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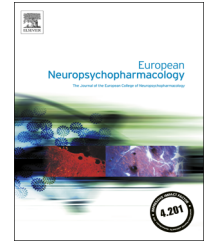
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# Limbic versus cognitive target for deep brain stimulation in treatment-resistant depression: Accumbens more promising than caudate<sup>☆</sup>



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## Abstract

High-frequency deep brain stimulation (DBS) represents a major stake for treatment for treatment-resistant depression (TRD). We describe a preliminary trial of DBS of two potential brain targets in chronic TRD: the nucleus accumbens (Acb) and, in the event of failure, the caudate nucleus. Patients were followed for 6 months before surgery (M0). From M1 to M5, they underwent stimulation of the Acb target. PET scans allowed us to track metabolic modifications resulting from this stimulation. The caudate target of nonresponders was stimulated between M5 and M9. Patients then entered an extension phase, in which it was possible to adapt stimulation parameters and treatments. Six patients were included and four were operated on. At M5, none of the patients were either responders or remitters, but we did observe a decrease in Hamilton Depression Rating Scale (HDRS) scores. Three patients were switched to caudate stimulation, but no improvement was observed. During the extension phase, the Acb target was stimulated for all patients, three of whom exhibited a significant response. A decrease in glucose metabolism was observed after Acb stimulation, in the posterior cingulate gyrus, left frontal lobe, superior and medial gyrus, and bilateral cerebellum. An increase in metabolism was observed in the bilateral frontal lobe (superior gyrus), left frontal lobe (medial gyrus), and right limbic lobe (anterior cingulate gyrus). The results of this trial suggest that Acb is a more promising target than the caudate. NCT01569711.

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## 1. Introduction

Major depressive disorder (MDD) is one of the leading causes of handicap worldwide (Lopez et al., 2006). It contributes to an increase in mortality (Murphy et al., 1987), through suicide and cardiovascular disease (Musselman et al., 1998). Its consequences include recurrences, with a five-year rate of 80%, and chronicity for 20% of patients (Eaton et al., 2008; Keller, 2003). 30% of depression cases prove resistant to antidepressant drugs (Fava, 2003). The medical histories of these patients are marked by multiple hospitalizations, and by multiple trials of ultimately ineffectual and therefore discouraging treatments. This so-called chronic, treatment-resistant depression (TRD) is a major public-health issue, as well as a pathophysiological conundrum. Several data suggest that dysfunctional brain circuits are implicated, and that high-frequency deep brain stimulation (DBS) could represent an adjustable and reversible method of modulating these brain areas, just as it does for neurological disorders (Houeto et al., 2005; Houeto et al.,

2007) and obsessive-compulsive disorder (OCD) (Mallet et al., 2008).

In TRD, a number of case reports have been published, describing a range of different targets, including the lateral habenula (Sartorius et al., 2010), inferior thalamic peduncle (Jimenez et al., 2005), and the medial forebrain bundle (Coenen et al., 2011). Using larger samples, Mayberg and Lozano reported striking results over the short (Lozano et al., 2012, 2008) and longer-term (Holtzheimer et al., 2012) effects of DBS targeting the subgenual cingulate cortex. Their results have been confirmed by Puigdemont et al. (2012). Other teams (Bewernick et al., 2010; Bewernick et al., 2012; Malone et al., 2009; Schlaepfer et al., 2008) have also obtained promising results with brain targets corresponding to the ventral part of the striatum, including the ventral caudate and nucleus accumbens (Acb).

There are currently many arguments in favor of using Acb as the main target. This structure lies at the center of a circuit involved in depression that is connected to the ventral tegmental area, amygdala, hippocampus,

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orbitofrontal and medial prefrontal cortices, motor territories of the caudate nucleus and globus pallidus. It also indirectly projects to cortical regions including the subgenual cingulate in Brodmann area (BA) 25 (Cg25) and the medial prefrontal cortex, ventral pallidum, thalamus, and amygdala (Dinieri et al., 2009; Mogenson et al., 1983). Acb is a critical reward and pleasure center, and thus constitutes a key target in the treatment of depression, given that anhedonia is one of the disorder's key defining symptoms (Schlaepfer et al., 2008). Meta-analyses of neurosurgical procedures carried out to treat TRD have found that nearly 80% of patients benefit when the lesions affect Acb and the ventral part of the head of the caudate (Greenberg et al., 2003; Hodgkiss et al., 1995). Several studies have demonstrated the effectiveness of targeting the ventral striatum in depressive symptoms, especially when it is stimulated close to Acb (Aouizerate et al., 2005a; Aouizerate et al., 2005b; Bewernick et al., 2010,2012; Malone et al., 2009; Schlaepfer et al., 2008).

