Case Report

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Deep Brain Stimulation of the Anterior Limb of the Internal Capsule May Be Efficacious for Explosive Aggressive Behaviour

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Key Words

Intermittent explosive disorder · Aggressiveness · Anterior limb of internal capsule · Psychosurgery · Deep brain stimulation · Obsessive-compulsive disorder

Abstract

Background: Intermittent explosive disease (IED) is a psychiatric disorder characterized by intermittent attacks of rage and violence frequently resistant to pharmacological therapy. Deep brain stimulation (DBS) of the posteromedial hypothalamus has been applied with fair results and clinical improvement with some surgical morbidity due to neurovegetative side effects. The anterior limb of the internal capsule/ventral capsule/ventral striatum (VC/VS) has never been used alone as a target for this disease. ***Objectives:*** The aim of this study is to evaluate the efficacy of bilateral DBS of the VC/VS for the treatment of IED. ***Methods:*** We performed bilateral DBS of the VC/VS in a 21-year-old patient with IED. This young man had a traumatic birth complicated by hypoxia, and he showed a mild mental impairment. Different pharmacological treatments were carried out with no results before DBS was proposed to the patient's relatives after multidisciplinary approval. ***Results:*** After 22 months of high-frequency monopolar bilateral DBS of the VC/VS, the patient showed a significant improvement. Postoperative ^{18}F-FDG PET-CT studies ruled out a reduction of the hypermetabolic areas located in the limbic system previously detected in pre-operative investigations. ***Conclusions:*** Bilateral DBS of the VC/VS may be considered for the treatment of IED without the risk of neurovegetative side effects.

Introduction

Erethism or intermittent explosive disease (IED) is a psychiatric disorder characterized by episodes of impulsive aggression usually associated with mental impairment and acquired or congenital brain lesions [1–10].

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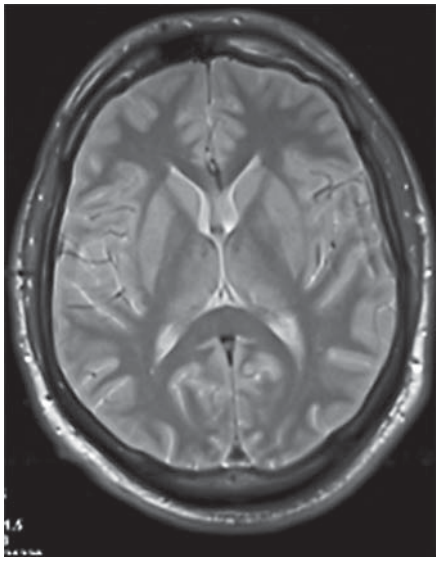

Fig. 1. Axial T2W 1.5-tesla MR scan showing a slight periventricular hyperintense signal.

Different lesional stereotactic procedures were proposed to treat IED with good outcomes [1, 2, 11–17]. Deep brain stimulation (DBS) may replace destructive procedures with encouraging results as a validated treatment for movement disorders [18, 19] and some psychiatric diseases like obsessive-compulsive disorder (OCD) [20, 21] and Tourette's syndrome [22]. Three different DBS targets have been used for IED: the bilateral posteromedial hypothalamus [5–8, 10], unilateral right orbitofrontal projection [9], and more recently a combination of bilateral posteromedial hypothalamus together with bilateral anterior limb of internal capsule/ventral capsule/ventral striatum (VC/VS) and nucleus accumbens [23].

We performed bilateral monopolar high-frequency VC/VS DBS in a 21-year-old patient with IED and ritualistic behaviours achieving a significant and stable reduction of rage and violent attacks after 22 months of follow-up. The clinical findings, surgical technique and 22-month outcome are reported in this paper.

