



Case Report

N-of-1 trial following deep brain stimulation in a patient with obsessive–compulsive disorder

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ABSTRACT

N-of-1 trials are an effective evidence-based approach in individual patient management. It has been suggested that deep brain stimulation (DBS) of the ventral capsule/ventral striatum (VC/VS) is effective in the treatment of refractory obsessive–compulsive disorder (OCD). However, it has not been documented in the literature whether a perioperative acute stimulation test can provide substantial information for chronic stimulation. A 21-year-old man with a 6-year history of medication-refractory OCD underwent bilateral DBS on the VC/VS. Two weeks after surgery, an acute stimulation test was performed in an N-of-1 trial. Olfactory hallucinations, laughter, and euphoria were observed during the acute stimulation test. At follow-up after 17 months, the patient's scores improved from 34 at baseline to 14 on the Yale–Brown Obsessive Compulsive Scale, from 34 to 20 (41.2% improvement) on the Hamilton Anxiety Rating scale, and from 41 to 71 (75% improvement) on the Global Assessment of Functioning scale. According to our N-of-1 trial, olfactory hallucinations, in addition to laughter, induced by a perioperative acute stimulation test may be an indicator of good outcome in OCDBS during chronic stimulation.

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1. Introduction

It has been suggested that deep brain stimulation (DBS) of the ventral capsule/ventral striatum (VC/VS) is effective in the treatment of refractory obsessive–compulsive disorder (OCD). The current presumed pathophysiology of OCD is an abnormality in the cortical–striatal–thalamic–cortical (CSTC) circuit [1,2]. Numerous magnetic resonance imaging (MRI) studies have revealed that OCD patients have more gray matter in regions comprising CSTC circuits than healthy volunteers [3,4]. Functional neuroimaging also showed increased regional cerebral blood flow and basal metabolic activity in the orbitofrontal cortex (OFC), anterior cingulate cortex, striatum, and thalamus in OCD patients [3,5]. Disruption of CSTC circuits would theoretically suppress neuronal activity in these regions. Current neurosurgery for OCD includes anterior capsulotomy, anterior cingulotomy, subcaudate

tractotomy, limbic leucotomy, and DBS to the VC/VS [6,7]. In one study, the mean firing rate of OFC neurons was reduced during nucleus accumbens (NAc) DBS in rats [8]. Digital subtraction analysis of fluorodeoxyglucose positron emission tomography scans also showed prominent decreases in metabolic activities over the OFC during chronic NAc DBS stimulation in OCD patients with clinical improvement [9,10]. These results suggest that thorough disruption of the CSTC circuit by DBS would be associated with an improvement in OCD patients. However, it has not been documented in the literature whether a perioperative acute stimulation test can provide substantial information for chronic stimulation. N-of-1 trials are multi-cycle, within-patient, randomized, double-blind, crossover comparisons of a drug or intervention and a placebo [11]. It is a method commonly used in evidence-based practice when there is only one patient enrolled in a test. Olfactory hallucinations, laughter, euphoria, chest vibration, dizziness, nausea, and heat sensation have been observed during NAc DBS stimulation in OCD patients [12]. In this case report, we constructed an N-of-1 trial protocol based on knowledge of the circuit within the basal ganglia and the stimulation parameters, and tried to translate the effects during acute stimulation into chronic stimulation.

Conflict of interest: none.

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2. Case report

2.1. Patient history

Our patient was a 21-year-old man with a 6-year history of medication-refractory OCD. His cardinal symptoms were recurrent thoughts or images of sexual illusion and repetitive self-hurt behavior to dispel these images. The patient was referred by the Department of Psychiatry for DBS surgery. This study was approved by the national institutional review board (IRB) (Department of Health, Executive Yuan, Taiwan; No. 0960210149) and the local IRB (Tzu Chi General Hospital, Hualien, Taiwan; No. 094-33).

