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RESEARCH ARTICLE

Deep brain stimulation in five patients with severe disorders of consciousness

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Abstract

Objective: The efficacy of deep brain stimulation in disorders of consciousness remains inconclusive. We investigated bilateral 30-Hz low-frequency stimulation designed to overdrive neuronal activity by dual pallido-thalamic targeting, using the Coma Recovery Scale Revised (CRS-R) to assess conscious behavior. **Methods**: We conducted a prospective, single center, observational 11-month pilot study comprising four phases: baseline (2 months); surgery and titration (1 month); blind, random, crossover, 1.5-month ON and OFF periods; and unblinded, 5-month stimulation ON. Five adult patients were included: one unresponsive-wakefulness-syndrome male (traumatic brain injury); and four patients in a minimally conscious state, one male (traumatic brain injury) and three females (two hemorrhagic strokes and one traumatic brain injury). Primary outcome measures focused on CRS-R scores. Secondary outcome measures focused notably on baseline brain metabolism and variation in activity (stimulation ON – baseline) using normalized fluorodeoxyglucose positron emission tomography maps. Statistical analysis used random-effect models. **Results**: The two male patients (one minimally conscious and one unresponsive wakefulness syndrome) showed improved mean CRS-R scores (stimulation ON vs. baseline), in auditory, visual and oromotor/verbal subscores, and visual subscores respectively. The metabolism of the medial cortices (low at baseline in all five patients) increased specifically in the two responders. **Interpretation**: Our findings show there were robust but limited individual clinical benefits, mainly in visual and auditory processes. Overall modifications seem linked to the modulation of thalamo-cortico-basal and tegmental loops activating default mode network cortices. Specifically, in the two responders there was an increase in medial cortex activity related to internal awareness.

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Introduction

Only 22% of minimally conscious state (MCS; minimal and inconsistent awareness) and 17% of unresponsive wakefulness syndrome (UWS; vegetative state; open-eyes, no evidence of awareness) patients return to an approximation of their former levels of functioning 4 years after injury[1]; bearing in mind that disorder of consciousness (DOC) is associated with an increased risk of death,[2–4] and that exceptionally, late, satisfactory recovery occurs (e.g.[5–8]). Among foremost concerns are expectations of significant recovery offset by very low rates of discharge to the home environment without disability, and the predicament of permanent DOC, which should be considered at 6 months post stroke, 12 months post trauma in UWS, and between three and 5 years or less in MCS.[9] Expectations come from drug-based,[10] physical and non-pharmacological interventions.[11] Seven studies (58 UWS or MCS patients; only two series in excess of three patients) used deep brain stimulation (DBS) to trigger recovery.[12–22] Stimulation frequencies were mostly low 25 Hz-50 Hz[13–19] (two times at 100 Hz[21,22] and one at 250 Hz[12]). Unilateral (left-side two case-reports; right-side one series) or bilateral (two case-reports; one series) implantations were performed (data unknown in one series). The most common targets were the reticular polar, anterior and laminar (centromedian and parafascicular) thalamic nuclei, and the so-called central thalamus.[23] The tegmentum (in two patients)[17] and the right pallidum (in one patient; combined with the left anterior thalamus)[13] were very seldom targeted. The overall results in terms of clinical benefit are as yet inconclusive due to patient heterogeneity, means of assessment (scales, follow-ups), time since injury (1 month to 6 years), devices, and contact locations. In this context we aimed to conduct a prospective 11-month observational pilot study designed to assess the relevance of DBS at the bedside, using the Coma Recovery Scale Revised (CRS-R).[24] Anoxic patients were excluded because of high long term disability and low expectancy of recovery.[25,26] CRS-R was administered repeatedly during each phase of the study taking into consideration the variability of signs of awareness.[27] With respect to inclusion we considered neither structural nor functional brain imaging regarding the lack of consensus on this aspect, however identification of covert activity is promising.[11,28,29] The thalamus and the pallidum were targeted because experimental stimulation has evoked cortical activity resembling consciousness.[30,31] Hence dual-site electrode implantation was used, hypothesizing that it would be more effective in boosting overall brain hypo activity, and could further enable independent dual-site modulation of the cognitive and motor thalamo-cortico-basal loops involved in DOC paradigms.[32–34] We considered that either activation of preserved loops or reactivation of silent loops, would induce modifications of CRS-R score. 30-Hz low frequency stimulation was selected according to clinical[13–19] and experimental data.[31,35] Our goal was to override remote cortical structures in the frequency band where beta and gamma waves, both of which are linked with consciousness processes,[36] overlap, while also overriding pallidal activity. In this study, surgery was conducted at a single center, and an ecological approach was adopted at each center where patients were recruited and monitored. Primary measure was based on CRS-R scores, and secondary outcome measures on CRS-R subscores, open-eye condition at night, and fluorodeoxyglucose (FDG) positron emission tomography, obtained prior to and during DBS. The impact on sleep, of continuous, twenty-four hours a day, stimulation, was checked at night, looking at open-eye condition.

Patients and Methods

Study design and participants

Five patients were consecutively included from April 2012 to February 2015 (Table 1; Fig. 1), fulfilling inclusion criteria (age $\geq$ 18 years; stable, chronic DOC status of UWS or MCS, $\geq$6 months after cerebrovascular accident and $\geq$1 year after traumatic brain injury) with no evidence of exclusion criteria (cerebral death, anoxic diagnosis, locked-in syndrome, blindness or deafness); study authorizations (Appendix S1). The protocol was divided into four phases: (1) Baseline condition (*baseline*), lasting at least 2 months, using FDG and magnetic resonance imaging (MRI); (2) DBS surgery and titration, lasting 1 month; (3) blind, 3-month crossover (*CO*) phase, with two randomized periods of 1.5 months, 1.5-month ON (*CO-ON*) and OFF (*CO-OFF*); (4) unblinded stimulation phase of at least 5-months (*DBS-ON*) using FDG. The two randomized crossover periods were termed first period (just after titration) and second period (before DBS-ON), whatever the CO-ON or CO-OFF status.

