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**Research article**

**Long-term outcome of thalamic deep brain stimulation in two patients with Tourette syndrome**

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## **ABSTRACT**

**Objective:** Thalamic deep brain stimulation for intractable Tourette Syndrome has been introduced in 1999 by Vandewalle et al. In this follow-up study we report on the long-term (6 and 10 years) outcome in terms of tic reduction, cognition and mood and side-effects of medial thalamic DBS in two previously described Tourette patients.

**Methods:** We compared the outcome of two patients at 6 and 10 years after surgery with their preoperative status and after 8 months and 5 years of treatment, respectively. Standardized video recordings were scored by three independent investigators. Both patients underwent (neuro)psychological assessment at all time points of follow-up.

**Results:** Tic improvement observed at 5 years in patient 1 (90.1%) was maintained at 10 years (92.6%). In patient 2 the tic improvement at 8 months (82%) was slightly decreased at 6 years (78%). During follow-up, case 1 revealed no changes in cognition, but case 2 showed a decrease in verbal fluency and learning which was in line with his subjective reports. Case 2 showed a slight decrease in depression but overall

psychopathology was still high at 6 years after surgery with an increase in anger and aggression together with difficulties in social adaptation. Besides temporary hardware related complications no distressing adverse effects were observed.

**Conclusion:** Bilateral thalamic stimulation may provide sustained tic benefit after at least 6 years but to maximize overall outcome, attention is needed for postoperative psychosocial adaptation, already prior to surgery.

## **INTRODUCTION**

Tourette Syndrome (TS) is a chronic complex neuropsychiatric disorder characterized by tics. Tics are sudden, repetitive, stereotyped muscle contractions (motor tics) or sounds (vocal tics).[1] Tics can be seen as fragments of normal motor action or vocal productions that are misplaced in context and that can be easily mimicked and at times confused with goal-directed behavior.[2] For many patients, especially those with mild symptomatology, medication and/or psychobehavioural strategies are sufficient. For patients, refractory to any treatment, surgery may be the treatment of last resort. Electrical deep brain stimulation (DBS) of the thalamus has been introduced as a new surgical technique for the treatment of intractable TS in 1999.[3] Vandewalle et al.[3] selected a trajectory that included the centromedian (CM), the ventral oral internal thalamic nuclei (Voi) and the substantia periventricularis (Spv) mimicking the lesions performed by Hassler and Dieckman[4], who used to perform more than 10 up to 14 lesions in each hemisphere. The promising effects of bilateral thalamic DBS have been described in three patients with a follow-up period of 5 years, and 8 months respectively.[5] There was a reduction in tics of 72-90% and an improvement of associated behavioural disorders.

Since then, thalamic DBS in TS has received increasing attention. A growing number of patients undergoing thalamic DBS have been reported in the literature.[5-13] However, most published series included either few cases or relatively short follow-up periods. The aim of the present study was to describe the long-term effects of bilateral thalamic DBS on tics and overall outcome (i.e., associated behavioural disorders, cognition and mood and possible adverse effects), in 2 of the 3 earlier mentioned patients with TS.

## **METHODS**

Patients were selected for thalamic DBS based on the following criteria: the adult patient has definite TS with frequent and disabling motor and vocal tics not responsive to treatment with multiple neuroleptics and psychotherapy. In both patients, there was no co-morbidity except for associated behavioural symptoms. The patient selection criteria and operation procedure have been previously described.[3] Two out of 3 patients were evaluated during a period of 10 and 6 years respectively. The third patient was lost to follow up due to emigration.

The target was defined 5 mm lateral to the anterior commissure (AC) – posterior commissure (PC) line, and 4 mm posterior to the midcommissural point, and at the AC-PC plane. Because of a stimulation-induced feeling of fear during test stimulation, in patient 1 the right electrode was placed 2 mm more medial and the left electrode in patient 2 was placed 3 mm lateral to the AC-PC line. We saw the patients every time the internal pulsegenerator (IPG) had to be replaced. The patient in case 1 received 2 IPG replacements in 10 years and the patient in case 2 received 7 replacements in 6 years. We changed stimulation parameters when a satisfactory response was not achieved or if adverse events were thought to be related to stimulation. Both patients were videotaped before and after surgery and were assessed at 3 different time points starting with preoperative assessment and at 5 and 10 years postoperatively in case 1, and 8 months and 6 years postoperatively in case 2. During postoperative follow-up we made 20 minutes video-registrations in chronic bilateral ON-stimulation and after 12 hours OFF-stimulation. More detailed information about video-protocol and follow-up has been previously described in 2003.[5] Video-fragments of 10 minutes were scored by 3 blinded investigators (A.W., F.P. and L.A.). Both patients underwent psychological examination at all time points including assessment of cognition and mood.