In addition, within our consortium, Yelnik et al. (2007) and Bardinnet et al. (2009) have developed a specific atlas distinguishing between three territories (sensorimotor, associative and limbic) of the basal ganglia related to cortical areas within the cortico-subcortical circuits (Bargad and Bergman, 2001; Parent and Hazrati, 1995a, 1995a). If we assume that DBS works by modulating the effects of the cortico-subcortical loops on a pathological dysfunction, as it is the case for subthalamic DBS in OCD (Le Jeune et al., 2010), when attempting to improve TRD, it seems relevant to target limbic areas in the basal ganglia, rather than cognitive or sensorimotor ones. For this reason, the French STHYM network decided to compare a limbic target (i.e., Acb) with a cognitive one (i.e., caudate), using an electrode capable of stimulating both nuclei.

## 2. Experimental procedures

The protocol was approved by the local ethics committee in Angers, France (no. 2008/16). All patients gave their written informed consent to take part. The study was registered with the clinicaltrials.gov database (NCT01569711).

### 2.1. Patients

Patients with chronic and recurrent TRD were recruited in 10 French centers. Inclusion criteria were 1/ age between 30 and 60 years, 2/ DSM-IV-TR criteria for MDD, and 3/ episode duration > 2 years.

Treatment resistance had to meet Thase and Rush Stage V (Thase and Rush, 1997). Furthermore, patients simultaneously had to have a 17-item Hamilton Depressive Rating Scale (HDRS) total score > 21, a Global Assessment of Functioning (GAF) score < 50, and a Clinical Global Impression (CGI) score  $\geq 4$ , despite the use of all the following strategies: 1/ monotherapies: two SSRIs, one SNRI, one tricyclic; 2/ the association of one antidepressant and one of the following treatments: lithium, thyroid hormone, buspirone, pindolol; 3/ an irreversible MAOI: iproniazid; 4/ the association of two antipsychotics, with at least one second-generation antipsychotic; 5/ the association of two antidepressants; 5/ electroconvulsive therapy; 6/ structured psychotherapy. The severity of the MDD had to be constant before surgery.

Exclusion criteria were 1/ serious and unstable medical condition; 2/ cognitive deterioration; 3/ abnormal brain MRI;

4/ contraindication for MRI; 5/ Axis 1 disorder other than MDD (except for generalized anxiety disorder, social phobia, and panic disorder); 6/ a substance use disorder (with the exception of nicotine); 7/ suicide risk in the previous month; 8/ psychotic features or a history of psychotic features; 9/ personality disorders according to DSM-IV-TR Cluster A or B; 10/ involuntary commitment, guardianship or trusteeship; and 11/ woman of childbearing age without effective contraception.

### 2.2. Preoperative imaging and surgical procedure

Preoperative imaging consisted of an MRI under stereotactic conditions (Bejjani et al., 2000), that is, allowing the stereotactic coordinates to be determined. The AC-PC line running between the anterior and posterior commissures was used as a reference, together with the vertical plane through AC-PC in the middle of V3. In order to check that there was no vascular disorder adjacent to the stereotactic target, a vascular MRI was also performed. The location of the Acb target was agreed upon by the neurosurgeons and the neuroanatomist, who was in charge of defining the target's coordinates according to its functional characteristics. These coordinates were identified using a deformable 3D atlas that distinguished among the motor, associative and limbic subdivisions of the basal ganglia, and which was adapted to the brain geometry of each patient (Bardinnet et al., 2009; Yelnik et al., 2007). An example of this targeting is shown in Figure. 1 for a patient with an AC-PC distance of 26 mm and a V3 width of 6 mm. The electrode for stimulation was placed in the Acb in a frontal plane 5.5 mm in front of AC, with a laterality of 9 mm and a depth of 6.5 mm below AC-PC. The trajectory was precisely determined by the neurosurgeon according to the structure of local blood vessels, taking particular care to avoid the anterior communicating artery and its branches.

The second target, the caudate nucleus, was located in a more rostral, dorsal and lateral position than Acb (14 mm, 12.5 mm and 14 mm, in the case of Figure. 1). For each patient, the trajectory was optimized (in order to pass in the frontal plane) between the lateral ventricle medially and the internal capsule laterally. In the sagittal plane, an oblique trajectory was adopted, in order to cross the limbic and associative areas of the caudate nucleus, but avoid its sensorimotor territory. In order to retain the ability to stimulate the two different targets (Acb and caudate nucleus) defined by the protocol (Figure. 1) along the same trajectory, we chose to use the 3891 Medtronic Pisces Z-Quad<sup>®</sup> lead which is longer than the 3389 lead and in which the four electrodes each measure 3 mm long and are spaced 4 mm apart (i.e. 7 mm from one center to the next).