Procedures and outcomes

Three patients were operated prior to imaging and electrode implantation (Table 1): the cerebrospinal fluid shunt valve was moved from the skull to the subclavicular region, enabling artefact-free brain MRI (P1, P2, P3); the right cranioplasty of P3 was corrected for further electrode implantation. Electrodes (DBS 3389, Medtronic, Minneapolis, MN, USA) were positioned under general anesthesia. The intended targets were: the medial pallidum, around the midpoint of its anteromedial-posterolateral axis, with the electrode tip in a ventral

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Table 1. Characteristics of the five patients.

	Clinical consciousness status, gender, age (year), handedness; time elapsed since initial injury	Neurologic status	Surgery	Comorbidities	Diagnosis	Date
P1	UWS, male, 32, right handed; 12 years and 2 months	hypertonic quadriplegia predominant on right-side; flexion or extension of upper limbs, and extension of lower limbs; chewing	May 2012, replacement of right VAS by left VPS (SC valve); July 2012, DBS surgery	right VAS, tracheostomy and gastrostomy post injury	traumatic head injury; left intracerebral hematoma; intraventricular and subarachnoid hemorrhage; multiple cerebral contusions; hydrocephalus	Dec 1999
P2	MCS-, female, 62, right handed; 1 year and 2 months	hypertonic triplegia, left hemibody and right lower limb; flexion of lower limbs, and extension of the left upper limb; chewing	November 2012, replacement of right VAS by left VPS (SC valve); Dec 2012, DBS surgery	right VAS, gastrostomy, tracheostomy, right cranioplasty, and left neurogenic paraosteopathy (lower limbs) post hemorrhage; essential hypertension; migraine; hepatitis C; cataract right eye	rupture of right sylvian aneurysm; endovascular occlusion; intracerebral hematoma, intraventricular and subarachnoid hemorrhage; right sylvian artery vasospasm; right decompressive craniectomy; hydrocephalus	July 2011
P3	MCS-, male, 24, left handed; 3 years and 1 month	hypertonic triplegia, left hemibody and right lower limb; flexion of the lower limbs and the left upper limb	November 2012, repair of right cranioplasty and repositioning ofVPS valve in the SC region; March 2013, DBS surgery	bilateral decompressive craniotomy followed by cranioplasty, right VPS, bilateral pulmonary embolism, tracheostomy and gastrostomy post injury; multidrug-resistant bacteria; depression and schizophrenia without medication; neurogenic pain of the right inferior limb; pollen allergy	traumatic head injury; brain edema; right and left subdural hemorrhage; cervical spine injury and C2 fracture; hydrocephalus; pneumothorax	Nov 2009
P4	MCS-, female, 22, right handed; 4 years	quadriplegia; flaccid paralysis of axial muscles and lower limbs; slight hypertonia of the upper limbs; chewing	Jan 2015, DBS surgery	tracheostomy, gastrostomy, lobar pneumonias (multidrug-resistant bacteria) and suspected partial epileptic seizure post injury; unstable diabetes mellitus type 1; asthmatic bronchitis	traumatic head injury; polytrauma; bradycardia and asystole with 15 min of cardiopulmonary resuscitation; subarachnoid hemorrhage; multiple cerebral contusions; bilateral pneumothorax; right pulmonary embolism	Nov 2010
P5	MCS-, female, 47, right handed; 2 years and 3 months	hypertonic quadriplegia predominant on left; trismus; chewing; grunt	May 2015, DBS surgery	right VPS, tracheostomy and gastrostomy post injury; chronic consumption of alcohol and tobacco; chronic depression;	rupture of right internal carotid artery termination aneurysm; endovascular	Dec 2012

(*Continued*)

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Table 1. Continued.

Clinical consciousness status, gender, age (year), handedness; time elapsed since initial injury	Neurologic status	Surgery	Comorbidities	Diagnosis	Date
			eczema and keratitis in 2014-2015; pollen allergy	occlusion; right frontal hematoma, intraventricular and subarachnoid hemorrhage; hydrocephalus	

VAS, ventriculoatrial shunt; VPS, ventriculoperitoneal shunt; SC subclavicular; UWS, Unresponsive Wakefulness Syndrome; MCS-, Minimally Conscious State minus (patient demonstrating pursuit eye movement, ability to localize (and orient) noxious stimuli, and appropriate movements or affective behaviors).[49]