Because of stimulation with increasing voltages in case 2, we made a multi-slices CT-scan to control the position. The same type of CT-scan was performed in case 1 to exclude a cholesteatoma, because of complaints of chronic otitis media and tinnitus. Both CT-scans did not show any abnormalities (see figure 1). In our centre it is contraindicated to perform Magnetic Resonance Imaging (MRI) in patients with any kind of neurostimulator.

## **RESULTS**

### **Effect on tics and associated behavioural disorders**

The absolute numbers of tics per 10 minutes for both patients are presented in Table 1.

*Case 1:* This 42 year old male was operated in 1997 by VVV. Before surgery motor tics consisted mainly of turning movements of the neck, licking and biting his shoulder, and adduction movement of the knees. Blowing and uttering sounds were the most prominent phonic tics. Compared to the number of tics prior to surgery, there was a 90.1% tic-reduction at five years after surgery<sup>5</sup>, increasing to 92,6% (from 422/10min to 31/10min) at ten years after surgery. The patient still demonstrated some turning movements of the head, eye blinking and blowing. During stimulation (on) there was no self-injurious behavior like biting in his shoulder and checking compulsions resolved completely.

*Case 2:* This 45 year old male was operated in 2002 by VVV. Motor tics like head turning, flexion movements of the head, eye blinking, touching eyelid, contracting the abdominal muscles, and grimacing, and phonic tics like sniffing, coughing and screaming were present before surgery. Pounding the stomach and screaming were the most disabling tics prior to surgery. The patient also had compulsive behavior like breaking glasses with his hand or head. Eight months after the operation there was a tic-reduction of 82%<sup>5</sup> and 78% (from 196/10min to 42/10min) after 6 years of follow-up. Major tics such as pounding his stomach, screaming, sniffing, coughing and flexion movements of the head had disappeared but he still demonstrated motor and phonic tics, especially grimacing, abdominal contractures and small uttering sounds. The compulsive behavior was in control.

In both patients, all major tics and compulsions had disappeared. In the stimulation-OFF condition with the stimulator switched off for 12 hours, there was still a tic-reduction in patient 1 of 78% (422/10min to 90/10min) and in patient 2 of 54% (196/min to 90/10min).

### **Effects on cognition and mood**

*Case 1:* Postoperatively (both 5 years and 10 years after DBS), measures of cognition (e.g., verbal and non-verbal memory, executive function, mental speed and attention) showed little or no change compared to those assessed preoperatively. The Beck Depression Inventory (BDI)[14] was administered during the postoperative follow-up only and showed mild to moderate signs of depression (total scores were 14 and 17, respectively). At 10 years after surgery the patient reported to be very pleased with the results without a need to discard Tourette from his self-image.

*Case 2:* The neuropsychological assessment battery in case 2 was more extended than that in case 1. Compared to the baseline assessment prior to surgery, there was a postoperative decline in verbal fluency, in particular letter fluency, and in the total number of words learned in five trials of an auditory verbal learning task. Reproduction scores (free recall and recognition) showed no change over time. The time needed to perform the color word task of the Stroop[15], a measure of selective attention, increased substantially at 8 months after surgery but decreased to the baseline level at 6 years after surgery. Psychiatric questionnaires including the BDI[14] (total scores were 19 prior to surgery and after surgery 15 and 10, respectively) and the Minnesota Multiphasic Personality Inventory-2 (MMPI-2)[16] showed a slight decrease in depression but the overall psychopathology based on the clinical scales of the MMPI was still high at 6 years after surgery. Figure 2 shows the measures on the respective clinical scales of the MMPI before surgery, 8 months (short-term follow-up) and 6 years (long-term follow-up) after surgery. The measures on the validity scales L (Lie), F (Infrequency) and K (Correction) fulfilled the criteria for interpretation at all moments of follow-up with high F scores indicating a cry for help. Both before and after surgery the profile of measures was pathological with relatively low scores for items related to somatisation and sexual identity. Compared to preoperative levels there was an increase in scores on items related to social adaptation, aggression and anger. Anger scores were very high (T-score = 87) at 6 years after surgery and were also confirmed during the interviews. The patient suffered from many events including serious marital problems, recurring financial problems and health problems. Although his energy level had significantly decreased he was content with the effect of surgery at 6 years after surgery. In contrary to the patient in case 1 he was very eager to abandon Tourette from his self-image but so far he could not enjoy a life unrestricted by tics.