2.2. Surgical procedure

A high-resolution, T1-weighted image with a slice thickness of 0.7 mm was obtained 1 day before the surgery using a 1.5-T MRI scanner. We applied a Leksell stereotactic frame under local anesthesia. High-resolution head computed tomography (CT) with a slice thickness of 1.25 mm was performed. The images were sent to a workstation equipped with BrainLAB (Munich, Germany) and then the MRI and CT images were fused. According to the Schaltenbrand–Wahren atlas [13], the coordinates of the NAc are 3 mm rostral to the anterior commissure, 7 mm lateral to the midline, and 3–4 mm ventral to the anterior–posterior commissure line. We adjusted the coordinates and the entry point to make the trajectory along the long axis of the anterior limb of the internal capsule with the tip at the NAc. The implanted quadripolar electrodes (model 3387, Medtronic, Minneapolis, MN, USA) consisted of four cylindrical contacts, each of which was 1.5 mm long and separated from the adjacent contact by 1.5 mm (Fig. 1, Table 1).

2.3. N-of-1 trial protocol

Two weeks after surgery, an acute stimulation test was performed using N-of-1 trials on each contact of the bilateral electrodes combined with videotaping. The stimulation settings were 210 microseconds, 130 Hz, and 0, 2, 4, 6, and 8 V. Olfactory hallucinations, laughter, euphoria, chest vibration, dizziness, nausea, and heat sensation were assumed to be the target symptoms that might translate into a good outcome during chronic stimulation (Table 2).

Table 1
Coordinates of each contact.

	Left			Right			
	X	Y	Z	X	Y	Z	
Target	6.7	2.9	−3.1	Target	6.8	2.4	−2.8
0	7.1	1.2	−2.3	0	6.0	0.6	−3.6
1	8.4	2.4	0.4	1	7.2	2.4	−1.1
2	10.4	3.6	3	2	8.8	3.6	1.6
3	12.5	4.6	5.7	3	11.3	4.9	3.5

Coordinates were obtained in relation to the anterior commissure of the corpus callosum according to fused images between presurgical planning and postoperative MRI. The anterior commissure–posterior commissure distance was 24.4 mm.

3. Results

Obvious olfactory hallucinations (smell of bananas) were observed on stimulation of the left-side electrode for contacts 0 (8 V), 1 (4, 6, and 8 V), and 3 (2 V). No olfactory hallucinations were observed on stimulation of the right-side electrode. Laughter or euphoria was observed on stimulation of the left-side electrode for contacts 0 (6 and 8 V), 1 (6 and 8 V), and 3 (6 and 8 V), and of the right-side electrode for contacts 0 (8 V), 1 (4, 6, and 8 V), 2 (4, 6, and 8 V), and 3 (4 V). Chest vibration, dizziness, nausea, and heat sensation were also noted (Table 2). We set the lowest contact (contact 0) for chronic stimulation. The score on the Yale–Brown Obsessive Compulsive Scale (Y-BOCS) decreased from 34 at baseline to 14 at follow-up after 17 months (58.8% improvement). The score on the Hamilton Anxiety Rating Scale also improved from 34 preoperatively to 20 (41.2% improvement) and the Global Assessment of Functioning score decreased from 41 at baseline to 71 (75% improvement) (Table 3).

4. Discussion

When faced with therapeutic uncertainty, an N-of-1 trial is a safe alternative for individualization of a treatment protocol based on the concept of evidenced-based randomized control trials (RCTs). The ultimate goal is to determine the optimal strategy for patient management. An N-of-1 trial probably requires the least resources of any RCT option, but is an excellent tool for knowledge translation into tailored individualized medicine [14–16].

The results of this study revealed several important findings for DBS in the VC/VS during acute stimulation, especially that olfactory hallucinations occur in addition to laughter, euphoria, heat sensation,