Case Description

History and Examination

The patient was a 21-year-old man born by caesarean delivery complicated by perinatal hypoxia. Since early childhood, he had suffered from severe psychomotor delay and when 5 years old he developed a self- and hetero-aggressive behaviour with unexpected violent rage attacks and hyperkinetic stereotyped movements with obsessive rituals. During his life the patient received many psychotropic drugs (lithium, clozapine, haloperidol, sertraline, chlorpromazine, clomipramine, valproic acid, risperidone, clonazepam) without any significant benefit. Due to his clinical picture, he required frequent physical restraining during various hospitalizations. Extended laboratory tests, including lipid, protein and whole hormonal profiles, were completely normal. A 1.5-tesla brain MRI showed only a slight periventicular hyperintense signal on T2-weighted imaging (T2WI) and FLAIR-T2WI sequences (fig. 1) due to perinatal hypoxia. At the time of the presurgical work-up he was receiving clozapine, carbamazepine and valproic acid at maximum tolerated doses without any clinical effect. The patient was able to understand simple verbal sentences; he communicated his requests touching his mother's hand; his speech was not completely articulated and not easy to understand, speaking only single or pairs of words. Coloured progressive matrices (CPM) [24], an intelligence quotient (IQ) test, was used to evaluate his non-verbal reasoning abilities. He correctly performed 13 out of 36 coloured progressive matrices resulting in an IQ score of 45, meaning a moderate mental retardation. To evaluate our patient's aggressive behaviour, we used the Modified Overt Aggression Scale (MOAS) [25, 26]. This scale (range 0–40) provides a reliable measure of verbal aggression, self- and/or hetero-aggressive behaviour, and has been shown to be a reliable measure of aggressive behaviour in people with intellectual disability [26, 27]. The parents were separately interviewed and asked to describe their son's behaviour before and after surgery. The items that better described the patient's behaviour were then directly selected from each of the parents. Preoperative MOAS behavioural scores were 34 for both parents. A detailed neuropsychological evaluation was impossible because of the patient's low IQ and lack of collaboration.

The patient's case was discussed in a multidisciplinary conference, and the surgical treatment by DBS of the anterior limb of the internal capsule (VC/VS) was approved on the basis of chronicity and severity of the condition and refractoriness to conservative treatment; furthermore there were neither medical comorbidities nor contraindications to surgery. The choice of the VC/VS as target of DBS was made because it was successfully used for lesional procedures in 'anterior capsulotomy' [13, 15–17] and because it could have controlled the patient's obsessive and ritualistic behaviour [20, 21]; furthermore the same target had already been applied for similar clinical settings [9, 23].

His parents were informed about the purpose of the treatment and related potential risks and benefits in detail. Informed consent was signed by the parents according to our Institution Ethics Rules.

Surgery and Stimulation

Under general anaesthesia the patient underwent stereotactic bilateral electrode implantation for VC/VS DBS. A Leksell Frame G model (Elekta Instruments®, Sweden) was used to acquire a stereotactic CT scan, then merged with axial 3-dimensional T1WI plus gadolinium enhancement and axial 3-dimensional T2WI 1.5-tesla magnetic resonance (MR). The target coordinates were calculated and planned using MR sequences by Framelink Neuronavigation Software (Medtronic Inc.®, Minneapolis, Minn., USA). The final tentative coordinates according to the Schaltenbrand-Wahren atlas [28] were 10.56 (left VC/VS) and 10.15 (right VC/VS) anterior, 1.10 dorsal to the midcommissural line, and 7 mm