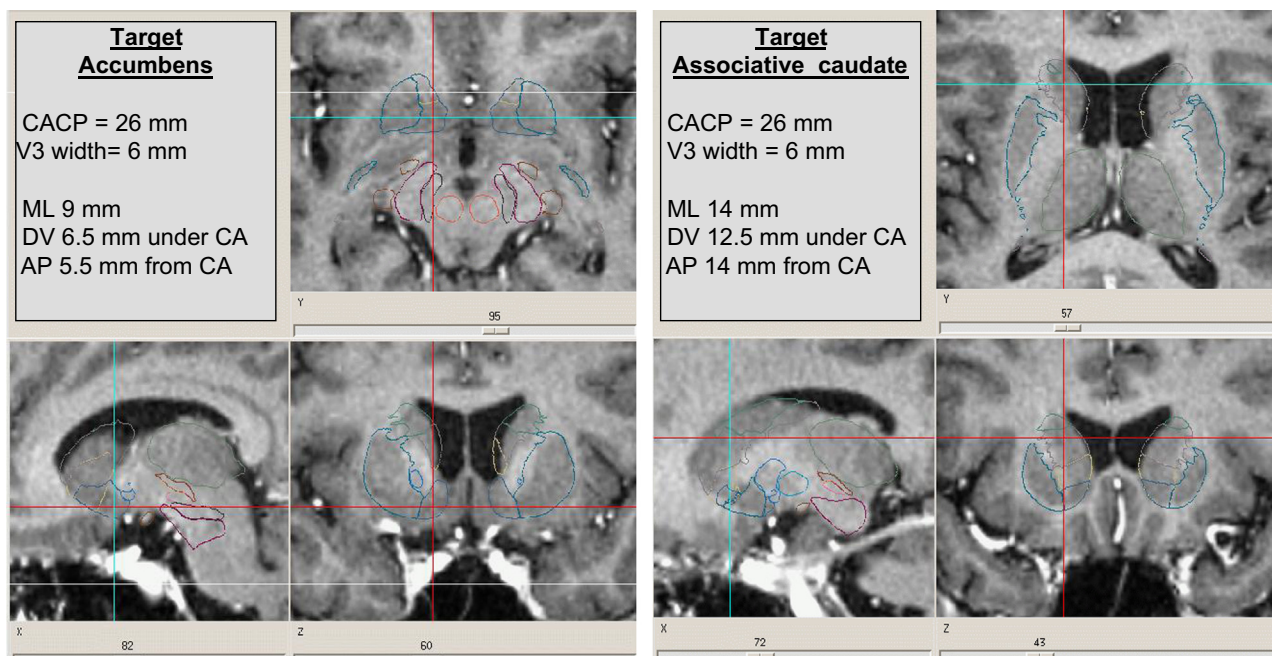
### 2.3. Study design

We designed a pilot multicenter prospective, noncomparative, and open trial. All patients were followed for six months before surgery (between M-6 and D-7), to verify the stability of their illness. Surgery was performed at M0. The implanted patients were not stimulated for the first month. From M1 to M5, Acb target was stimulated. Nonresponders at M5 underwent stimulation of the caudate target until M9. After these two periods, patients entered a six-month extension phase (up to M15), in which it was possible to adapt stimulation parameters and associated treatments.

### 2.4. Initiation of stimulation

The stimulation frequency was set at 130 Hz and the impulse duration at 60  $\mu$ s according each investigator. The initial voltage was 4 V. This level of stimulation was maintained from M1 to M9, but could subsequently be increased up to 8 V during the extension phase, keeping the same frequency and width pulse as before.





**Figure. 1** Electrode placement (nucleus accumbens and associative territory of the caudate) after readjustment of the Yelnik & Bardinet atlas (Yelnik et al, 2007) on the MRI of each patient. The 3D cursor shows the exact position of each target in the three anatomical planes (transverse, sagittal, and coronal). The mediolateral (ML), dorsoventral (DV) and anteroposterior (AP) coordinates in the coordinate KABP were also calculated for each patient.

## 2.5. Outcomes

The primary outcome measure for the study was the clinical response, assessed after four months of DBS (M5). We adopted the most widely used response criterion (50% decrease in the HDRS score). Remission, as defined by an HDRS score  $\leq 7$  after four months of DBS was a secondary outcome. The other secondary outcomes assessed during follow-up visits were duration of remission, depression severity, as measured on the HDRS, the overall score on the Hamilton Anxiety Rating Scale (HARS)  $\leq 10$ , a rating of 1 (*very much improved*) or 2 (*strongly improved*) for Item 2 of the CGI, a score  $\geq 60$  on the GAF, and increased scores on the Social Adjustment Scale Self-Report (SAS-SR) and Beck Depression Inventory (BDI).

