, ZNS 400	5 → 0	1 → 0	CD	Right frontal
9	M	23	14	CLB 20, LTG 150, VPA 1500, ZNS 400	14 → 11	4 → 2	Encephalitis	Multifocal
10	F	31	3	CLB 20, LCM 0 → 500, OXC 1000, ZNS 500 → 200	16 → 16	6 → 8	Encephalitis	Multifocal
11	M	47	38	CBZ 400, CLB 15, ZNS 400	1 → 7	1 → 4	Unknown	Frontal
12	M	49	44	CBZ 600, LCM 400	4 → 7	2 → 9	Encephalitis	Right temporal
13	M	40	32	CLB 20 → 25, OXC 1650, ZNS 400	NA	NA	CD	Multifocal
14	M	56	42	OXC 1800	0 → NA	0 → NA	Unknown	Multifocal
15	M	29	20	OXC 1800, VPA 1300, ZNS 200	19 → 0	1 → 0	Unknown	Right frontal
16	M	22	7	LCM 200, OXC 900, ZNS 500	7 → 9	4 → 10	Encephalitis	Left hemisphere

necessary. Her seizure frequency improved further to three seizures/month (a 90% reduction compared with pre-DBS baseline). Her mood stabilized, and the psychotic symptoms had relieved when evaluated in the one-year follow-up.

3.2. Patient 2 (Fig. 2)

A woman in her mid-20s had refractory epilepsy after presumed encephalitis since 8 years. She lived alone and worked part-time as an assistant. Her seizures had failed to improve with multiple AED trials, and she was not a candidate for resective surgery. Vagus nerve stimulation was tried without any meaningful response. Epileptic seizures (biparietal seizure onset zone) occurred 14 to 32 times/month. She had had depressive symptoms and antidepressant medication after the onset of epilepsy but not before that time. She was receiving long-standing and still ongoing CIT 20-mg medication at the time of ANT DBS operation. At the baseline psychiatric evaluation, no depressive symptoms were present.

Stimulation was induced with active contacts 2/10 (voltage: 5/5 V, 90 μs pulse width, and 140 Hz frequency). Voltage was gradually increased to 6.5 V, which induced melancholia, tiredness, sadness, and somatic complaints which appeared within two days. The effect was seen in BDI, she had a score of 33 points i.e., evidence of severe depression.

This depressive effect vanished (BDI: 9) when the voltage was decreased to 5 V, again within two days. With these parameters, there was no change in her seizure frequency. When the contacts were changed to 3, 10, and 11 with the same parameters, the seizure frequency was further decreased. Furthermore, changing the contacts to 3 and 11, 5/4 V, the response to the stimulation in seizure frequency was even better, a 61% reduction.

A similar emergence of melancholia, sadness, crying, and depressive thoughts was seen three times when the current or pulse width in any of the chosen contacts was increased; and these were managed by decreasing the voltage and ultimately, by changing the contacts more cranial to 3 and 11. The AEDs used were oxcarbazepine (OXC) 1500 mg, topiramate (TPR) 400 mg, and CLB 20 mg. Citalopram 20 mg was also continued.

3.3. Patient 3 (Fig. 3)

A man in his late 20s had refractory temporal lobe epilepsy due to bilateral subependymal heterotopia since 10 years. The patient was not a candidate for resective surgery. Epilepsy was refractory; seizures in the patient had failed to improve with multiple AED trials, and epilepsy surgery was also considered. Postictal neuropsychiatric symptoms of aggression and confusion had been present, but the patient had no former or present psychiatric symptoms at the time of the ANT DBS operation. Stimulation was initiated with active contacts 2/10 (voltage: 2.5/2.5 V, 90 μs pulse width, and 140 Hz frequency). The voltage was increased gradually to 6.5 V. One year after the operation, the patient started to complain about low mood, but both BDI and MADRS scores indicated a euthymic mood (2 and 5, respectively). In the SCL-90 assessment, obsessions and depression were evident, and the patient also felt anguished. He reported fear, irritation, and memory problems. Intermittent periods with paranoid thoughts were also present. Mirtazapine (MZP) 30 mg and risperidone (RIS) 1 mg were started, which improved the situation. Contacts 3 and 11 were added. The current was 10 mA on each side. The seizure frequency was improved by 80% as compared with baseline, but the patient still had paranoid thoughts, somatic