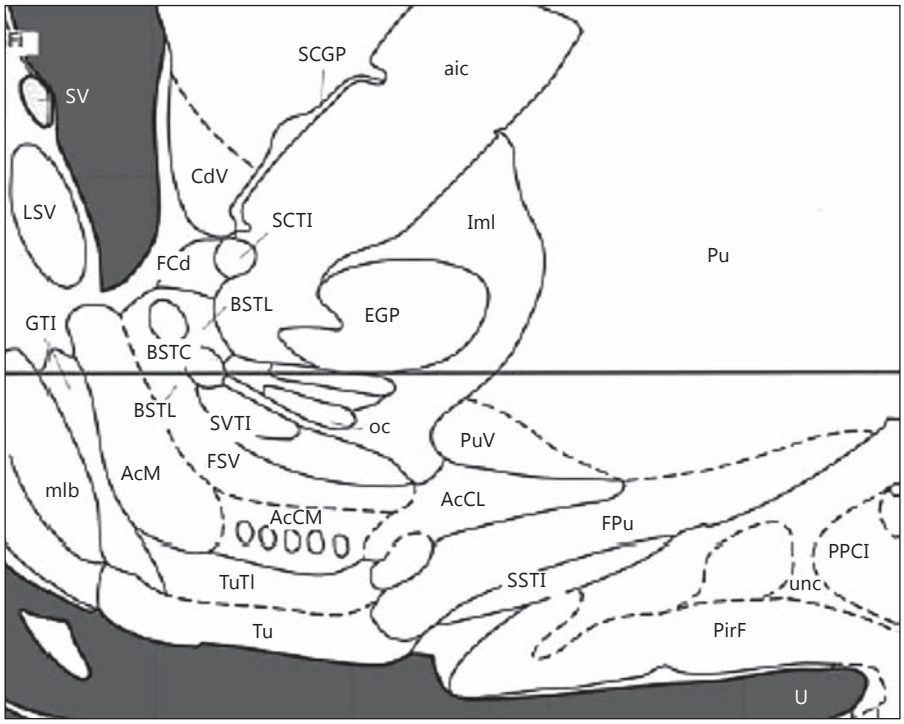

Fig. 2. Diagrammatic coronal schema 16 mm rostral to the midcommissural plane corresponding to the VC/VS region traversed by the electrode. Ac = Nucleus accumbens; aic = anterior internal capsule; BSTL = bed nucleus of stria terminalis; Pu = putamen. Adapted from Maley et al. [9].

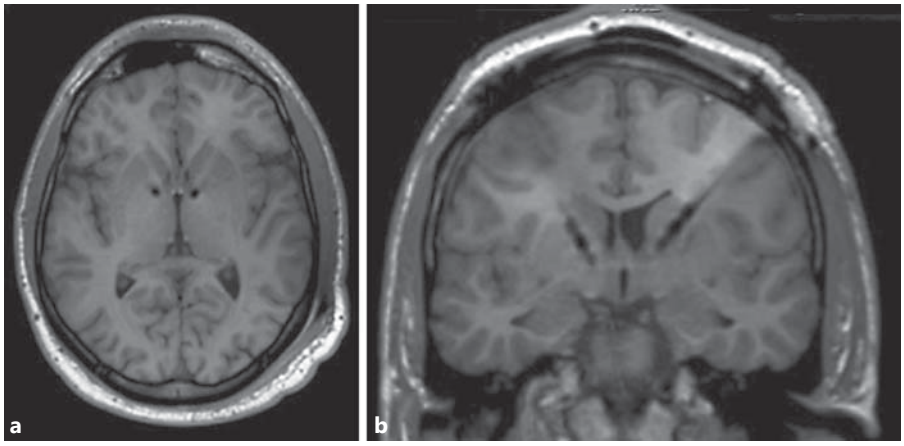

Fig. 3. Postoperative T1W 1.5-tesla MR showing the correct electrode placement in axial (**a**) and coronal (**b**) scans into the VC/VS.

(left VC/VS) and 10 mm (right VC/VS) lateral to the sagittal plane (fig. 2). Two quadripolar DBS lead electrodes (Model 3391, Medtronic Inc.®) were implanted through 2 precoronal 14-mm diameter burr holes located 10 mm anterior to the coronal suture, and 30 mm lateral to the midline following an oblique trajectory on each side with an anterior angle of approximately 75° to the intercommissural line; the stimulating contacts were numbered from 0 to 3 and from 4 to 7 in the first and second electrode, respectively: contacts 0 and 4 were nearest to the bed nucleus of the stria terminalis (the right contact 0 was about 10 mm lateral, 3.2 mm superior, and 1 mm anterior from the anterior commissure; the left contact 4 was about 7.6 mm lateral, 3.2 mm superior, and 1 mm anterior from the anterior commissure), contacts 1–2 and 5–6 inside the region of the VC/VS, and contacts 3–7 (the furthest from the tip of the electrode) dorsally to the internal capsule. On the same operation day, a Kinetra Intermittent Pulse Generator (IPG; Medtronic Inc.®) was implanted in a left subclavicular subcutaneous pocket. The postoperative period was uneventful, and a postoperative 3-dimensional T1WI MR ruled out any complication and confirmed the correct placement of electrodes (fig. 3). One month later a bilateral low-frequency monopolar stimulation (cathode as positive contact corresponding to the IPG battery) was started using as anode (negative contact) the deepest contacts of electrodes (0 on the right side, 4 on the left side) positioned at the target. The stimulation parameters were progressively titrated to 130 Hz, 2.5 V, 210 μs in 2 months.