### **Stimulation parameters**

The stimulation parameters for each patient at 5 years in case 1 and 8 months in case 2 and at long-term follow-up (10 and 6 years respectively) are shown in table 2.

During the follow-up period in case 2, there have been major adjustments to the stimulation parameters with a progression of monopolar stimulation towards bilateral bipolar stimulation. The stimulation has been increased from 2,5 to 8,5V with bipolar stimulation. The patient in case 1 needed a lower voltage to avoid side-effects (dizziness, blurred vision) at long term follow-up.

### **Adverse events**

Both patients reported a reduction in energy when the current intensity reached the level necessary for an optimal effect on tics. Therefore the patient in case 1 turned down his stimulation a few times during the day. The patient in case 2 did not adjust the stimulation settings and preferred the feeling of drowsiness above his tics. Both patients had hardware related complications, consisting of traction of the lead in the neck. Multiple revisions of the wound and local injections have been done with partial effect in both patients. Whereas the patient in case 1 received 2 IPG replacements in 10 years, the patient in case 2 received 7 replacements in 6 years due to his high voltage stimulation.

Effects on sexual functioning including an increased sexual drive in case 2 at 8 months after surgery have been described previously in detail. [17-18] Sexual functioning (see table 3) was measured by the International Index of Erectile Function (IIEF) including five domains.[19]

At long term follow-up, there was a decrease in erectile and orgasmic function of the patient in case 1 when compared with scores before and 5 years after surgery. The IIEF scores in case 2 showed a substantial improvement in sexual functioning at 8 months after surgery but a slight decrease at the long-term follow-up except for sexual drive that increased to the maximum level.

The patient in case 2 reported difficulty with his visual adaptation and vertigo but both complaints did not interfere with his daily life. Examination by an ophthalmologist did not show any disabilities. Given the complaints in case 2 we made inquiries about vision and vertigo in case 1 and he appeared to have difficulty driving his car with the stimulator on, because of a so called blurred vision by looking ahead. Turning down the voltage by his patient programmer reduced these complaints.

## **DISCUSSION**

In both patients with TS treated by bilateral thalamic stimulation, the substantial improvement in tics observed at the initial 5 year and 8 months follow-up examination (90% and 82% improvement of tic score) was maintained after a total period of 10 and 6 years (92.6% and 78%, respectively). Corresponding to the short term follow-up assessments of the present cases[5] only video-tic rating scales were used for evaluating the long-term efficacy of surgery. The adverse events observed in both patients were related to the hardware, energy level and vision but were not distressing at long term follow-up. The cognitive decline in case 2 concerning both verbal learning and verbal fluency is in line with findings related to left-sided thalamotomy and thalamic stimulation but the effect on daily functioning is considered small.[20] Although there might be involvement of the left thalamus in memory and language function[21], thalamic stimulation did not affect the postoperative performance of case 1. Besides, a postoperative decline in verbal fluency has also been reported after stimulation of the subthalamic nucleus, but again the impact on daily life is regarded as small.[22] The increase of stimulation strength seen during the follow-up period in case 2 could be the result of tolerance. Because of normal long-term follow-up CT-scan compared with the standard CT-scan, immediately after surgery, electrode malposition seems unlikely. As cited by Blomstedt et.al., increased use of bipolar stimulation over time can be interpreted as a consequence of development of tolerance to a level where monopolar stimulation cannot be increased further without eliciting side-effects.[23] This was the case in patient 2: monopolar stimulation of pole 1 and 5 led to bipolar stimulation of pole 1,2,3 and 5,6,7 at long term follow-up.