The effect of DBS of the caudate nucleus in the event of a nonresponse at M5 was assessed at M9 using the same scales. During the extension phase, depression severity was assessed using HDRS.

Individual data are set out in the tables, and summarized numerically, with the median (range) for quantitative outcomes and the number (percentage) for qualitative outcomes.

## 2.6. Tolerance and side effects

Tolerance was assessed at each follow-up visit after surgery. Patients were offered close supervision (telephone contacts and consultations on request) if they experienced severe side effects.

As DBS of the basal ganglia in Parkinson's disease is known to be associated with weight gain (WG), and because Acb has been demonstrated to play a key role in different behaviors, including eating and sexuality (Baldo and Kelley, 2007; Kelley et al., 2005), we specifically monitored these two behaviors. Eating behavior was assessed via a multidimensional approach that encompassed anthropometric measures (weight, expressed as body mass index (BMI), hip and abdomen circumferences), hormone levels and daily energy

intake (DEI). The latter was assessed via structured dietary questionnaires administered by a dietician, and self-reported food consumption over a seven-day period. Food habits, feelings and thoughts about food, and eating disturbances were assessed on the Questionnaire of Eating and Weight Pattern Revised (QEWPR) (Spitzer et al., 1993), the Eating Attitudes Test-26 (EAT-26) (Garner et al., 1982), a questionnaire on thoughts and feelings about food (Rigaud, 2005), and the Food Craving Questionnaire (Guy-Grand, 1997). The International Erectile Function scale was used to explore sexual behavior.

A comprehensive battery of neuropsychological tests was also administered at D-7, M1, M5, and M9, to explore the possible cognitive toxicity of DBS. This battery included the Mattis scale (Mattis, 1988) for general cognitive efficiency, and a series of tests assessing memory abilities: the Hopkins test (Rieu et al., 2006) for verbal episodic memory, and forward (visuospatial) and backward (auditory-verbal) digit span tests for working memory. Patients also underwent a series of tests assessing frontal executive functions: the Trail Making Test (Reitan, 1958), the Categorical and Literal Fluency Test (Cardebat et al., 1990), the Action Verbs fluency task (Woods et al., 2005), and the Stroop Test (Stroop, 1935). Finally, visuospatial abilities were measured by the copying of the Rey complex figure (Rey, 1942).

## 2.7. Brain imaging

In order to correlate the effects of stimulation with changes in brain metabolism, the patients underwent two [ $^{18}\text{F}$ ]FDG PET scans before and after Acb stimulation. The data, acquired on different PET cameras, were analyzed using statistical parametric mapping software (SPM2; Wellcome Department of Cognitive Neurology, London) written in Matlab version 7 (MathWorks). This analysis, using an isotropic smoothing 12-mm full-width at half-maximum Gaussian kernel filter to compensate for interindividual anatomical

variability and render the imaging data more normally distributed, allowed us to overcome technical differences in machines. Significant modifications in the brain metabolism of the four patients were pinpointed by comparing their pre- and post-surgery  $^{18}\text{F}$ FDG PET scans. We used the “single subject, conditions and covariates” routine. We studied different thresholds to find regions affected by the stimulation in this very small sample. Clusters of at least 10 contiguous voxels, with a threshold  $p$  Value of 0.05, were identified.

### 3. Results

#### 3.1. Preoperative period: recruitment and baseline data

Due to the stringent inclusion criteria and the high number of potential candidates who responded to Stage-IV or V treatments for TRD (Thase and Rush, 1997), only six patients were recruited between 12/04/2008 and 03/09/11. Two of these patients were excluded before surgery, the first because a cancer was diagnosed, the second because he remitted during the six-month preoperative period.

#### 3.2. Deep brain stimulation

Four patients were operated on in the neurosurgery departments of university hospitals in Rennes, Paris (Sainte Anne), Grenoble and Nice, in accordance with the usual stereotactic surgical procedure. The two electrodes were implanted during the same operation under local anesthesia or intermittent sedation. The neurologist and psychiatrist attended each perioperative procedure, as did the study coordinator. Table 1 presents the baseline data.

In the four patients who underwent surgery, the electrodes were implanted as per the preoperative calculations, that is, with Contact 0 (ventral) located in Acb, Contact 1 in the limbic caudate nucleus and Contacts 2 and 3 (dorsal) in the associative caudate.

#### 3.3. Postoperative period

##### 3.3.1. Nine-month follow-up

In accordance with the study design, Acb was the initial stimulation target (Contact 0 on both sides).

None of the patients were responders (primary outcome) or remitters at the M5 time point, although we did observe a fluctuant decrease in the HDRS score in three patients during this period (maxima of  $-28\%$ ,  $-64\%$  and  $-93\%$ ). Furthermore, none of the patients achieved an overall score on the HARS  $\leq 10$  (e-Table 1) or reached a GAF score  $\geq 60$  during the nine-month postoperative follow-up. The remission duration criterion was not applicable in the year of follow-up.