Table 1. Location and peak Z scores of cortical areas showing increased regional cerebral glucose metabolism rates before (A) and after (B) surgical treatment with bilateral high-frequency VC/VS-Nacc DBS

	K_E	Location (functional area, Brodmann area)	Coordinates			Z score
			x	y	z	
A	847	Left cerebrum, limbic lobe, uncus, amygdala	–20	–6	–21	3.96
		Left cerebrum, temporal lobe, subgyral (BA 20)	–46	–12	–22	3.74
		Left cerebrum, temporal lobe, fusiform gyrus (BA 20)	–44	–36	–20	3.45
		Left cerebrum, limbic lobe, uncus (BA 20)	–36	10	–32	3.31
	619	Left cerebrum, temporal lobe, inferior temporal gyrus (BA 20)	–40	–2	–38	3.21
		Left medial frontal gyrus (DMPFC; BA 8, 9)	–6	18	46	3.68
			–10	54	10	3.24
			–12	50	–6	3.20
			–14	38	20	3.18
		Left inferior frontal gyrus (BA 47)	–40	30	–2	3.14
B	436	Left inferior frontal gyrus (BA 47)	–40	26	10	3.73
			–36	30	–4	3.55

Results were obtained by image analysis for regionally specific effects using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) implemented on the MATLAB platform (The Mathworks Inc., USA). Categorical comparisons were performed between the adjusted regional cerebral glucose metabolism voxel values of the patient and those of a normal age-matched database (100 subjects) by using the 'single-subject t test' option in SPM8 ($p < 0.01$ uncorrected for multiple comparisons, clusters comprised of ≥100 adjacent voxels). Talairach brain coordinates were given by a non-linear transform to Talairach space, and Talairach Daemon software was used for conversion into Brodmann localization. The table lists the Z scores ($p < 0.01$ uncorrected), the spatial extent of clusters in voxels (K_E), the Talairach coordinates in millimetres together with their anatomical location and the corresponding functional and Brodmann areas (BA). DMPFC = Dorsomedial prefrontal cortex.

Effects on Behaviour

The patient was monitored with periodical consultations with his parents. At the last follow-up, 22 months after surgery, the patient appeared more quiet and collaborative with fewer rage attacks and a better response to drug therapy together with better sociability and less need for continuous care. The postoperative MOAS scores [25, 26] were 11 and 7 according to his father and mother, respectively, corresponding to a score difference of –23 (67.7% improvement) and –27 (79.5% improvement), respectively, indicating a significant reduction in aggressive behaviour. Neither side effects of stimulation nor hardware complications were observed. Furthermore, the patient underwent a brain ^{18}F-FDG PET-CT scan before and after surgical treatment (fig. 4; table 1). The pre-DBS PET scan showed a significant hypermetabolism ($p < 0.01$) in the left amygdala and uncus (limbic lobe, BA 20), left fusiform gyrus, sub-gyral and temporal inferior gyrus (temporal lobe, Brodmann area, BA, 20), left medial frontal gyrus (frontal lobe, dorsomedial prefrontal cortex, BA 9, 10) and left inferior frontal gyrus (frontal lobe, BA 37) (fig. 4; table 1). In contrast, a reduction in hypermetabolism was documented in the left inferior frontal gyrus (frontal lobe, BA 37) in the PET scan performed after DBS (fig. 2; table 1). Moreover, the efficacy of surgery was unintentionally confirmed by switching off the device to perform an ^{18}F-FDG PET-CT scan in the off state: this manoeuvre induced a violent rage storm against parents and objects which was dramatically terminated by means of an immediate reactivation of VC/VS DBS stimulation at preexisting parameters.

Discussion

We report the successful treatment of a 21-year-old male patient suffering from IED by bilateral VC/VS DBS after 22 months of high-frequency monopolar stimulation.