Table 2
Nonresponders (n = 7). Age, years with epilepsy, and medication are defined at the time of implantation. Only AEDs and psychiatric medication are detailed. Responder status is defined by at least a 50% seizure reduction in the dominant seizure type at 1 year after the surgery [22]. One patient is marked with an asterisk; that patient was still a nonresponder during the first year, however, reaching responding status later with optimal stimulation parameters. The case history of patient 4 is described in more detail in the text.
Abbreviations: CIT, citalopram; CLB, clobazam; ESL, eslicarbazepine acetate; LCM, lacosamide; LEV, levetiracetam; NA, not available; OXC, oxcarbazepine; PAM, perampanel; TPR, topiramate; VPA, valproic acid; ZNS, zonisamide.

Patient	Sex	Age	Years with epilepsy	AED/PSY medication (mg) baseline → at 1 year	BDI baseline→ at 1 year	MARDS baseline→ at 1 year	Etiology	Epileptic zone
4*	F	54	35	LCM 500 → 600, TPR 400 → 300	7 → 13	5 → 9	Hippocampal sclerosis + CD	Left temporal
17	M	22	10	VPA 2500	NA	NA	Encephalitis	Multifocal
18	M	48	37	CLB 20 → 40, LCM 400, OXC 1500	0 → 1	2 → 2	CD	Right temporal
19	M	24	5	CLB 30, LEV 2000, OXC 1800, TPR 600	18 → 24	8 → NA	Unknown	Left parietal
20	M	45	9	CIT 20, LCM 400, LEV 3000, OXC 1200	5 → 11	2 → 8	Unknown	Right frontal
21	M	50	49	CLB 10, LCM 400, PAM 8	2 → 4	0 → 0	Ischemic lesion	Right frontal
22	F	31	8	ESL 2000, LEV 3000, ZNS 400	7 → NA	3 → NA	Encephalitis	Multifocal