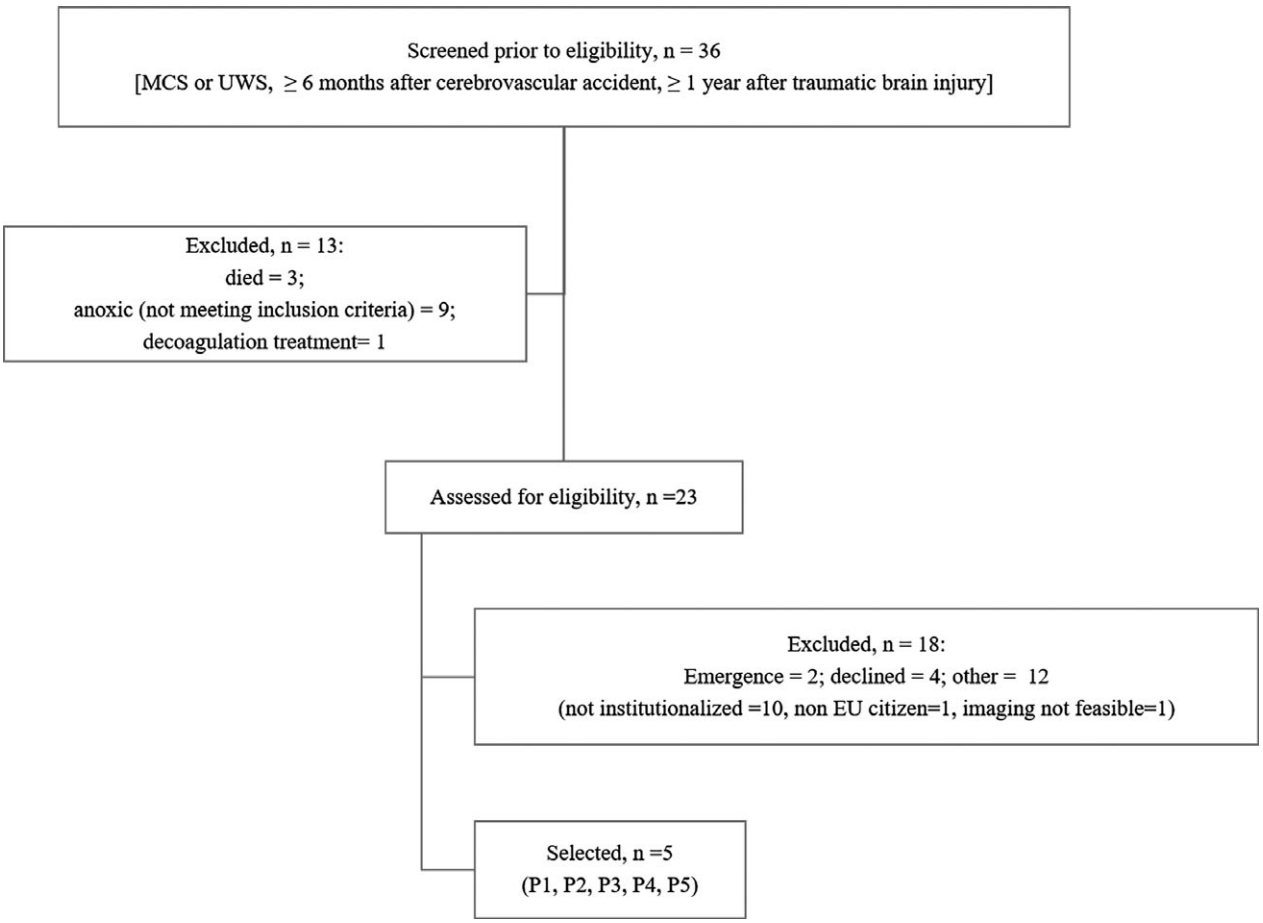


Figure 1. Enrolment of patients. MCS, Minimally Conscious State; UWS, Vegetative State; EU, European Union.

position; the anterior intralaminar region midway up the thalamus (central-anterior thalamus). The targeting was personalized (Appendix S1). Immediately after surgery a postoperative CT-Scan (voxel size = 0.488 mm × 0.488 mm × 0.625 mm) was coregistered with preoperative stereotactic imaging (Fig. 2A) for electrode contact location. The active contacts (1.27 mm diameter, 1.5 mm length; inter-contact distance 0.5 mm) were positioned

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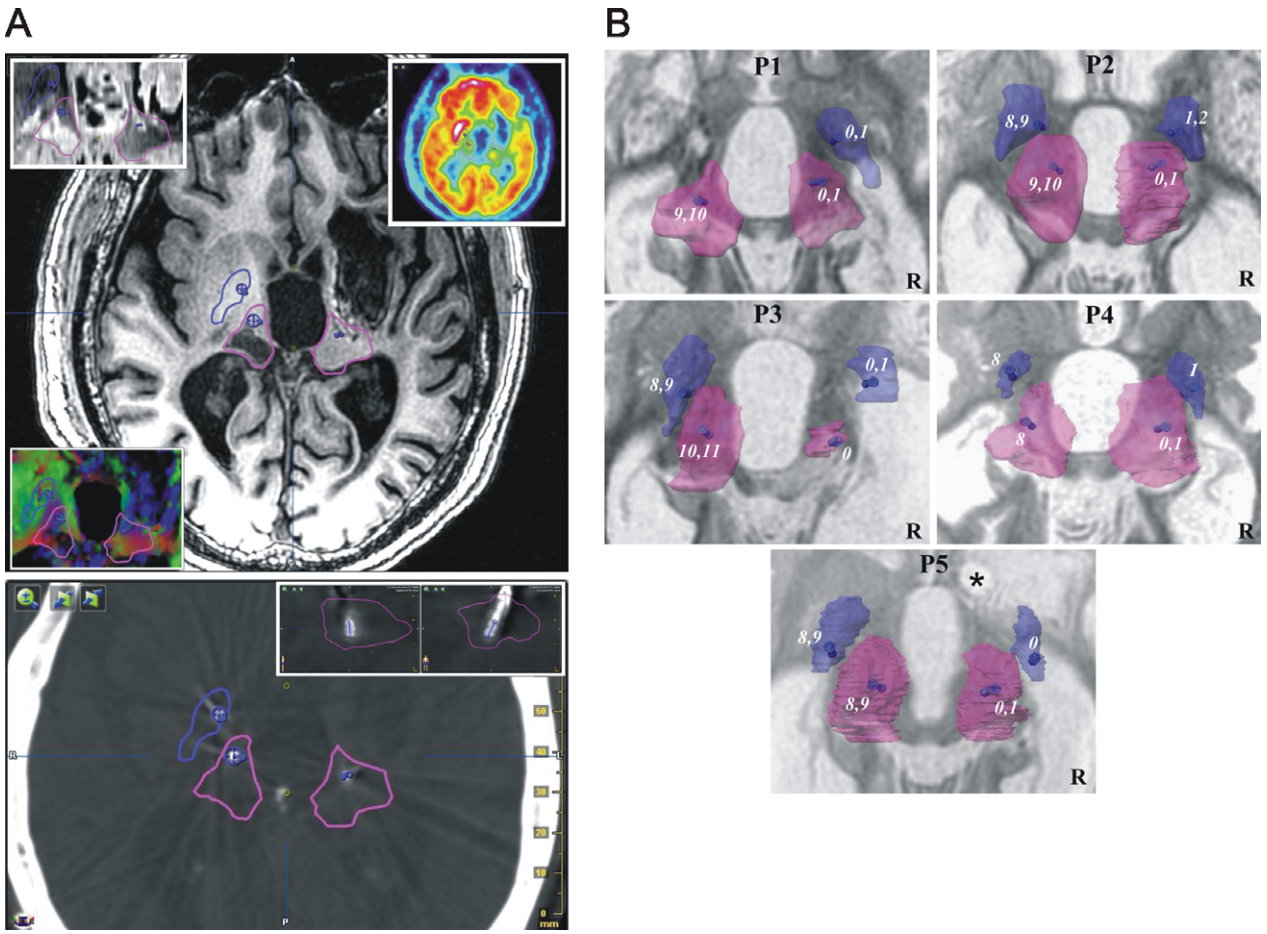


