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Long-term results after deep brain stimulation of nucleus accumbens and the anterior limb of the internal capsule for preventing heroin relapse: An open-label pilot study

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ABSTRACT

Background: Deep brain stimulation (DBS) is currently used to treat addiction, with the nucleus accumbens (NAc) as one promising target. The anterior limb of the internal capsule (ALIC) is also a potential target, as it carries fiber tracts connecting the mesocorticolimbic circuits that are crucially involved in several psychiatric disorders, including addiction. Stimulating the NAc and ALIC simultaneously may have a synergistic effect against addiction.

Methods: Eight patients with a long history of heroin use and multiple relapses, despite optimal conventional treatments, were enrolled. Customized electrodes were implanted through the ALIC into the NAc, and deep brain stimulation (DBS) treatment began two weeks after surgery. The patients were followed for at least 24 months. The duration of drug-free time, severity of drug cravings, psychometric evaluations, and PET studies of glucose metabolism before and after DBS were conducted. All adverse events were recorded.

Results: With DBS, five patients were abstinent for more than three years, two relapsed after abstaining for six months, and one was lost of follow-up at three months. The degree of cravings for drug use after DBS was reduced if the patients remained abstinent ($p < 0.001$). Simultaneous DBS of the NAc and ALIC also improved the quality of life, alleviated psychiatric symptoms, and increased glucose metabolism in addiction-related brain regions. Moreover, stimulation-related adverse events were few and reversible.

Conclusions: Simultaneous DBS of the NAc and ALIC appears to be safe, with few side effects, and may prevent long-term heroin relapse after detoxification in certain patients. (This trial was registered at *ClinicalTrials.gov*, NCT01274988).

Introduction

Drug addiction is a mental disorder characterized by compulsive drug consumption and seeking, together with difficulty quitting [1]. Currently, the abuse and addiction to opioids, such as prescription pain killers, morphine and especially heroin is a serious global problem. The treatment strategy for addiction generally follows a two-fold approach – promoting detoxification [2] and preventing relapse [3]. The latter is the key for successful treatment. Current treatments for addiction include medical therapies and cognitive behavioral interventions. However, conservative treatments are effective in detoxification but unsuccessful in relapse prevention [4].

The development of an optimal approach for treating addiction is predicated on a detailed understanding of the mechanisms underlying this brain disorder. To date, several theoretical mechanisms [5] have been proposed, and the incentive sensitization theory may address central issues of drug addiction [6]. The core thesis of this

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theory is that repeated exposure to addictive drugs may render the brain hypersensitive ("sensitized") in a way that results in pathological levels of incentive salience being attributed to drugs and drug-related stimuli [7]. It has been well established that incentive salience critically relies on dopamine-mediated neurotransmission as one link in a larger chain of mesocorticolimbic circuits and signals [6]. Furthermore, it has been posited that abnormal regulatory effects of mesocorticolimbic circuits due to repeated drug use increases the addicts' craving for drugs, leading to repeated compulsive seeking and consumption of drugs [7].

Based on this theory, direct interventions to regulate the function of mesocorticolimbic circuits, which may help to rectify the drug-induced incentive sensitization process, are believed to be promising approaches for treating drug addiction. Since the 1960s, neurosurgeons have performed brain surgeries to treat addiction that target structures constituting the mesocorticolimbic circuits, i.e. hypothalamotomies [8], cingulotomies [9] and lobotomies [10]. As the nucleus accumbens (NAc), which is situated centrally among the mesocorticolimbic circuits [11], plays a key role in drug-mediated reward and addiction, we first performed stereotactic ablation of the NAc in 2000 [12]. A 5-year follow-up study demonstrated a greater long-term abstinence rate after surgery compared to conservative treatments [13]. However, ablation surgery for addiction remains controversial, as it is destructive, and can lead to irreversible complications [14], such as apathy, motivation decline, and memory deficits.

In recent decades, deep brain stimulation (DBS) has been shown to be effective in treating neurological diseases such as Parkinson's disease, essential tremor and dystonia, as well as some intractable psychiatric disorders, most notably treatment-resistant depression (TRD) and obsessive-compulsive disorder (OCD) [15]. Furthermore, some case reports suggest that DBS can alleviate addiction to alcohol [16–20], nicotine [21,22], amphetamine [23] and heroin [24,25]. Most of these studies have targeted the NAc with outcomes ranging from partial remission to total cessation, while no serious side effects were reported. Taken together, the results indicate that NAc DBS may be a safe and effective option to treat addiction.

In addition to the NAc, which acts as the central node of the reward circuit, there is abundant evidence that the medial forebrain bundle (MFB), which carries ascending dopaminergic projections from the ventral tegmental area (VTA) to numerous limbic forebrain nuclei, acts as another central component of the addiction circuit [26,27]. Consequently, the MFB was also considered to be a promising target for neuromodulation-based addiction therapy [28]. Diffuse tensor image (DTI) analysis confirmed that the human MFB contains two branches: the infero-medial (imMFB) branch and supero-lateral (slMFB) branch. The slMFB subsequently joins the inferior and medial portion of the anterior limb of the internal capsule (ALIC) [29,30], making the ALIC a potential neuromodulation target for addiction treatment. The anatomical proximity of the ALIC with the NAc makes it feasible to stimulate these two structures simultaneously with a single lead. Considering that the NAc and MFB travelling within the ALIC and are both crucial for addiction, we inferred that bilateral stimulation of both structures might be a powerful intervention to prevent heroin addiction relapse. The present preliminary study aimed to assess the outcome of this therapy, while the possible mechanism was tentatively explored as well.