IED is a psychiatric disorder characterized by intermittent impulsive rage bursts frequently associated with hyperkinesia, destructiveness, hetero- and self-aggressiveness, and mental impairment with a 2–3% prevalence in the general population [1–10, 25]. Different aetiologies have been reported: epileptic, postencephalitic, posttraumatic, perinatal hypoxia in preterm delivery, and brain malformations [1, 2, 5–8, 10] with brain lesions mostly located in the frontobasal cortex [9, 29]. This patient was delivered by a dystocic caesarean and suffered from perinatal hypoxia. He showed a neurological and cognitive delay and at the age of 5 developed violent behaviour characterized by bursts of rage attacks toward parents, objects and himself. The clinical picture included compulsive stereotyped movements and obsessive rituals. Many drug treatments failed, and the diagnosis of IED

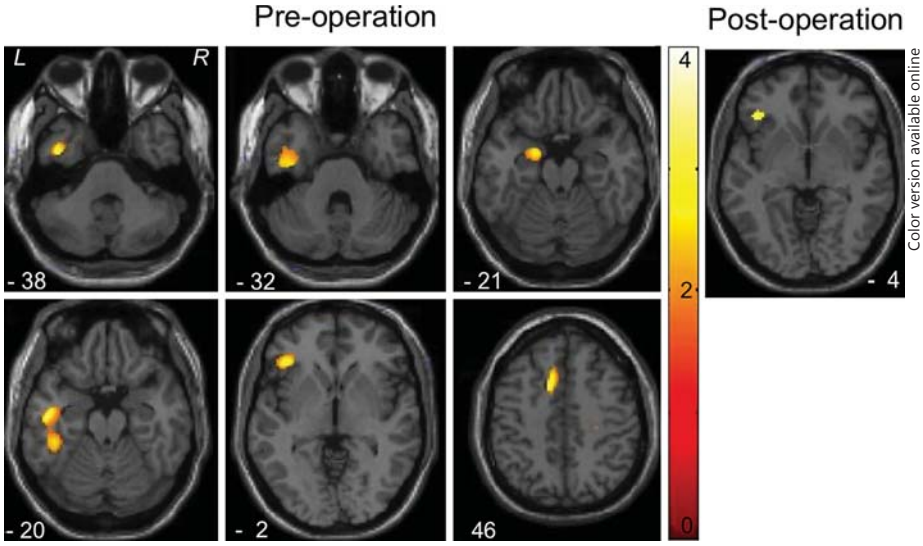

Fig. 4. The cortical areas characterized by increased regional cerebral glucose metabolism rates before (left side) and after (right side) DBS are displayed. In the pre-DBS condition (left side), a significant hypermetabolism was found to be present in the left amygdala (Z –21) and uncus (Z –32) (limbic lobe, BA 20), left fusiform gyrus (Z –20), subgyral (Z –22) and temporal inferior gyrus (Z –38) (temporal lobe, BA 20), left medial frontal gyrus (Z 46) (frontal lobe, dorsomedial prefrontal cortex, BA 9, 10) and left inferior frontal gyrus (Z –2) (frontal lobe, BA 47). In contrast, only a residual hypermetabolism was present in the left inferior frontal gyrus (Z –4) (frontal lobe, BA 37) in the PET scan performed after DBS (right side).

was reached according to DSM-IV [3, 4]. The patient did not show any comorbidity; laboratory screening was normal. The degree of mental retardation was classified as moderate according to the coloured progressive matrix score [24], and his aggressiveness against both parents was related to a high degree of IED according to the MOAS score [25, 26].

The IED neurophysiopathology probably relies on a disturbance in the 'emotional brain circuitry' including the anterior cingulate cortex, amygdala, insular cortex, hypothalamus, and ventral striatum, all connected by the lymbic system [5, 8–10, 30–33]. The posteromedial hypothalamus, known as the 'aggression area' [1, 2], is involved in the control of aggressive behaviour [1, 2]. Furthermore, different regions such as the orbitofrontal cortex, amygdala, and anterior cingulate cortex have been demonstrated to activate some prefrontal cortex regions during episodes of threats and aggression, and the right frontobasal cortex is particularly involved in modulating the level of individual anger [9, 31–33]. Thus, from a theoretical viewpoint, each type of brain lesion within these areas could unbalance the 'emotional brain circuitry', which is finally involved in IED aetiology. In our case, there were no focal brain lesions; the periventicular hyperintense signal at T2WI/FLAIR-T2WI MR was probably due to the perinatal hypoxia. On the other side, a preoperative ^{18}F-FDG PET-CT scan showed a significant hypermetabolism ($p < 0.01$) in the left amygdala and uncus (limbic lobe, BA 20), left fusiform gyrus, subgyral and temporal inferior gyrus (temporal lobe, BA 20), left medial frontal gyrus (frontal lobe, dorsomedial prefrontal cortex, BA 9, 10) and left inferior frontal gyrus (frontal lobe, BA 37) (fig. 4; table 1) corresponding to the aforementioned 'emotional brain circuitry'.