Figure 2. Contacts. (A) Deep brain targets and electrode positioning: Example (P1) of right and left targeted structures, pallidum (blue) and thalamus (pink) and location of effective (used in chronic stimulation; blue segments) contacts: top, T1 axial slice (4 mm above the anterior-posterior commissure plane; inlays, clockwise from top left, Inversion-Recovery sequence, FDG, and color-coded diffusion tensor map); bottom, coregistered (with preoperative imaging) postoperative CT-Scan, axial slice going through the center of the two effective contacts of the left thalamus, inlays, top-right, sagittal and coronal slices going through the effective contacts within the thalamus. (B) Contact locations: Contacts (number, from distal to proximal, right from 0 to 3, left from 4 to 11) within the pallidum (blue) and thalamus (pink) of the 5 patients (P): superior view of 3D (semi-transparent) anatomical structures, the effective contacts (numbers) are displayed as blue segments; background axial T1-weighted MRI slice (inverted gray scale) going through anterior-posterior commissure (ACPC) plane; *coil artefact; R, right.

within the targets. We performed double-contact monopolar stimulation 14 times (on five occasions the small size of the anatomical target precluded double-contact monopolar stimulation) out of the 19 leads implanted (no pallidum in P1) (Fig. 2B). Two neuropacemakers (ACTIVA SC® or ACTIVA PC®, Medtronic, Minneapolis, MN, USA, respectively, depending on unilateral or bilateral electrodes) were implanted subcutaneously under general anesthesia, one in the chest wall (subclavicular fossa) connected to the pallidal electrodes, and one in the abdomen wall connected to the thalamic electrodes. Titration of stimulation parameters was carried out 1 month after surgery for 5 days, by pairs (right and left) of thalamic or pallidal electrodes, to evaluate observable clinical tolerance using targeted values as follows: 30-Hz, pulse duration = 60 microseconds and voltage = 6 V. These parameters were identical to those used in DBS, except in P5, whose voltage was set at 4V due to facial tension and limb hypertonia at 6V.

The primary outcome measure was CRS-R scores across the different phases. This enabled (a priori definition) the identification of responder, that is. patient whose mean CRS-R score increases significantly from baseline to unblinded DBS-ON; the crossover phase was used to observe early-acute effects. We used the French version[37] of the CRS-R. Scores vary from 0 to 23, with six subscores quantifying auditory (au; 0 to 4), visual (vi; 0 to 5), motor (mo; 0 to 6), oromotor-verbal (ov; 0 to 3),

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communication (co; 0 to 2) and arousal (ar; 0 to 3) processes; MCS status is evoked when au = 3, vi = 2, mo = 3, ov = 3 or co = 1 (MCS-thresholds), and emergence from MCS when mo = 6 or co = 2 (emergence-thresholds). At night, spontaneous eye-opening was observed (yes or no response). CRS-R subscores, MCS-thresholds and emergence-thresholds and open-eye state were analyzed as secondary outcomes. Bedside clinical evaluation was performed by the qualified medical and healthcare care staff of each clinical facility; we aimed to perform CRS-R and eye-opening assessments twice a week. Data collection time was established at the time of inclusion, according to each individual care protocol (in line with patient and medical unit habits). The procedure was the same for each patient; the nurses were trained by the same person. Only the time during the day, or the day during the week, was slightly different for each patient according to the organization of teams (work schedule; care schedule according to patient, visits of relatives. . .). However, the timetable of data collection were regular for each patient (e.g. Monday and Thursday at 10 a.m.). The measure of FDG metabolism during baseline and DBS-ON phases (secondary outcome) was the only functional imaging technique authorized for use in implanted stimulation devices, and enabling comparison of phases. The voxels of normalized FDG PET were colored according to the relative activity, red for high and blue for low (Fig. 3A; Appendix S1). We computed (voxel-based) maps of metabolic variation DBS-ON – Baseline, depicting increase (DBS-ON > Baseline) in green, and decrease (Baseline > DBS-ON) in beige (Fig. 3A; Appendix S1). Activity (low, high or intermediate) and variation (upward, increased activity; downward, decreased activity) were specified regarding 23 cortical regions of the right and left hemispheres in all five patients ($n = 230$) by 3D-rendering, then the 23 regions were grouped into three cortical areas for further analysis (Fig. 3B; Appendix S1): the internally-oriented area including the limbic and medial cortices of the default mode network[38] (DMN), related to internal awareness[39]; the externally-oriented area, including lateral association fronto-parietal cortices of the DMN,[38] related to external awareness[39]; and other areas.

Statistical analysis

Statistical analysis (Stata software; Version 13, StataCorp, College Station, TX) was conducted based on a two-sided Type I error of 5%. Continuous data were described as mean ± standard-deviation or median [interquartile range] according to statistical distribution, and categorical parameters as the number of patients and associated percentages. Individual and group analysis of primary outcome CRS-R scores and subscores was performed, using random effects (mixed) models accounting for between- and within-patient variability (repeated measures or longitudinal data collected from the same individual). The secondary outcome was FDG imaging (globally and by hemisphere) and the same analysis (random-effects models) was conducted for the three cortical areas (internal, external and other): (1) at baseline, based on the number of high, intermediate, low, and lesioned cortical regions by area and by CRS-R-based response, that is. responder status; (2) following DBS (DBS-ON – Baseline), based on the number of increased and decreased cortical regions by area and by CRS-R-based response, and for the external and internal cortical areas, by CRS-R-based response and FDG PET variation, with or without adjustment by baseline FDG.