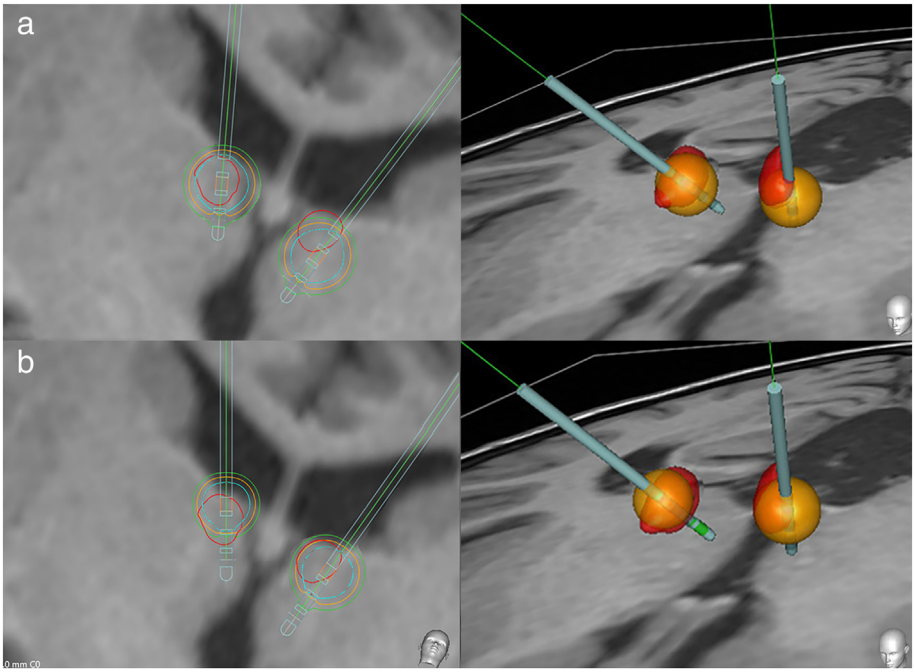

Fig. 1. Patient 1. The stimulation was initiated with contacts 2 and 10. Gradually, the patient started to experience a change in mood and had feelings of being monitored and eavesdropped. Bizarre thoughts i.e., feeling that she was magnetic started to appear (a). The stimulated contacts were changed to being more cranial to 3 and 11 and her psychotic symptoms started to dissipate (b).

complaints, and self-observation. He did not continue to take the psychiatric medications. His psychiatric symptoms were gradually worsening, and patient had become more paranoid with aggressive thoughts. The active contacts were changed to 3 and 11, voltage was 6.5/6.5 V, and pulse width was 90 μs with a frequency of 140 Hz, which resulted in a reduction in his psychiatric symptoms. In this case, the slowly initiating, alternating, and gradually worsening irritation, anxiety, and paranoid thoughts were seen as adverse effects to the stimulation. His symptoms became reduced when more cranial contacts were chosen, and the current was decreased. This patient was rather similar with case 1. He was prescribed with carbamazepine (CBZ) 100 mg and CLB 10 mg as AEDs.

3.4. Patient 4 (Fig. 4)

This patient was similar to case 2. A woman in her mid-50s had temporal lobe epilepsy due to hippocampal sclerosis and cortical dysplasia since 34 years. She was also diagnosed with rheumatoid arthritis. She had had no former psychiatric symptoms. Temporal resection and amygdalohippocampectomia was conducted at the age of 45 years. After epilepsy surgery, she was initially seizure-free for other seizure types except auras. The following AEDs were used: CBZ 1050 mg and TPR 200 mg. Five years after her surgery, seizures with impaired awareness (FIAS) reappeared with increasing frequencies. Simultaneously, the patient felt depressive, and CIT 20 mg was started from which she benefited. Five years later, ANT DBS was chosen to treat the patient's temporal lobe epilepsy. In the preoperative psychiatric interview, the patient had no depressive symptoms, BDI: 7, MADRS: 5. She felt tense after the surgery and was afraid of the seizures, and this induced some anxiety in the patient. Stimulation was initiated with bipolar settings, contacts 2 and 10 were positive, and 3 and 11 were negative (voltage: 3.5/4 V, 90 μs pulse width, and 140 Hz frequency). The current was gradually increased to 6 mA, and after 6 months, the seizure frequency was decreased by 75% compared with baseline. The minimal depressive symptoms and the fear of seizures had become alleviated; CIT was discontinued. Nonetheless, her seizure frequency was not optimal. Stimulation was changed to being monopolar, active contacts were 3 and 11, voltage 4.5/5 V, other parameters were not changed. With these settings, the patient experienced again sudden depressive thoughts, but when the current was decreased to 7 mA bilateral, her depression vanished. Rating scale was not collected during sudden depressive thoughts. The total seizure frequency was improved by 32% when compared with baseline.

4. Discussion

At the group level, no significant changes on mood were observed after ANT DBS treatment in our study. Two patients experienced abrupt depressive symptoms related to the DBS programming settings; these were quickly alleviated by decreasing the intensity of the stimulation but without changing the active contacts. In addition, two patients gradually experienced paranoid and anxiety symptoms which again improved slowly after changing the programming settings from contacts inferior to ANT to ones inside ANT.