Medical treatment and electroconvulsive therapy are often inefficacious, and these patients require frequent hospitalizations and restraining measures [5–7, 10]. In the past, Narabayashi et al. [11] perfomed bilateral stereotactic amygdalotomy with an 80% success rate. Since then and up to the late 80s, many other lesional surgeries were performed: anterior cingulotomy, anterior capsulotomy, subcaudate tractotomy, dorsomedial thalamotomy, fornicotomy, subfrontal gyrectomy, limbic leucotomy (cingulotomy plus subcaudate tractotomy), and posteromedial hypothalamotomy, with different but encouraging results [1–2, 12–17]. The first homogeneous and significant IED surgical series were reported by Sano et al. [1, 2], who performed bilateral stereotactic posteromedial hypothalamotomy leading to clinical improvement in about 85% of patients with surgical morbidity due to neurovegetative side effects. As regards the stereotactic lesional anterior capsulotomy, performed to treat different psychiatric diseases including IED, it is noteworthy that the target corresponding to the anterior limb region of the internal capsule adjacent to the VC/VS contains fibres connecting the prefrontal cortex to the subcortical nuclei and thalamus [16, 17, 34]. Nevertheless, the development of new drugs with a better efficacy profile led to the abandonment of some of these lesional but efficacious procedures. DBS started a new era of psychosurgery [34]: at present it is a recognized treatment for movement disorders and in recent decades has been performed to treat

chronic pain, drug-resistant epilepsy and psychiatric disorders like OCD, major unipolar depression, Tourette's syndrome, and aggressive behaviour [19–22, 35–38]. The very mechanism of DBS is not completely known yet but two main hypotheses are probably combined: (1) DBS may induce a *functional lesion* by inhibiting the target through a neuronal depolarization blockage by synaptic depression or inhibition ('neuronal jamming'); (2) DBS may induce a final *remodulation* of the pathological circuitry [18, 19].

Regarding OCD treatment, the neurophysiological basis of VC/VS DBS functioning relies on many pieces of evidence supporting the orbitofrontal cortex (especially the inferior tracts of the right hemisphere), the anterior cingulate cortex, the basal ganglia, and the thalamus as the main anatomical substrates of most psychiatric diseases [20, 34, 36]. These hypotheses are supported by the hyperactivity in the orbitofrontal cortex ruled out by metabolic PET studies and functional MRI [31, 33, 39, 40]. DBS of the posteromedial hypothalamus for IED has been performed by different authors with 14 patients reported in the literature with good long-term results [5–10]. In a recent paper, Harat et al. [23] performed bilateral VC/VS-nucleus accumbens DBS after the failure of a previous bilateral posteromedial hypothalamus DBS, achieving a satisfying resolution of rage and anxiety attacks and anxiety. It is important to note that the stimulation targets of VC/VS DBS [20–21, 36] and posteromedial hypothalamus DBS [5, 8, 7, 10] were the same as those used in anterior capsulotomy [16, 17] and posteromedial hypothalamotomy [1, 2], respectively.

The present patient suffered from a severe drug-resistant IED complicated by obsessive ritualistic behaviours and shared the same features as published patients treated by DBS of the posteromedial hypothalamus [5, 7, 8, 10], and right orbitofrontal projections [9]. As reported by Maley et al. [9], DBS of the right orbitofrontal fibres involves many small nuclei and regions like the anterior limb of the internal capsule, nucleus accumbens, bed nucleus of the stria terminalis, striatum and putamen (fig. 2). This target is approximately the same used for OCD [20, 21, 36] and has indeed the advantages of avoiding neurovegetative side effects as in the posteromedial hypothalamus [5, 8, 10]. Taking into account our patient's psychiatric profile and according to the confirmed efficacy of VC/VS DBS in OCD [20, 21, 36], and its potential effect on IED as reported by Maley et al. [9], we decided to use VC/VS as a DBS target. In order to stimulate the majority of the fibres running from the thalamic and subcortical nuclei to the prefrontal cortex and to the cingulate gyrus, we inserted the electrode through the anterior limb of the internal capsule as far as the region of the VC/VS.