Results

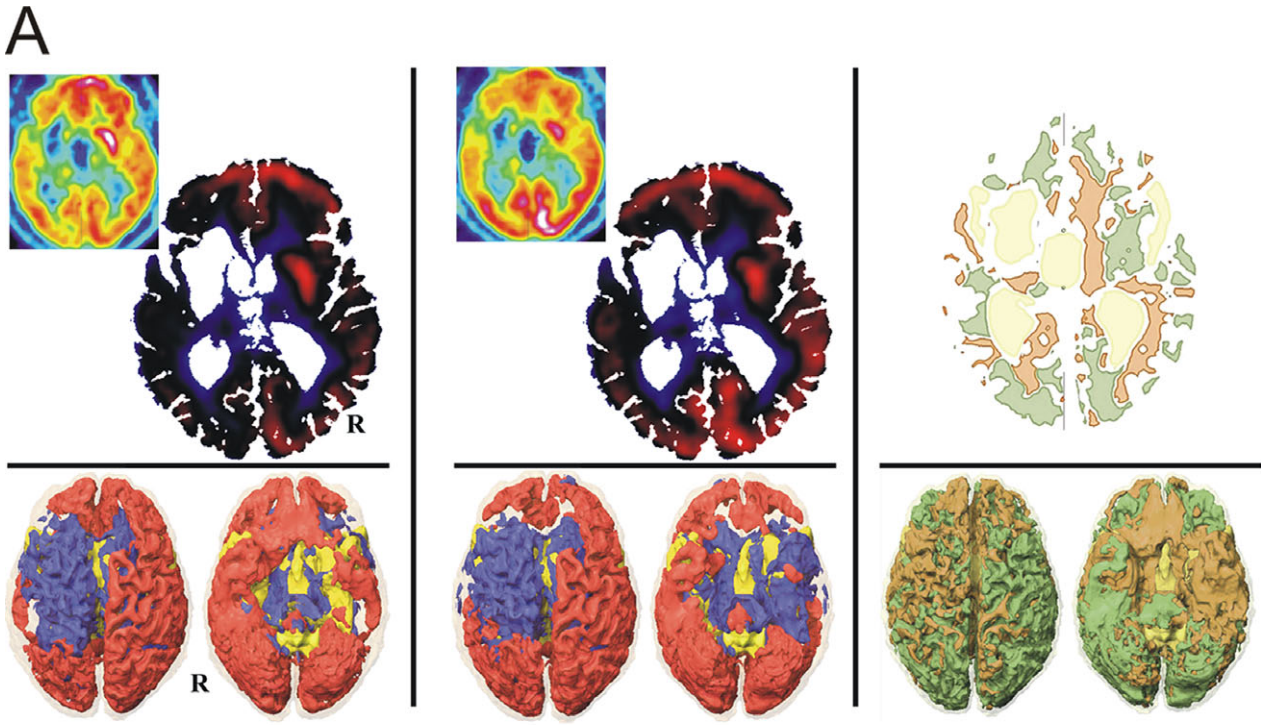
Group level analyses of overt behaviors and - CRS-R subscores, MCS-threshold and emergence-threshold – tables, are in the Appendix S1.

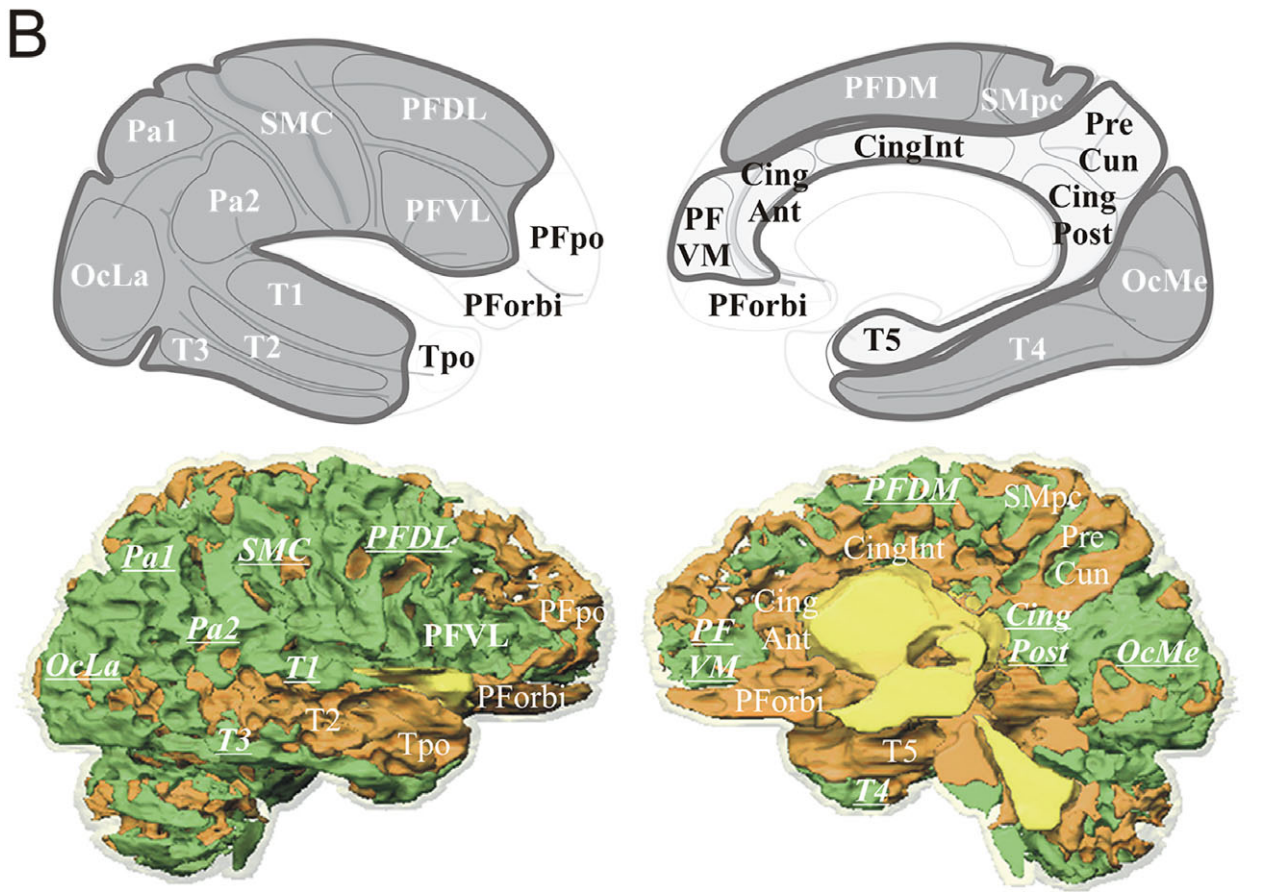
Baseline

DOC status before inclusion was confirmed in all five patients; mean baseline CRS-R scores (Table 2) varied from 4.2 (P5) to 11.7 (P3) and overall MCS status relied