Nevertheless, an improvement was observed in two patients (Patients 1 and 4), who had remained stable throughout the preoperative period, and whose mood improved with Acb stimulation (see Figure. 2). These two patients rated Item 2 of the CGI either 1 (*very much improved*) or 2 (*strongly improved*) at various times during the year of postoperative follow-up, although these changes fluctuated.

Even though Patient 4 did not strictly meet response criteria at M5, his clinical improvement led us to continue Acb stimulation. The other three patients, who were switched to the caudate nucleus (Patient 1: Contact 2 on left side, Contact 3 on right side; Patients 2 and 3: Contact 3 on both sides), showed no such improvement (maximum decrease in the HDRS score of 29%, 16% and 20%; Figure. 2). Concerning social functioning, scores on the SAS-SR did not noticeably change during the nine-month postoperative follow-up (e-Table 1).

Table 1 presents the time course of the secondary outcomes.

##### 3.3.2. Extension phase of the study

During the extension phase, all patients underwent Acb stimulation:

Patient 1: the same contact 0 was used. Voltage was increased at 6 V (M9) then 8 V (M12); aripiprazole was added at M11; those changes allowed for a stable improvement, eventually reaching the response threshold.

Patient 2: Contact 0 and contact 1 alone or simultaneously were used with a voltage ranged from 4 to 8 V. No significant improvement was observed.

Patient 3: the same contact was used. Stimulation was increased to 5 V (M9) and the patient showed a dramatic improvement, reaching remission at M12 without any concomitant pharmacological treatment.

Patient 4: the same contact was used. Despite voltage changes between 5 and 7 V, he experienced the same mood fluctuations that he had done during the 9-months follow-up, frequently reaching the response threshold.

#### 3.4. Tolerance and side effects

##### 3.4.1. Safety

Table 2 lists all the adverse events recorded during the study. One patient made a suicide attempt and presented suicidal thoughts.

##### 3.4.2. Effect on eating and sexual behaviors

Full data were available for three patients. At baseline (M0), Patient 1 had a BMI of 26.8, a balanced diet, and no eating disturbances, cravings or abnormal thoughts about food. After surgery, his diet and habits remained unchanged, he did not have any abnormal thoughts or eating behaviors, and the different questionnaires did not reveal any changes. Compared with the preoperative values, changes in BMI, anthropometric measures, DEI and most hormone levels were within  $+/-5\%$ . The exceptions were prolactin, which was found to have increased by 182% at M1 and by 264% at M9, leptin 161% increase at M9), and cortisol (161% increase at M9). The levels of prolactin and leptin remained within the normal range, but cortisol slightly exceeded the normal value (261 ng/ml versus 250 ng/ml). No change in sexual behavior was reported. Patient 2 had a high BMI of 30.1 at baseline and presented marked food craving, especially at night and for carbohydrates. This explained his abnormal score of 29 on the EAT-26. His DEI remained normal because he did not eat breakfast. Prolactin was at the upper normal limit (370  $\mu\text{U}/\text{ml}$ ,  $N < 380$ ) and ACTH was slightly on the high side (62 pg/ml,  $N < 52$  pg/ml). In the first few months after surgery, both prolactin and ACTH decreased by 60%. Craving had decreased in both intensity and frequency by M5, at which point the patient stopped restricting his food intake. As a consequence, his DEI underwent moderate increases of 8% and 12% at M5 and M9, but his BMI remained unchanged. The EAT-26 score had dropped to 13 by M5. Thoughts and feelings about food tended to be more positive, with greater interest in its gustatory qualities. Excessive food intake was observed at M0 and an increased appetite for sweets at M11. These two manifestations were recorded as two adverse events. A substantial increase in sexual desire (in term of frequency and intensity) was reported at M1 (as an adverse event) and M5. Patient 4 intentionally restricted his food consumption at baseline, adopting a low-calorie diet, but exhibited daily compulsive food consumption in the afternoon. Craving decreased over the first few months after surgery, but then increased from M4 onwards. He reported a highly conflicting position regarding food, with intense bouts of anxiety followed by compulsive food consumption, especially of carbohydrates. These bouts occurred daily, both in the night and the afternoon, and were followed by guilt-laden feelings toward eating and negative thoughts about food. His overall DEI had increased by 82% and his BMI by 7% at M9 (from 28.5 before surgery to 29.8). His hormone levels remained normal and unchanged

**Table 1** Characteristics at baseline and efficacy of DBS (individual data are reported at each time point). The measures are summarized numerically, with the median (range) for quantitative data and the number (%) for qualitative data.