In line with previous studies [8,23], there were no severe psychiatric adverse effects in these 22 patients who underwent ANT DBS for refractory epilepsy. Moreover, the four moderate psychiatric adverse effects could be clinically managed by reprogramming the stimulator in collaboration with specialists. Previously, depression has been reported to worsen in some patients who had had a previous depressive history [23,24], however, it has not been previously reported that there can be a sudden appearance and disappearance of depression with these fluctuations being dependent on the stimulation parameters. It is true that the present patients with depressive adverse effects had previously experienced depression, and therefore, it may be considered as a predisposing factor. Paranoid and anxious reactions occurred after the stimulation, a phenomenon that has also not been demonstrated before. This reaction scenario appears to be related to the stimulation of deep structures beneath the ANT, and it has a gradual onset. It is important to recognize these symptoms and react early since severe depressive and paranoid symptoms may endanger the success of the whole treatment. On the other hand, the described symptoms were transient in nature and reversible after changes to the stimulation parameters.

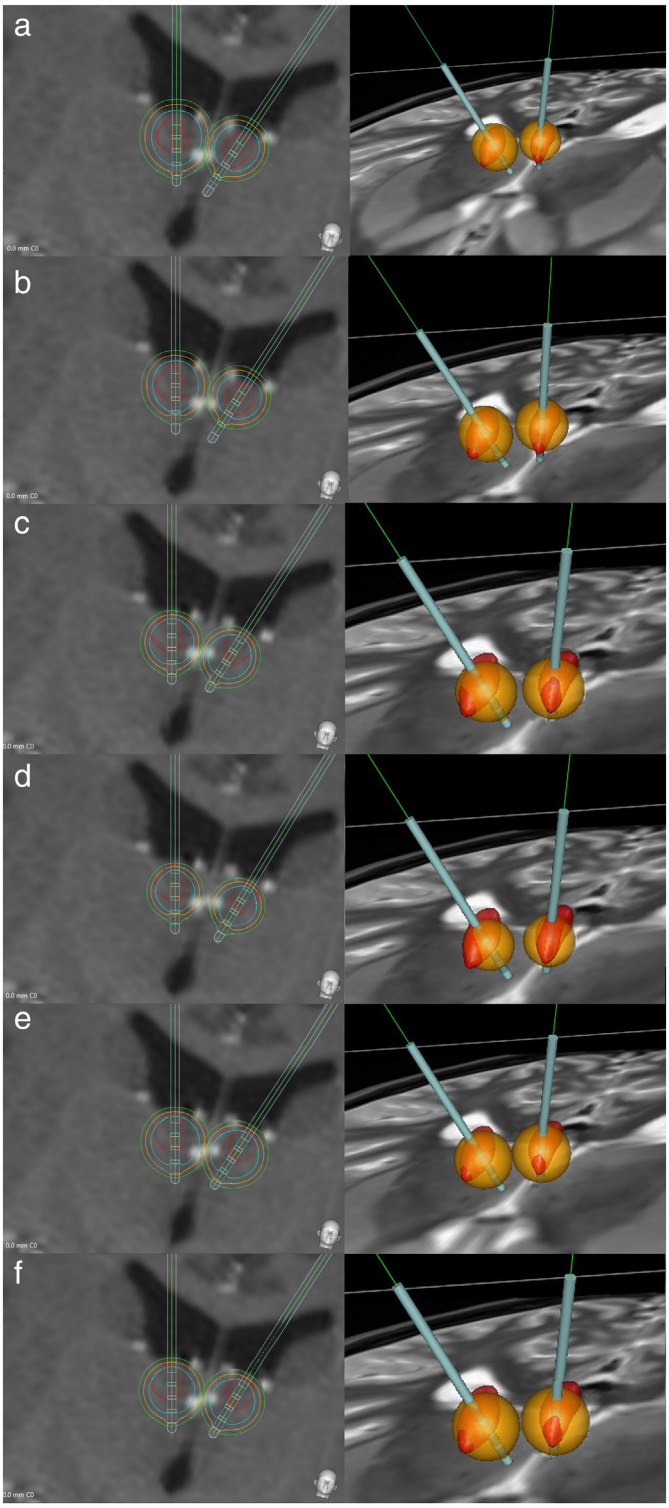

Fig. 2. Patient 2. (a) Contacts 3/10/11 were activated for stimulation, which resulted in an increase in the current from 5.8 mA on the left and 5.9 on the right to 6.1 mA on the left and 9.3 mA on the right. The patient developed depressive symptoms. (b) The voltage was switched to 5 V on the left and 4 V on the right. This resulted in a decrease in the current and a disappearance of depressive symptoms. (c) Voltage was raised from bilateral 5 V to bilateral 6.5 V, which led to the appearance of new depressive symptoms. (d) Adjusting the voltage back to bilateral 5 V eliminated the depressive symptoms. (e) Pulse width was increased from 150 μs to 180 μs again inducing depressive symptoms. (f) Reducing the pulse width back to 150 μs eliminated the depressive symptoms.

Patients with refractory epilepsy are a very heterogeneous group with regard to etiology, seizure burden, medication, and level of cognitive abilities. When evaluating mood and cognitive functions before and after DBS, there are several confounding factors that need to be considered. The psychiatric evaluation is challenging in this patient group although BDI and MADRS can be used to assess depressive symptoms and their severity. By using the SCL-90, the psychiatric symptoms can also be detected, but very often, patients with epilepsy are fearful about their seizures and are susceptible to self-observation, and these symptoms can be falsely interpreted as anxiety. The benefit of SCL-90 is the possibility to compare the symptoms at different time points. The burden of disease is also a fact that should be considered.