Figure 3. FDG methods. (A) FDG normalization: Baseline (left column) and DBS-ON (intermediate column) normalized FDG, and DBS-ON minus Baseline normalized FDG variation (right column), example for P1: top row (4 mm above the anterior-posterior commissure plane), left and intermediate columns (inlay, raw FDG slices), standardized uptake values of cerebral metabolic rate of glucose normalized by cerebral global mean (CGM) activity (red, above CGM; blue, below CGM), and right column, variation map (green, increase; beige, decrease); bottom row, 3D rendering (superior and inferior views) of normalized data (R, right hemisphere). (B) FDG metabolism by cortical region and area: Top row, cortical areas and regions: internal area (light gray) with prefrontal ventromedial (PFVM), precuneal (PreCun), cingulate anterior (CingAnt), intermediate (CingInt) and posterior (posterior, retrosplenial and isthmus; CingPost) and temporo mesial para hippocampal (T5) cortices; external area (dark gray) with prefrontal dorsolateral (PFDL), ventrolateral (PFVL) and dorsomedial (PFDM), sensorimotor central (SMC) and paracentral (SMpc), parietal superior (Pa1) and inferior (Pa2), occipital lateral (OcLa) and medial (OcMe), temporal T1 (T1), T2 (T2), T3 (T3) and fusiform gyrus (T4) cortices; other area (white) with prefrontal orbital (PForbi) and polar (PFpo), temporopolar (Tpo) and cerebellar (Cerb) cortices. Bottom row, specification of FDG activities by region: example P1, right hemisphere; bold underlined increased activity (upward variation).

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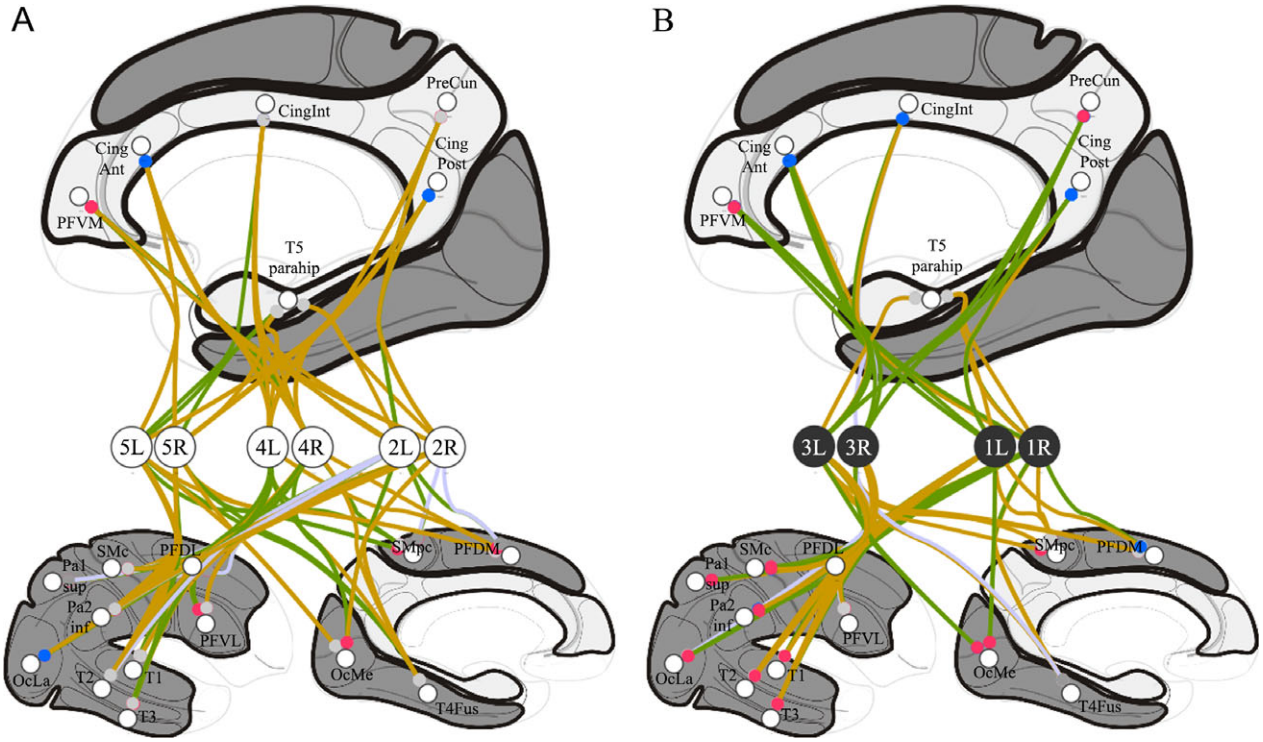


Figure 4. FDG results. Individual analysis of right (R) and left (L) hemispheres of the five patients (see Figure 3.B. for abbreviations): A, non-responders, P2, P4 and P5, (white circles); B, responders, P1 and P3, (black circles); top, medial view showing the internally-oriented cortices (light gray); bottom, lateral (left) and medial (right) views showing the externally-oriented cortices (dark gray); FDG metabolism variations are represented by connection lines toward cortices, green when the metabolism increased (DBS-ON > Baseline) and beige when the metabolism decreased (Baseline > DBS-ON) (connections with lesioned cortices are in light purple); baseline FDG metabolism is represented by colored circle, red for high relative activity and blue for low relative activity (gray for near cerebral global mean activity); the two responders exhibited significant increased FDG activity in the internally-oriented area.

Table 2. Mean CRS-R scores during baseline, DBS-ON, CO-ON and CO-OFF phases (the first period of the crossover phase is highlighted in gray); values are expressed as mean ± SD (number of assessments).

Patient	Baseline	DBS-ON	CO-ON	CO-OFF
P1	6.1 ± 1.3 (15)	8.4 ± 1.8 (41)[1]	7.3 ± 1.9 (11)	8.6 ± 2.0 (11)[1]
P2	9.6 ± 2.7 (17)	9.5 ± 1.5 (34)	10.3 ± 1.3 (11)[2]	8.5 ± 1.9 (8)
P3	11.7 ± 1.6 (18)	13.8 ± 2.2 (40)[1]	15.1 ± 1.9 (7)[1]	14.0 ± 3.4 (10)[1]
P4	4.8 ± 1.8 (57)	4.3 ± 1.8 (28)	3.9 ± 1.6 (11)[2]	6.6 ± 1.5 (14)[1]
P5	4.2 ± 3.3 (34)	3.0 ± 1.7 (27)	4.7 ± 2.0 (15)	5.1 ± 2.4 (10)
All	6.3 ± 3.5 (141)	8.4 ± 4.2 (170)	7.5 ± 4.1 (55)	8.4 ± 3.7 (53)[1]
All - P5	6.9 ± 3.3 (107)	9.4 ± 3.8 (143)[1]	8.6 ± 4.2 (40)	9.2 ± 3.5 (43)[1]

[1]Significant difference ($P < 0.05$) with baseline
[2]Significant difference ($P < 0.05$) of CO-ON with CO-OFF.

largely on auditory, visual and motor subscores. High FDG activity predominated in the left hemisphere (58.26%; $P = 0.004$) in the 5-patient group. Internally-oriented and externally-oriented areas were the source of primarily low (40%) and high (47%) activity ($P < 0.001$) respectively; the five patients shared these FDG features ($P < 0.001$).