The present results indicate that bilateral thalamic DBS is effective in producing sustained improvement of tics in Tourette patients followed for more than 6 years. In addition, these results confirm the relevance of this brain area in the pathogenesis of TS. When the stimulator is switched off, tics reappear, which indicates that thalamic DBS does not induce permanent tic improvement in TS. However, the tics did not return to the pre-operative level which might be an after stimulation effect. Therefore, when one aims to measure tics in the stimulation off condition, it is recommendable to switch the stimulator off for a longer period. The duration of this period is still debatable. Although one surgeon (VVV) performed both surgeries, the setting of surgery was different causing the dissimilarity in both time points of postoperative evaluation and pre- and postoperative assessments (e.g., the preoperative assessment of case 1 did not include the BDI).

Although the small number of patients did not allow performing a statistical analysis and confirmation is needed by double blinded randomized trails, our observations provide a rationale for an effective treatment of TS. One major concern however is the success of adaptation after the relatively sudden alleviation of tics. Whereas advances in medicine are aimed at alleviation of untreatable chronic conditions, there have been few attempts to study the process of adaptation which is provoked by such a sudden relief.[24] Given the consequences of TS for social, familial and professional life, patients have to deal with many challenges after surgery as shown by both cases but in particular the patient in case 2. Anticipating on this postoperative adjustment prior to surgery will be helpful to assist patients and their families in benefiting from tic reduction and maximizing the overall outcome and success of surgery.

## **CONCLUSION**

The present long term follow-up study of two Tourette patients further supports the beneficial effect of bilateral thalamic DBS on tic reduction. Development of tolerance occurred in one of two patients and attention is needed for the adverse effects and in particular whether these are incidental or structural. The results of this open-label study justify a larger, double blinded randomized clinical trial. This study should however include a strategy to deal with the postoperative psychosocial adjustment in order to maximize the overall outcome.

## **CONTRIBUTORS**

LA conceptualized and wrote this article. AD participated in collection and analysis of (neuro)psychological data. AD, YT, EB and VVV contributed to clinical care and to the writing of this article. FP, AW and LA participated in tic-data collection. LA had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication. All authors critically reviewed manuscript and have seen and approved the final version.

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Table 1: Total amount of tics per 10 min pre- an postoperatively in ON/OFF condition in two Tourette patients

patient	Video tics/10min									
	Pre-op		F-U ON		F-U OFF		Long term F-U ON		Long term F-U OFF	
	<i>motor</i>	<i>vocal</i>	<i>motor</i>	<i>vocal</i>	<i>motor</i>	<i>vocal</i>	<i>motor</i>	<i>vocal</i>	<i>motor</i>	<i>vocal</i>
1	380	42	23	19	83	23	13	18	71	19
2	142	54	24	10	94	36	36	7	60	30

Pre-op = pre-operative, F-U = follow up

Table 2: Stimulation parameters at follow-up of 2 Tourette patients who received bilateral thalamic stimulation

Patient	electrode settings				amplitude				rate		pulsewidth	
	F-U		long term F-U		F-U		long term F-U		F-U	long term F-U	F-U	long term F-U
	L	R	L	R	L	R	L	R				
1	4-,5-/6+,7+	0-,1-/2+,3+	4-,5-/6+,7+	1-/case+	2,2	2,4	1,8	1,5	100	130	210	90
2	5-/case+	1-/case+	5-,6+,7-	1-,2+,3-	2,4	2,8	8,5	8,5	100	100	210	150

Each electrode has 4 poles with 0 most ventral and 3 most dorsal for right stimulation, or 4 most ventral and 7 most dorsal for left stimulation

When case is +, the stimulation is monopolar.

L=left, R=right, 2m=at 2 months, F-U=at follow-up 5 years and 8 months for patients 1 and 2 resp.

Table 3: Results of IIEF in two Tourette patients who underwent thalamic DBS

subscores	patient 1			patient 2				
	no items	max score	preoperative	postoperative	long term	preoperative	postoperative	long-term
erectile function	6	30	30	30	23	13	20	15
orgasmic function	2	10	10	10	8	0	10	8
sexual desire	2	10	8	10	8	5	9	10
intercourse satisfaction	3	15	12	11	13	6	14	10
overall satisfaction	2	10	8	8	9	2	10	2

IIEFa = International Index of Erectile Functioning (Rosen et al 1997). High scores suggest a better sexual functioning

Figure 1: post-operative multi-slices CT-scan of both Tourette patients 10 and 6 years respectively