Mood disorders and cognitive decline are common comorbidities of epilepsy, and thus, the effects of DBS on psychiatric and neuropsychological states have attracted increasing interest. According to the current evidence, significant stimulation-related and persistent psychiatric symptoms are infrequent in ANT DBS patients [25–27]. In our sample, when these symptoms did emerge, they were reversible with reduction in stimulation. Mild reductions did not impede seizure control. In a randomized controlled trial, a subjective deterioration of mood and memory was reported during a blinded phase [8]. In the long-term follow-up, most neuropsychological test results improved [8,23,24]. The majority of patients with self-reported and objectively assessed depression had preexisting depression [24]. This was also the case in our two patients with depressive adverse effects. One study reported a deteriorated response inhibition and improved attention allocation towards a threat in ANT DBS patients [28]. It has been claimed that ANT DBS might exert positive effects on mood [8,24], verbal fluency, and delayed verbal memory [29] at 1–2 years after surgery, though the concurrent seizure reduction means that the interpretation of these results is susceptible to confounding. A voltage-dependent sleep disruption caused by ANT DBS has been reported; this may be related to subjective symptoms of cognition and mood [30]. Psychotic and depressive symptoms have been suggested to be associated with dramatic reduction of seizure frequency — a phenomenon referred to as forced normalization [31].

These patients were carefully evaluated before the surgery, and the clinical evaluation and management of possible psychiatric adverse effects were conducted in close collaboration with a neurosurgeon, a neurologist, and a psychiatrist. The adverse effects described here were all managed by changing the stimulation parameters. There seemed to be a pattern of the sudden appearance of a depressive effect in response to a high current, and there may be caudal contacts that were also managed rapidly by adjusting the parameters. At the group level, a history of psychiatric symptoms did not seem to predispose to psychiatric adverse effects of ANT DBS, although two patients with depressive adverse effects had previous histories of depression. Moreover, the feelings of paranoia and anxiety were more slowly appearing and harder to detect psychiatric adverse effects; they were also managed with reprogramming, but the recovery was slower. Although, even these adverse effects were clinically managed, in a worst-case scenario, they could well jeopardize the success of DBS treatment. The sudden appearance of severe depression may lead to serious consequences. Moreover, the patient with paranoid thoughts insisted that the device should be removed. In addition, the compliance with psychiatric medications and treatments can be poor in these occasions. Moreover, when the irritable feelings, anxiety, and paranoid thoughts are transient and fluctuating, they might be hard to detect during clinical outpatient appointments or settings. Therefore, the close collaboration between psychiatrists, neurologists, and neurosurgeons is crucial.