	Patient 1	Patient 2	Patient 3	Patient 4	Group
<b>1/ AT BASELINE</b>					
Sex	M	M	F	M	1 F/3 M
Current age	57	59	38	54	55.5(38, 59)
Current episode (years)	3.3	3.3	8.0	2.7	3.3(2.7, 8)
Personality disorder	Depressive	Depressive	None	None	2(50 %)
<b>2/ DURING FOLLOW-UP</b>					
<b>HDRS-17</b>					
M-6	24	31	22	21	22.5(21-31)
M-3	22	29	24	27	25.5(22-29)
D-7	25	29	24	27	26(24-29)
M1	22	24	25	26	24.5(22-26)
M2	10	22	25	22	23.5(10-25)
M3	9	24	23	2	16(2-24)
M4	10	30	23	7	16.5(7-30)
M5	24	24	25	25	24.5(24-25)
M6	22	20	22	14	21(14-22)
M7	25	22	23	3	22.5(25-3)
M8	22	24	20	18	21(18-24)
M9	17	24	26	21	22.5(17-26)
M12	11	24	4	9	10(4-24)
M15	8	27	3	14	11(3-27)
<b>CGI</b>					
M-6	7	6	6	7	6.5(6, 7)
M-3	6	6	6	7	6(6, 7)
D-7	6	5	6	7	6(5, 7)
M1	6	5	6	6	6(5, 6)
M2	5	5	6	7	5.5(5, 6)
M3	3	5	6	1	4(1, 6)
M4	5	6	6	2	5.5(2, 6)
M5	6	6	6	7	6(6, 7)
M6	6	5	6	5	5.5(5, 6)
M7	6	5	6	1	3(1, 6)
M8	5	5	6	5	5(5, 6)
M9	6	5	6	6	6(5, 6)
<b>BDI</b>					
D-7	16	20	27	21	20.5(16, 27)
M1	17	20	30	15	18.5(15, 30)
M5	16	22	30	19	20.5(16, 30)
M9	20	16	27	22	21(16, 27)
<b>GAF</b>					
M-6	42	31	22	30	30.5(22, 42)
M-3	35	33	27	31	32(27, 35)
D-7	31	36	23	31	31(23, 36)
M1	35	35	25	31	33(25, 35)
M5	31	31	27	31	29(27, 31)
M9	45	38	23	50	41.5(23, 50)

HDRS-17: Hamilton Depression Rating Scale 17 items.

CGI: Clinical Global Impression.

BDI: Beck Depression Inventory.

GAF: Global Assessment of Functioning.

throughout the follow-up period. An increase in his sexual life was only reported at M1. None of these changes led to an adverse event declaration.