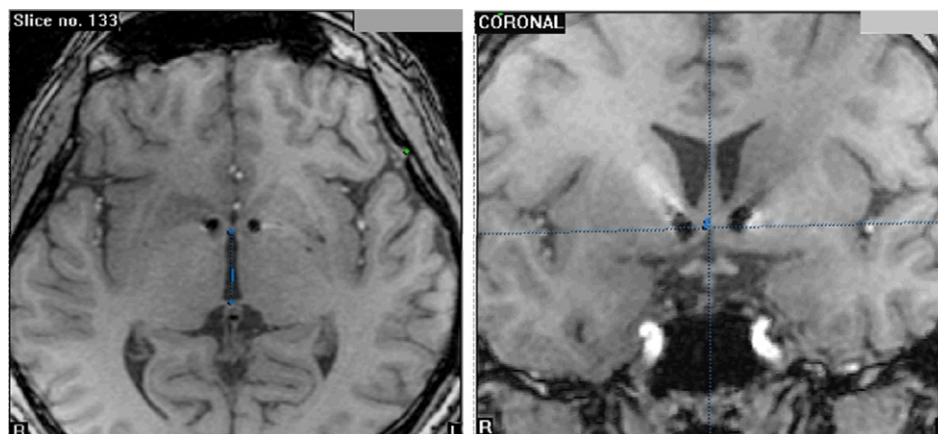


Fig. 1. Fused images from presurgical planning and postoperative brain magnetic resonance imaging.

Table 2
Acute stimulation test.

Response	Contact 0					Contact 1					Contact 2					Contact 3				
	0V	2V	4V	6V	8V	0V	2V	4V	6V	8V	0V	2V	4V	6V	8V	0V	2V	4V	6V	8V
Left																				
Laughter, euphoria	-	-	-	+	+	-	-	-	+	+	-	-	-	-	-	-	-	-	+	+
Smell	-	-	-	-	+	-	-	+	+	+	-	-	-	-	-	-	+	-	-	-
Chest vibration	-	-	-	-	-	-	-	-	-	+	-	-	-	+	+	-	-	-	-	+
Dizziness	-	-	+	-	+	-	-	-	+	+	-	+	+	-	-	-	-	+	-	-
Nausea	-	-	+	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-
Heat	-	-	-	+	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-
Right																				
Laughter, euphoria	-	-	-	-	+	-	-	+	+	+	-	-	+	+	+	-	-	+	-	-
Chest vibration	-	-	-	+	+	-	-	-	+	+	-	-	+	-	+	-	-	-	-	+
Dizziness	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	+	-	-
Nausea	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Heat	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

We used randomized and double-blind testing. One researcher controlled the DBS setting and the other recorded the result. + = positive response; - = no response.

dizziness, nausea, and chest vibration. According to the results for acute stimulation, we set the lowest contact of the electrode as the negative pole for chronic stimulation bilaterally. The Y-BOCS score decreased from 34 before DBS to 14 at follow-up after 17 months (58.8% improvement). This study suggested that the results of an N-of-1 trial using an acute stimulation test for the VC/VS are associated with long-term improvements in symptoms and function in OCD patients who have failed to respond to medicine and psychotherapy. Furthermore, according to our N-of-1 trial, olfactory hallucinations are an important observation and are repeatable at the same contact and voltage as long as 17 months after electrode implantation for DBS. It has been reported that laughter induced by intraoperative stimulation is an indicator of good outcome in OCD DBS, but habituation of this effect is usually observed on chronic stimulation [17]. In this case report, olfactory hallucination seemed to be a more stable observation. The chronic stimulation effect is also supported by its close relationship to the limbic system within the basal ganglia. Olfactory transmission originates from olfactory sensory neurons and is then transmitted to the olfactory bulb (OB). Axon projections from the OB are conveyed via the lateral olfactory tract and terminate in the primary olfactory cortex, including the anterior olfactory nucleus, olfactory tubercle (OT), piriform cortex, posterolateral cortical amygdaloid nucleus (PCAN), and entorhinal cortex [18,19]. The information is then propagated from the primary olfactory cortex to the OFC, mediodorsal thalamus (MD), hippocampus, and ventral striatum. This extended olfactory network encompasses a large portion of the limbic and paralimbic cortices [20]. We presumed that there are some connections between the olfactory circuit and CSTC circuit. One study demonstrated that the PCAN efferent projections are directed to the core of the NAc and the medial OT [19]. We hypothesize that olfactory hallucinations may be caused by current