Severe clinical adverse events

There was no surgery-related mortality. P4 (medical history of pneumonia and type-1 diabetes) developed postoperative bronchopulmonary infection (12-day stay in intensive care unit). At the end of the study (June 2016) four patients were alive. P4 died in April 2016,

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Table 3. Open-eye state at night during baseline, DBS-ON, CO-ON and CO-OFF phases (the first period of the crossover phase is highlighted in gray); values are expressed in number of observations (out of number of assessments; and percentage).

Patient	Baseline	DBS-ON	CO-ON	CO-OFF
P1	1 (14; 7.1%)	6 (25; 24%)	4 (14; 28.6%)	2 (10; 20%)
P2	6 (24; 25%)	1 (38; 2.6%)[1]	2 (8; 25%)	0 (9; 0%)
P3	11 (16; 68.8%)	1 (40; 2.5%)[1]	1 (6; 16.7%)[1]	2 (13; 15.4%)[1]
P4	2 (14; 14.3%)	3 (22; 13.6%)	3 (13; 23.1%)	3 (6; 50%)
P5	n.a.			
All - P5	20 (68; 29.4%)	11 (125; 8.8%)[1]	10 (41; 24.4%)	7 (38; 18.4%)

[1]Significant difference ($P < 0.05$) with baseline.

15 months after surgery and 5 years and 3 months after initial trauma. She died suddenly with no underlying infection or acute neurological signs (no autopsy in line with wishes of relatives). P5 was diagnosed with chronic filamentary keratitis seven months after surgery (DBS-ON phase) resulting in permanent palpebral closure.

CRS-R scores

Mean scores, DBS-ON in P1 ($P < 0.001$; responder) and P3 ($P = 0.001$; responder), CO-ON (first period, 15.1 ± 1.9) ($P < 0.01$) in P3, CO-OFF in P1 (second period, $P < 0.001$), P3 (second period, $P = 0.006$) and P4 (first period, $P < 0.001$), were superior to baseline scores (Table 2). Within crossover, the mean value of CO-ON (second period) was superior to CO-OFF in P2 ($P = 0.04$) and, conversely, inferior in P4 ($P = 0.001$).

CRS-R subscores

Mean subscores, visual in P1 ($P < 0.001$) and P3 ($P = 0.03$), auditory ($P < 0.001$) and oromotor-verbal ($P = 0.006$) in P3, increased from baseline to DBS-ON. Conversely mean subscores - auditory ($P = 0.01$), oromotor-verbal ($P = 0.001$), and arousal ($P = 0.02$) in P4, and motor in P5 ($P = 0.04$) - decreased. Within crossover, the mean value of CO-ON subscores - motor in P1 (first period, $P = 0.002$) and P4 (second period, $P < 0.001$) and visual in P5 (second period, $P = 0.009$) - was lower than the mean value of CO-OFF subscores and, conversely, motor subscores in P2 (second period, $P = 0.03$) and P3 (first period, $P = 0.03$) were higher.

MCS-threshold and emergence

There was an individual increase during DBS-ON in visual in P1 ($P < 0.001$) and auditory in P3 ($P < 0.001$) MCS-thresholds. Occurrence of MCS-thresholds was more frequent - motor in P4 ($P = 0.003$) and visual in P5 ($P = 0.001$) - during CO-OFF (second period).

Open-eye state at night

Open-eye state at night (Table 3) was reported in P1, P2, P3 and P4 (n = 272 values; P5 showed no evidence of open-eye - technical issues and keratitis). We observed that the eyes were open 47 times, 17.3% (data missing in one case). P2 ($P = 0.03$) and P3 ($P = 0.001$) showed a decrease in frequency of open-eye state at night during DBS-ON versus baseline; this was also true in P3 during crossover, in both CO-ON (first period, $P = 0.05$) and CO-OFF (second period, $P = 0.008$).

Variation in Brain Metabolism following DBS

The number of upward and downward variations in cortical areas (increased activity of internally-oriented area, 38%, externally-oriented, 42% and other areas, 53%; $P = 0.35$) and in CRS-R-based responses (increased activity of responder, 46%, and non-responder, 40%; $P = 0.39$) was equal in all five patients. However, the two responders (P1, P3) exhibited increased FDG activity during DBS-ON in the internally-oriented area (responder, 64%, and non-responder, 22%; $P = 0.002$; $P = 0.007$ when adjusted to baseline FDG activity), whereas variations in the externally-oriented area were unchanged (responder, 39%; non-responder, 44%; $P = 0.64$; $P = 0.85$ when adjusted to baseline FDG activity). Interaction between the externally-oriented area and CRS-R-based responses was significant ($P = 0.006$).

Discussion

The main finding in this trial is that low frequency DBS provoked tangible and reproducible clinical modifications (CRS-R items), long after the injury, with an increase in FDG metabolism of the internally-oriented cortex for the two responders. All five surgical interventions were safe (nil mortality), bearing in mind that only one case of intracerebral hematoma had been reported in earlier series.[22] However, our case of transient pulmonary infection