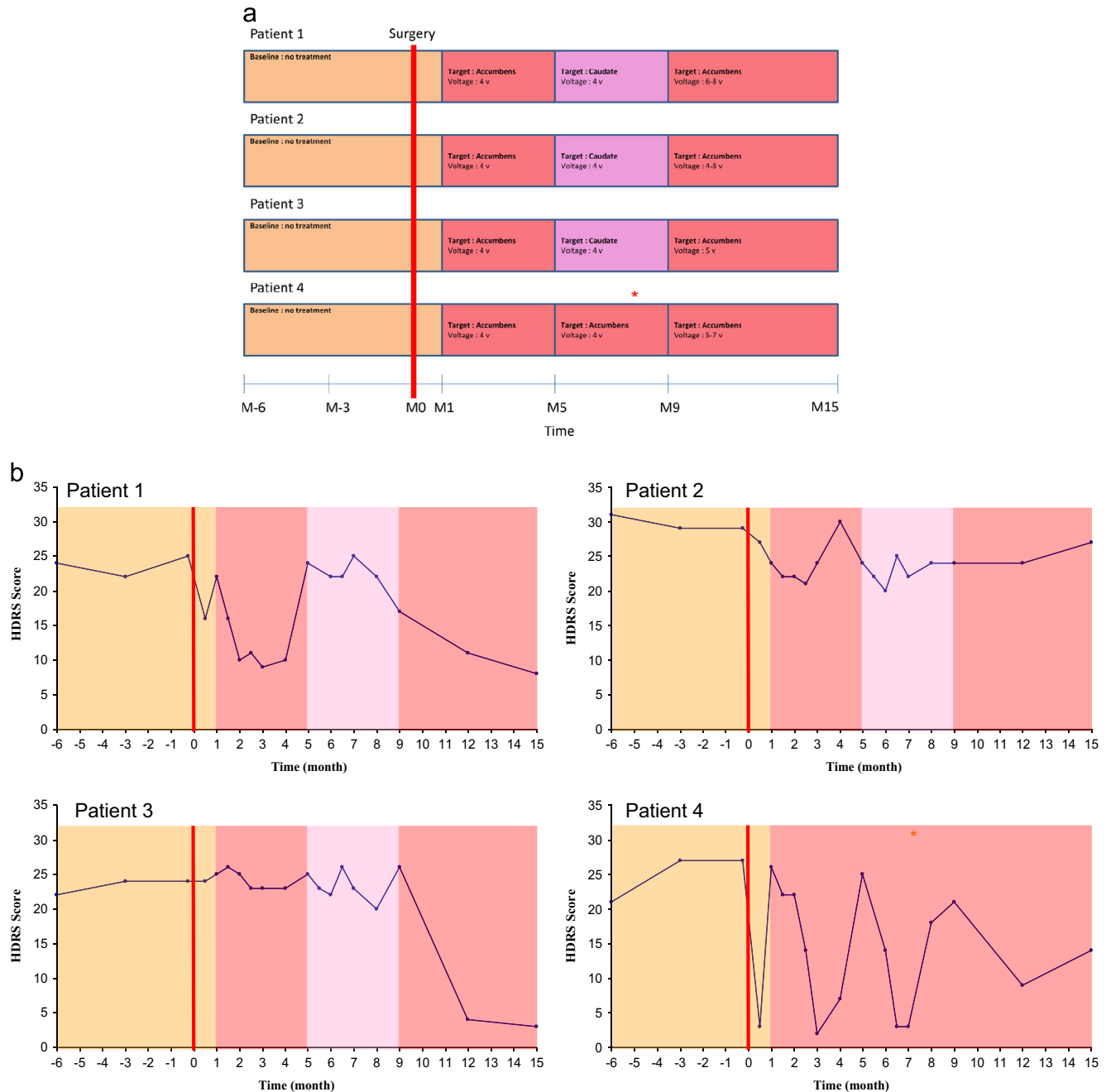
**3.4.3. Neuropsychological testing**

We did not observe any difference in any of the neuropsychological scores, especially not between D-7 and M5 (see Group column, e-Table 2). The only exception to this qualitative observation was the interference score of the Stroop test between D-7 and M5, pointing to an increase in inhibition difficulties.

**3.5. PET measures of regional blood flow at baseline and after surgery**

**3.5.1. Brain metabolism**

SPM analyses of postoperative (M5) and preoperative scans revealed several areas of metabolic modification in both hemispheres. Decreased metabolism after stimulation was observed in the posterior cingulate gyrus (BA 23 and 31) of the right limbic lobe, the superior (BA 6) and medial gyrus (BA 8) of the left frontal lobe, and the bilateral cerebellum. Increased metabolism after stimulation was observed in the superior gyrus (BA 9) of the bilateral



**Figure. 2** 2a) Stimulation parameters and 2b) change in HDRS-17 from baseline: individual data shown. Red line: M0 (surgery) ■ Preoperative period and first month with stimulator turned off ■ Accumbens stimulation On ■ Caudate stimulation On \* Spontaneous interruption of stimulation: stimulation was reactivated as soon as the interruption had been detected.



**Table 2** Safety of DBS, adverse events (AE) recorded over 15 months. The patient columns present the number of AEs (timeframe) per patient. The Group column presents the number of patients (percentage).

ADVERSE EVENTS	Patient 1	Patient 2	Patient 3	Patient 4	Group Patients (%)
Suicide attempt	1 (M9)	.	.	.	1(25%)
Suicidal thoughts	1(M10)	.	.	.	1(25%)
Worsening mood/anxiety	1(M5)	1(M15)	.	.	2(50%)
Worsening sleep	.	2(M1 and M6)	.	.	1(25%)
Memory problems	.	1(M3)	.	.	1(25%)
Excessive food intake	.	1(M0)	.	.	1(25%)
Increased appetite for sweets	.	1(M11)	.	.	1(25%)
Slightly increased libido	.	1(M1)	.	.	1(25%)
Perioperative headache or pain near the device	.	1(M0)	.	.	1(25%)
Paresthesia	.	.	1(M5)	.	1(25%)
Spontaneous interruption of stimulation	.	.	.	1(M7)	1(25%)

frontal lobe, the medial gyrus (BA 10) of the left frontal lobe, and the anterior cingulate gyrus (BA 32) of the right limbic lobe.

## 4. Discussion

### 4.1. Summary of evidence

High-frequency DBS proved to be a useful alternative treatment for our sample of patients diagnosed with stable TRD. For three of these four patients whose depression had resisted all previous forms of treatment, the surgical procedure provided a significant improvement in mood, as attested to by the lower HDRS scores across the 15 months following the start of stimulation even though no improvement was observed in GAF and social functioning. The expected improvement occurred later than we had expected, during the extension phase, when the parameters could be modified. Even though the changes were fluctuant for one patient, compared with the stability observed during the six-month pre-surgical period, a clear switch of mood was observed, allowing promoting a modification of parameters used. Due to the very precise targeting performed by each of the four neurosurgeons, and confirmed by the atlas-based method developed by the Parsi group, all four patients had very similar electrode implantations.