transmission from the CSTC circuit to the olfactory circuit via these connections. In addition, the OT and NAc are conceptualized as part of the striatal system. The medial OT and medial NAc shell receive strong dopaminergic innervation from the posteromedial ventral tegmental area and project to the medial ventral pallidum (VPM). The VPM sends its efferent signals to the MD. The MD then projects to the OFC and medial prefrontal cortex [21–23]. These two circuits are parallel and close. Olfactory hallucinations probably result from current spread into these close fiber bundles (Fig. 2) [1,2,18–23]. However, olfactory hallucinations could not be provoked on the right-side electrode. Since the target coordinates on both sides were within a difference of 1 mm, the result might be a lateralization phenomenon on olfactory processes. Several authors have stated that olfaction, as well as visual and auditory stimuli, leads to a regional increase in cerebral blood flow in the area of the OFC, temporal pole and superior frontal gyrus, and these findings are only found in the left hemisphere of the brain [24,25]. To summarize, the olfactory hallucinations observed on left VC/VS acute stimulation might have been caused by spread of the current to the nearby OT while the

Table 3
Clinical outcome after chronic stimulation.

Time	Contact	Amplitude (V)	Y-BOCS	HAM-A	GAF
Initial	—	—	34	34	41
1 m	0, C+	2	28	28	51
3 m	0, C+	2	10	22	61
6 m	0, C+	2	18	22	71
9 m	0, C+	2	18	24	71
12 m	0, C+	4	14	22	71
17 m	1, C+	4	14	20	71
Improvement at 17 m (%)	—	—	58.80	41.20	75

A pulse width of 210 microseconds and a rate of 130 Hz were used for stimulation. GAF = Global Assessment of Functioning; HAM-A = Hamilton Anxiety Rating Scale; Y-BOCS = Yale–Brown Obsessive Compulsive Scale.

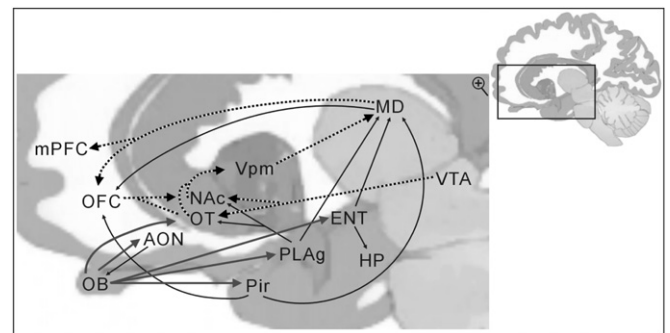


Fig. 2. The olfactory circuit, cortical–striatal–thalamic–cortical (CSTC) circuit, and dopamine reward system. Olfactory transmission originates from the olfactory sensory neurons and is then transmitted to the olfactory bulb (OB). Axon projections from the OB (thick lines) are conveyed via the lateral olfactory tract and terminate in the primary olfactory cortex, including the anterior olfactory nucleus (AON), olfactory tubercle (OT), piriform cortex (Pir), posterolateral cortical amygdaloid nucleus (PLAg), and entorhinal cortex (ENT) [18,19]. The information is then propagated from the primary olfactory cortex (thin lines) to the orbitofrontal cortex (OFC), mediodorsal thalamus (MD), hippocampus (HP), nucleus accumbens (NAc), and OT [20]. The CSTC circuit (dotted lines) includes the NAc, medial ventral pallidum (VPM), MD, OFC, and medial prefrontal cortex (mPFC) [1,2]. The dopaminergic reward circuit (dotted lines) and CSTC circuit have many similarities. The medial OT and medial NAc shell receive strong dopaminergic innervation from the posteromedial ventral tegmental area (VTA) and project to the VPM. The VPM sends its efferent signals to the MD. The MD then projects to the OFC and medial prefrontal cortex (mPFC) [21–23]. These two circuits are parallel and close.

stimulation setting was at contact 0, and to the close fiber bundles of the olfactory circuits while at contacts 1 and 3.

In conclusion, our *N*-of-1 trial indicates that olfactory hallucinations, in addition to laughter, induced by a perioperative acute stimulation test may be an indicator of good outcome in OCDDBS during chronic stimulation. An *N*-of-1 trial should be performed regularly during OCD DBS.

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