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shows that the most fragile patients are more prone to complications. Broadly our results corroborate with the largest pioneering series,[15–20] providing clues (institutional scales; prospective case series) that about 40–50% of patients may respond to low frequency DBS, and more precisely both UWS and MCS patients from our series. However, the overall clinical benefit of all trials, including ours, is limited. None of our five patients attained a level of verbal communication, but they sustained severe orofacial and language dysfunctions (Table 1; Appendix S1) which hindered progress. Improvement in verbal communication seems more attainable in less severe condition[21] than our patients. Indeed reasonable expectations following DBS in severe patients focused primarily on communication,[18] in any event. Our patients globally made progress in terms of auditory, visual, oromotor-verbal, motor and communication processes, and visual, auditory and communication MCS-thresholds (Appendix S1), most modifications having been perceived favorably by relatives and local healthcare staff. Specifically, the responders made progress regarding visual function and motor MCS-threshold (P1), and auditory, visual and oromotor-verbal functions and auditory MCS-threshold (P3). Indeed, visual and auditory attention would appear to be the most common improvement, more particularly in the two responders, facilitating both communication and spatial exploration. Visual modifications are of particular importance since visual CRS-R subscores have the highest diagnostic sensitivity among MCS and UWS patients.[37] We have also found that DBS modified open-eye state at night, possibly reflecting changes in sleep patterns, even if it was only significant on an individual basis in one responder (P3) and one non-responder (P2). Globally if we found across groups that CRS-R scores increased from baseline to crossover and DBS-ON phases (Appendix S1), it is when investigating individuals that detailed interpretation occurs. Indeed, changes in individual CRS-R scores observed during the DBS-ON phase were not as a matter of course either totally favorable or absent. Decreases in auditory, oromotor-verbal, arousal and motor, subscores in P4 and P5 demonstrated the diversity of DBS effects according to each specific type of brain damage. However, these unexpected effects were observed in non-responders alone, whose baseline CRS-R scores were the most severe and in whom the damaged brains were the smallest; P4 was a particularly severe case, cumulating trauma and anoxia and extensive higher function impairments (Appendix S1) with hypotonic quadriplegia. Our results also point to the spontaneous variability of global CRS-R scores due to the inconsistency of clinically observable awareness,[27] advocating recordings of repeated clinical status assessment in clinical studies. On the basis of our FDG metabolism data we found that MCS and UWS patients had preserved FDG activity (assuming spontaneous near at resting condition) in default mode network (DMN) cortices,[38] notably the lateral associative fronto-parietal cortices featuring MCS.[29] The plainly left-sided predominance of preserved metabolism has been interpreted, thus far, as a mere coincidence of lesion topography across patients. The spontaneous imbalance of internally-oriented and externally-oriented areas in the five patients, at the source of mainly low and high FDG activity respectively, echoes the link between cortices related to internal awareness and the severity of DOC,[40,41] as well as the increase in FDG activity of the internally-oriented cortical area of the two responders.

There are limitations to our pilot study. The results we derived from a limited number of patients provide insight into the potential clinical benefit of DBS, but also raise issues. More specifically, analysis of the crossover phase failed to show conclusive results when comparing first and second periods. This could be due to carryover DBS effect, possibly spanning several weeks, in association with lesion effects (surgery and titration lasting about one month, directly followed by the crossover phase). Indeed, only P2 and P4, non-responders, manifested significant changes in mean CO-ON versus CO-OFF CRS-R scores (CO-ON was the second period in both patients). The design of future crossover phases should likely be modified, example. assessment of DBS 3 months after surgery and 2 months after titration. Analysis of overt conscious behavior was only based on the CRS-R scoring, which is robust and standardized, yet less reliable regarding visual, oromotor verbal and arousal processes.[11,24] Moreover, analysis of behavior through distinct processes involving overlapping brain functions, impaired specifically because of extensive lesions (e.g. dyspraxia, dysgnosia and language disorders), likely influences sub-scale scores in a complex way. Our inclusion criteria were exclusively clinical and further studies should benefit from functional imaging according to clinical consensus,[29] along the same lines as our findings regarding FDG.

That being so, our findings contribute to an understanding of the mechanisms underlying low frequency DBS modulation. Cortico-basal ganglia-thalamo-cortical loops seem to activate affected networks, notably through thalamo- and pallido- cortical direct and indirect pathways in DOC models.[11,23,42–44] This effect would appear to be diffuse (FDG modifications within the 23 regions studied lacked statistical significance). In any case, DBS-mediated activation had overdriven internally-oriented areas, which may account for the recovery of conscious behavior. Modifications in open-eye state at night also suggest that pallido-tegmental circuits[45,46] may have been activated (along with thalamo-cortico-basal loops)

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particularly those involving the tegmental pedunculopontine nucleus. Neurons of the latter discharge specifically at low frequencies,[47] and the pedunculopontine nucleus is involved to the same extent in arousal-attention, paradoxical sleep, locomotor behaviors and tonus (see e.g.[35,48]). 100-Hz thalamus DBS can modify, partially alleviating[22] or increasing,[21] muscle tone in severe DOC patients. In our series, there was an increase in P5 muscle tone subsequent to implantation of pallidal or thalamic electrodes (titration phase). It is conceivable that different frequency settings, in the pallidum and/or the thalamus, may modulate tone in keeping with clinical context as hypertonia and pathologic posturing predominate in this population, aside from DOC.

In summary, recovery of certain brain processes that have been dysfunctional for many years in DOC patients is possible using low frequency DBS. Clinical response criteria comprise: UWS or MCS patients with high mean baseline CRS-R scores (of at least 2 months); multiple focal lesions following traumatic injury or hemorrhagic stroke with documented activity of DMN cortices. We stress that our results thus far have demonstrated limited individual benefits and quality of life remains unknown. Further lines of research should ideally decipher complex pathophysiology, refine techniques and indications, and include requisite societal debate that goes hand in hand with therapeutic advances. Meanwhile DBS techniques could be discussed in line with the rules governing deontology and ethics, on case-by-case basis, taking into account both the burden and the vulnerability of the population of permanent DOC patients, over long periods of rehabilitation that can last for decades.

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Author Contribution

JJL performed surgical procedures, prepared the figures, analyzed and interpreted the data; AS, BeP and SR, collected clinical data, organized imaging examinations, hospitalization and follow-up care; JG, AS, AK, TG and BJ performed structural (MRI, CT-Scan) and functional (FDG PET) imaging; BrP undertook statistical analysis; BeP and JJL performed titration; JC performed electrophysiological recordings, and JC and SR analyzed and interpreted the electrophysiological data; GC and AC performed preliminary surgery; FF and BR conceptualized and conducted PET FDG processing; JJL, BeP, AS, CS, JC, TG, FF and BrP conceptualized the study; JJL, AS, BeP, BrP, JC, CS, GC and FF drafted and revised the manuscript.

Conflict of Interest

None declared.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Supplementary Material

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