Our comparison of the outcomes of Acb versus caudate stimulation suggested that there was a better response to the former. These results, when added to the findings reported by [Bewernick et al. \(2010\),\(2012\)](#), support the usefulness of the Acb target. Our target was deeper and more forward than the one used by these authors, but our results did not allow us to consider some coordinates more accurate than another, making it difficult to compare their efficacy results with ours. However, it would seem relevant to stimulate Acb's shell, which is more closely related to the limbic system ([Sturm et al., 2003](#)), than its core, in order to interact with the neuroanatomical structures known to be implicated in the pathophysiology of depression.

We did not observe any of the frequent side effects during either the surgical procedure or the postoperative period, although one patient did attempt suicide during the 15-month follow-up. Regarding eating behavior, three of the

patients presented distinct profiles, for while eating behaviors remained unchanged for one of them, the opposite tendency was observed for the other two, regarding compulsive food consumption. From a qualitative point of view, 15 months after the operation, all four patients sounded better and none complained about the implanted device. Tolerance (including neuropsychological testing, eating and sexuality behaviors) was acceptable.

### 4.2. Limitations

Concerning internal validity, like other longitudinal studies of DBS in TRD, this study was not randomized and did not allow us to control for spontaneous improvements or a placebo effect. Placebo responses are indeed frequent in MDD, and raise many important methodological issues ([Walsh et al., 2002](#)). Moreover, a crossover design would have been more useful for comparing Acb with the caudate. Despite this limitation, given our results (no change observed during the stimulation of the caudate), it would be hard to justify selecting this target for further explorations. In addition, concerning the Acb target, the greatest improvements were seen at the highest voltages - voltages that were not used for the caudate target. Despite these limitations, given our results at the 9-month follow-up (no change observed during the stimulation of the caudate), it is nevertheless difficult to retain this target for further explorations. Finally, as the caudate stimulation was dependent upon the results of the Acb stimulation, we did not perform a PET scan after the caudate stimulation, which might have yielded some interesting results.

Concerning external validity, we found it extremely difficult to recruit patients suffering from pure TRD. Patients who meet the criteria for pure TRD are actually quite rare. In practice, TRD tends to be associated with comorbid disorders such as alcohol dependence, or else is a component of a hidden bipolar disorder ([Li et al., 2012](#)), which was revealed here by very careful screening.

In addition, many of the patients who had initially been recruited as potential candidates for high-frequency DBS turned out to be responders to one of the treatments available for TRD. In particular, many of the patients

initially classified as resistant according to Thase and Rush Stage III responded to irreversible MAOI.

To overcome these limitations, we plan to start a randomized, double-blind, controlled trial (RCT). We will retain the Acb target and drop the caudate one. To cope with the recruitment difficulties encountered in the present preliminary study, the STHYM team will consider broader inclusion criteria, especially in relation to patients suffering from bipolar depression, as previous studies have suggested that these patients could also benefit from DBS (Holtzheimer et al., 2012).

## 5. Conclusion

In conclusion, this preliminary study suggests that Acb, rather than the caudate, should be retained as a potential therapeutic alternative neuroanatomic target for patients suffering from TRD. During the follow-up, 3 out of 4 exhibited stable improvement. Our results highlight the involvement of Acb as a key structure within the cortico-striatal loop in the pathophysiology of TRD.

The time has come to assess the efficacy of this surgical procedure using an RCT, in order to see whether this new technique does indeed represent a fresh source of hope for patients who have been suffering from severe depression for many years.

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## Contributorship statement

BM had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: BM and JMR;

Data acquisition: BM, NJ, MP, NB, BG, CH, SC, DF, BD, and JY;

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## Conflict Of Interest

All authors declare that (1) B.M. has relationships (consultancy and Travel/accommodations expenses covered/reimbursed) with Janssen, BMS, Otsuka, Lundbeck, Lilly, Servier, Astra Zeneca, Medtronic, and Syneika and has received grants for research from Medtronic, Lilly and Astra Zeneca in the previous 3 years; P.F. has relationships (board membership or Travel/accommodations expenses covered/reimbursed) with Servier and Lilly and benefit from a grant of Servier who might have an interest in the work submitted in the previous 3 years; F.N. has relationships (board membership or Travel/accommodations expenses covered/reimbursed) with Servier, BMS, Lundbeck and Janssen who might have an interest in the work submitted in the previous 3 years; (2) M.B.'s spouse is an employee of Janssen; and (4) none of the authors has any non-financial interests that may be relevant to the submitted work.

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## Appendix A. Supporting information

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