Regarding IPG stimulation, there are no recommended parameters of DBS for IED in the literature. Hernando et al. [7] used low-frequency bilateral posteromedial hypothalamus stimulation (15 Hz, 450 μs, <1 V) in a combined monopolar (left 1–/C+) and bipolar (right 0–/1+) pattern, while Franzini et al. [5, 8] applied a bilateral high-frequency stimulation (180 Hz; 60 ms, 1–1.5 V). Using the same target, 5 out of 6 patients reported by Torres et al. [10] experienced a significant improvement after 5 years of follow-up with high/low-frequency mono/bipolar stimulation current (185 Hz, 60–210 μs, 1.3–2.5 V). Kuhn et al. [6] successfully treated by high-frequency (130-Hz) posteromedial hypothalamus DBS a severe form of self-mutilation in a woman mentally retarded after head injury. Regarding the orbitofrontal projections and VC/VS region, Maley et al. [9] performed low-frequency unilateral DBS of right orbitofrontal fibres (55 Hz, 270 μs, 2.8 V) with favourable outcome in aggressiveness control at the 1-year follow-up. In DBS of the VC/VS for OCD treatment, the parameters are usually settled on high frequency and high voltage with similar parameters (100–185 Hz, 90–450 μs, 3.5–10 V) in reported papers [20, 21, 36]. Furthermore, there is only 1 report on the efficacy of low-frequency VC/VS DBS for IED, as compared to larger and multicentric series for OCD [20, 21, 36] successfully treated by high-frequency stimulation. Considering our patient's ritualistic forced behaviours associated with IED, we decided to perform high-frequency bilateral DBS of the VC/VS region in a monopolar mode to recruit a wider range of connecting fibres running in the anterior limb of the internal capsule. During stimulation we did not observe any kind of side effects and the patient well tolerated the progressive titration to high-frequency bilateral monopolar stimulation with these final parameters: cathode/IPG battery (+); anode/contact 0/4 (–); 130 Hz, 2.5 V, 210 μs. The final outcome after the 22 months of follow-up was good since the patient showed a better response to drug therapy, a significant reduction in aggressive behaviour appearing more calm and collaborative, with no further need for hospitalization. The level of aggressiveness as assessed by the MOAS score was reduced. The persistent benefit almost 2 years after surgery and the patient's low intellectual level argued against a placebo effect, although we cannot exclude such an effect for the parents. The ^{18}F-FDG PET-CT scan findings ruled out hypermetabolism in the limbic (amygdala, uncus), temporal (fusiform gyrus, subgyral, and inferior temporal gyrus), and medial frontal

regions (dorsomedial prefrontal cortex, inferior temporal gyrus) in the pre-DBS condition and only a small residual hypermetabolism in the inferior frontal gyrus in the post-DBS condition, thus suggesting a dysregulation of the aforementioned pathway and a role of DBS in reversing such a pathological functional condition (fig. 4; table 1). Furthermore, the patient showed a sudden relapse of rage attacks with self- and hetero-aggressive behaviour after the device had been switched off to perform an ^{18}F-FDG PET-CT scan in the off-treatment condition. Similar to our experience, a number of reports have shown dramatic rebounds and a worsening of preexisting psychiatric symptoms preceded by a worsening of mood and anxiety after a sudden interruption of stimulation due to a voluntary stop or device failure [41, 42].

Conclusions

We report the successful treatment of a 21-year-old man affected by IED by bilateral monopolar high-frequency DBS of the VC/VS region. After 22 months of follow-up, the patient showed a stable improvement in aggressive behaviour together with a better response to drug treatment. In the past the VC/VS target has already been used for stereotactic lesional neurosurgery with the same purposes, and today it is a well-established target in DBS for OCD treatment. This report provides some evidence for possible future applications of DBS of VC/VS regions for aggressive behaviour and other psychiatric disorders, and highlights the risk of a sudden and dramatic rebound and a worsening of preexisting psychiatric symptoms due to sudden interruption of stimulation.

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Disclosure Statement

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