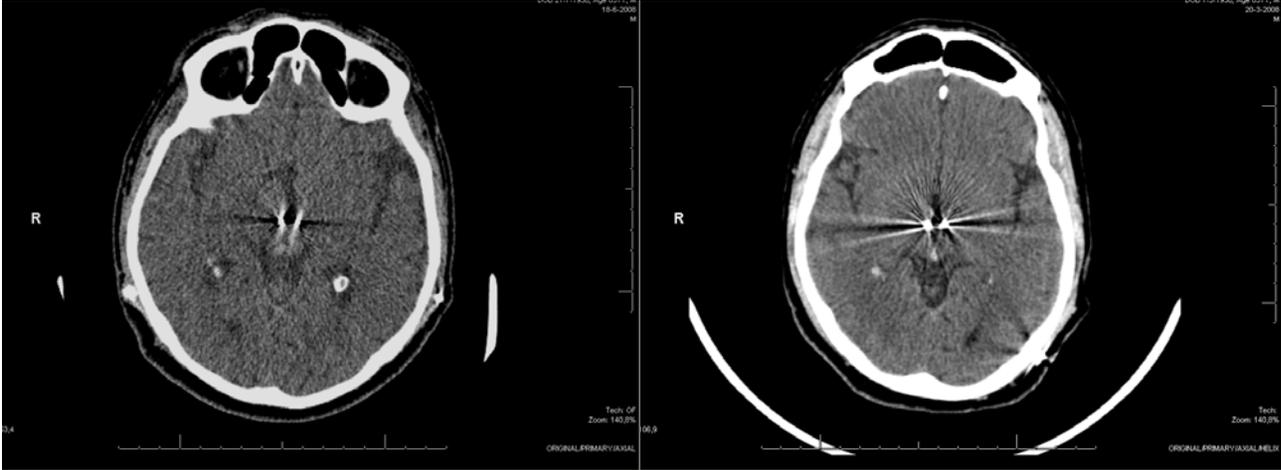
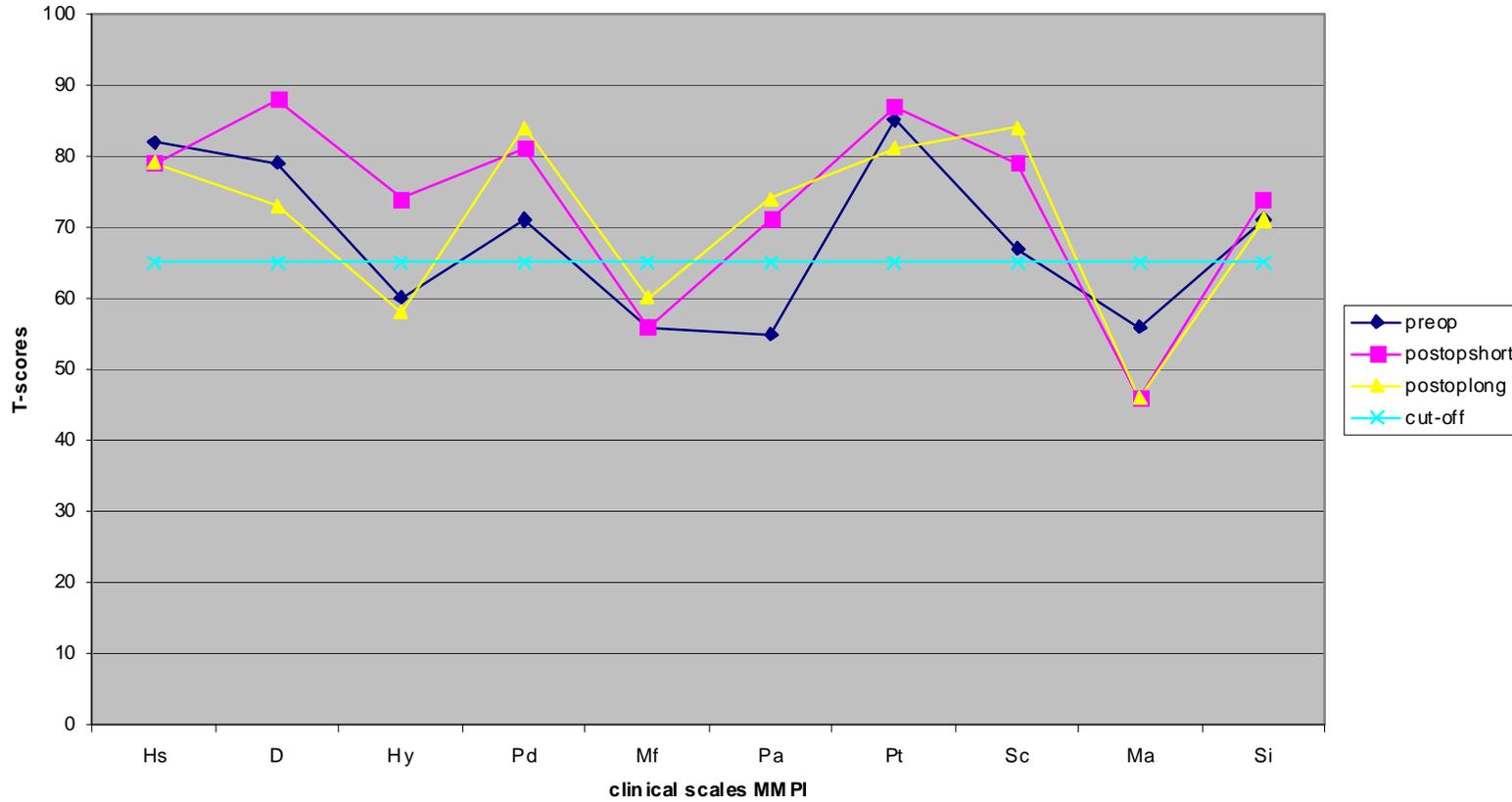
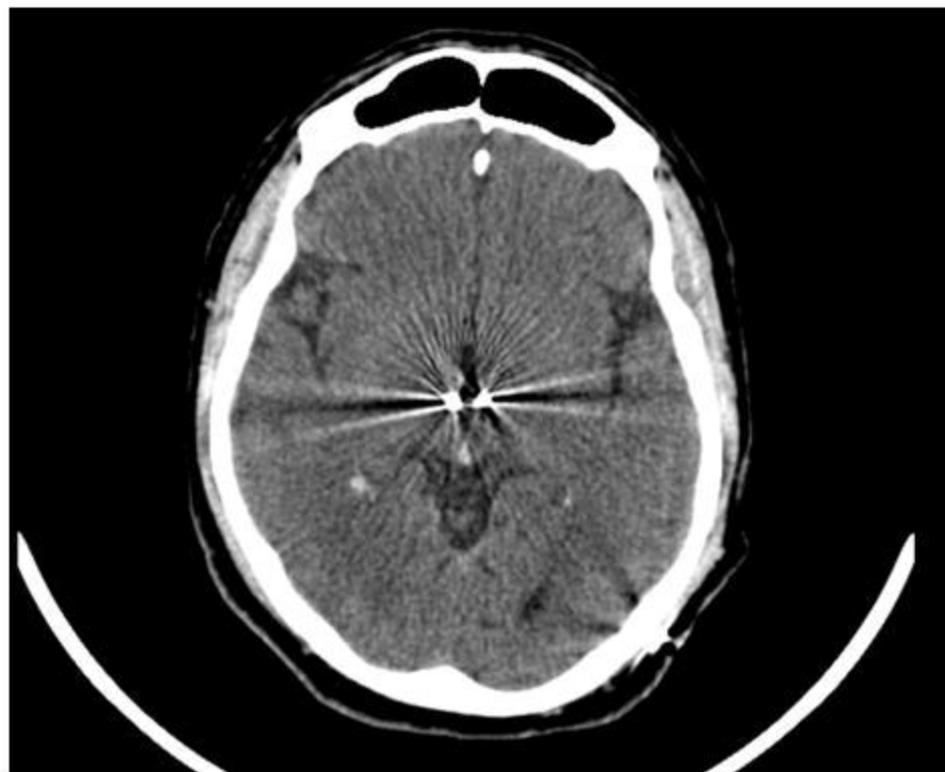


Figure 2: MMPI of case 2 pre, post DBS



MMPI = Minnesota Multiphasic Personality Inventory; Hs = Hypochondriasis; D= Depression; Hy = Hysteria; Pd = Psychopathic Deviate; Mf = Masculinity/Femininity; Pa = Paranoia; Pt = Psychasthenia; Sc = Schizophrenia; Hypomania and Si = Social Introversion. Cut-off score: T=65.



MMPI case 2 pre. post DBS