Overall, the majority of our ANT DBS patients did not experience psychiatric adverse effects. Although, certain DBS parameters might predispose to the sudden appearance of depressive or slowly manifesting paranoid symptoms, these were found to be reversible via programming changes. If left untreated, these symptoms might compromise the ANT DBS treatment. Because of self-reported depression and memory problems and the crucial positioning of the ANT within the Circuit of

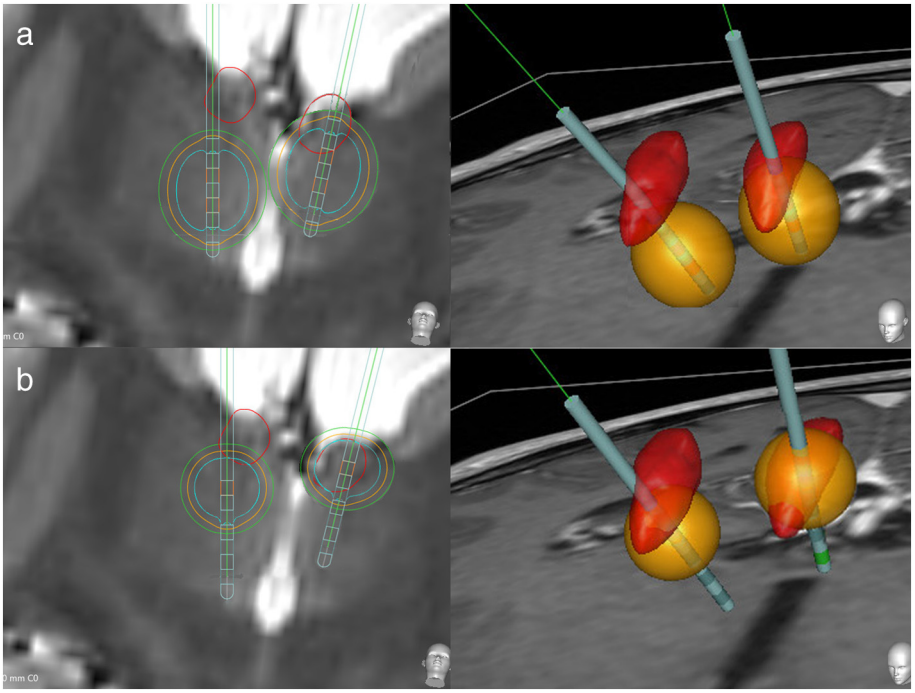

Fig. 3. Patient 3. (a) Initially stimulated with contacts 2 and 10, deeper contacts 1 and 9 were also activated for stimulation. The patient started to feel anxious soon after the change. Psychiatric symptoms were relieved by initiation of RIS therapy. The patient contacted doctors and nurses frequently with overly long incoherent messages; he started to experience psychotic symptoms and repeatedly refused reprogramming of DBS contacts. Three years after the initiation of stimulation with deep contacts, the patient was nervous and tense at the follow-up appointment and was found in the clinic's bathroom in a confused state. (b) Finally, the patient consented to changing the stimulated contacts to the uppermost 3 and 11. After this change, the psychotic symptoms became gradually relieved.

Papez, a reputed regulator of mood and memory, it is recommended that a neuropsychological and psychiatric evaluation of ANT DBS patients should be done routinely prior to and after the surgery. The current evidence on psychiatric adverse effects has been mostly limited to studies with small sample sizes and confounding factors. More studies with reliable designs, standardized neuropsychological and psychiatric assessment protocols, and larger sample sizes will be needed to investigate the independent effects of ANT DBS and the significance of particular stimulation parameters on mood and cognition.

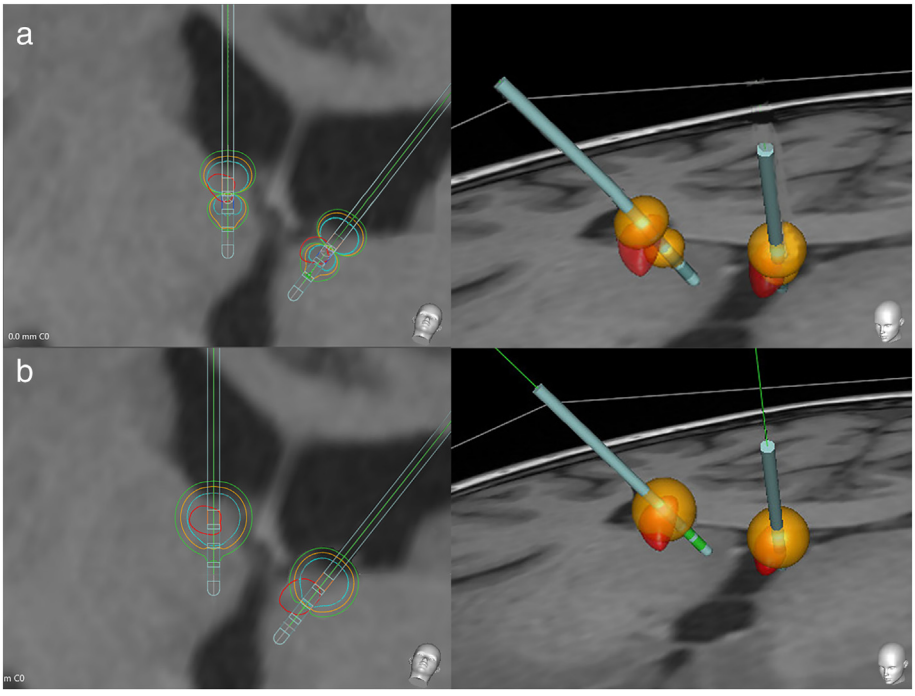

Fig. 4. Patient 4. The current increased from 6.8 mA to 9 mA on the left and from 6.6 mA to 8.3 mA when transitioning from bipolar stimulation of anodes 2 and 10 and cathodes 3 and 11 (a) to monopolar stimulation of 3 and 11 (b). The patient started experiencing depressive symptoms, which were relieved by lowering the voltage on the left from 4 V to 3.5 V while voltage on the right remained at 4.5 V. This lowered the currents to 7.1 mA on the left and 7.4 mA on the right and resulted in relief of her depressive symptoms and a decrease in the seizure frequency.

Authors and contributors

SJ contributed to study conception, creating of 3D-models, and drafted the manuscript. JP contributed to study conception, neurological follow-up, and drafted the manuscript. SR contributed to patient follow-up and analysis and drafted the manuscript. EL contributed to drafting of the manuscript. KL contributed to study conception and drafted the manuscript. KJ contributed to study conception, psychiatric interviews and evaluations, and drafted the manuscript.

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Ethics statement

The study was approved by the Ethics Committee of Pirkanmaa Hospital District. Written informed consent was obtained from each of the patients.

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Conflict of interest declaration

SJ and SR declare no conflict of interest. JP has received speaker and consultation fees from Medtronic. KL has received speaker honoraria from Medtronic, Boston Scientific, and Abbot. KJ has received lecture fees from Medtronic, Otsuka Pharmaceutical, and Lundbeck and has been sponsored to travel and attend to a medical congress by Medtronic.

Data sharing

Additional unpublished data from the study are available for psychiatric, neurological, and neurosurgical patient files and psychiatric interview test results accessible to all the authors. Also, full patient demographics and diaries of patient visits, dated stimulation parameters, and monthly seizure frequencies are available. Three-dimensional modeling of implanted DBS contacts created in Medtronic SureTune 2 are available for SJ and KJ.

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