Materials and methods

Patients and study design

Eight patients with heroin addiction refractory to medication and conservative treatment received bilateral NAc and ALIC DBS between March 2014 and December 2014. All patients were recruited voluntarily and independently signed the informed consent forms. Patients were eligible for enrollment if they were diagnosed with heroin addiction according to the DSM-V criteria; were 18–50 years of age; had abused heroin for 3 years or more; relapsed at least 3 times after previous conservative treatment including methadone maintenance treatment; and had reliable family members to support them. Exclusion criteria were as follows: 1) severe cognitive disorders, 2) acute psychosis and/or other severe mental disorders such as schizophrenia or dementia, 3) previous neurosurgical procedures or ablative therapy, and/or 4) any contraindication to surgery.

This study was conducted in accordance with the principles stipulated in the Helsinki declaration, and was approved by the institutional ethics commission of TangDu Hospital, the Fourth Military Medical University, China, and has been registered in the *ClinicalTrials.gov* (Identifier: NCT01274988).

Assessment

The primary outcome was the duration of drug-free time after surgery, which was monitored by urine morphine tests and family reports. The patients and their families were followed once per month by telephone interview to confirm the patients' abstinence status and general condition. In addition, the patients underwent urine tests at 1, 3, 6, 12, and 24 months after surgery as well as 3 randomly assigned tests within the 2-year period, for which the patients underwent face-to-face interviews. The subjects were considered to have relapsed if the individual or their family members reported such behavior. The patients and their family were encouraged to contact our team members whenever they encountered problems.

The secondary outcome measures included abstinence rates at 24 months after surgery, severity of cravings, quality of life and other psychometric tests, including the Symptom check list-90 (SCL–90), Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) and Hamilton depression rating scale (HDRS-17). A10-point visual analogue scale (VAS) was used to assess the severity of craving, similar to the pain assessment scale. Quality of life was evaluated using the Medical Outcomes Study 36-Item Short-Form Health Survey (SF–36). All of the assessments were conducted preoperatively and at 3, 6, 12, and 24 months after surgery. All adverse events were recorded.

Surgery

Prior to implantation, all subjects were required to complete a physiological detoxification program and demonstrate a negative morphine urinalysis and naloxone challenge test. On the morning of surgery, a Leksell stereotactic frame (Elekta Instruments, Stockholm, Sweden) was applied under local anesthesia and a 3.0T MRI Scan (General Electric Company, United States) was obtained to select the anatomical targets (T1-weighted MRI; repetition time (TR) = 1900 ms; echo time (TE) = 8 ms; slice thickness = 2.0 mm, and slice spacing = 0 mm). The images were processed using the Leksell Surgical planning system (Surgiplan, Elekta Instruments, Sweden) to calculate the NAc coordinates and generate the trajectory paths.

All patients were implanted with bilateral DBS leads under general anesthesia with a trajectory through the ALIC into NAc. Bilateral burr holes were drilled, and the electrodes (custom quadripolar electrodes 1.27 mm in diameter with four 3-mm stimulating contacts at intervals of 2.0, 4.0 and 4.0 mm, respectively) were implanted. The two ventral contacts were designed to be located in the NAc, while the two dorsal contacts were designed

to be in the ALIC based upon the trajectory. The mid commissural point (MCP) was set as the reference point, and the coordinates for the NAc were as follows: 6–9 mm lateral, 16–18 mm anterior, and 4–6 mm inferior to the MCP. The target was identified as the posterior portion of the NAc, as this region is the most prominent. The post-operative coordinates were confirmed to be as follows: 8–10.5 mm lateral, 15.5–18.5 mm anterior, 4.5–8.5 mm inferior to MCP. The most ventral portion of the electrodes were 3 mm anterior to the position reported in a previous study [31]. The trajectories were $29.00 \pm 3.25^{\circ}$ lateral to the sagittal plane, and $22.55 \pm 4.42^{\circ}$ anterior to the coronal plane. The trajectory was designed to go through the ALIC into the NAc (Fig. 1). After the electrodes were placed, the extension wires and internal pulse generator (IPG) were implanted into a subcutaneous pocket in the subclavicular region under general anesthesia. Both the electrodes and IPG were manufactured by Suzhou Sceneray Co. Ltd, China. The location of the electrodes was confirmed postoperatively via a 1.5T MRI scan (3D T1-weighted MRI; repetition time (TR) = 12 ms; echo time (TE) = 5 ms; slice thickness = 1.2 mm, and slice spacing = −0.6 mm) (General Electric Company, United States) (Supplemental Fig. 2).

Follow-up

The patients were discharged when deemed medically stable, and programming was initiated two weeks after the electrode implantation. In the initial programming session, contact optimization was conducted. Different stimulation parameter combinations were tested, evaluating for acute effects on the craving for drug use and adverse effects, such as dizziness or agitation. The NAc and ALIC were stimulated simultaneously (Fig. 1B), with a frequency of 130–185 Hz, pulse width of 150–240 μs, and voltage of 1.5–7 V. The VAS score (Supplemental Table2) was used to assess the acute effect of DBS on the cravings for drug use. The patients' implanted devices were programmed once every 24 h for 3–7 days based upon the acute responses of the patients, feedback from their family members, and observation by investigators (Table 2). Stimulation parameters were determined based upon mood, changes in vigor, VAS scores, and adverse events. The programming was aimed to achieve the optimal parameters for producing anti-craving effects without adverse side-effects (Supplemental Table 1). After obtaining the optimal stimulation parameters (39 total adjustments in all patients, Supplemental Table 1), the DBS parameters were kept constant for the duration of the study, except in three patients (two relapsed patients and one abstinent patient) who had a total of nine adjustments during the study (three before and six after relapse) (Supplemental table 3).

It should be noted that all patients were informed preoperatively that stimulation would cease after the battery ran out of power (approximately 24 months). Patients decided whether the DBS electrode and/or generator would be explanted after the battery ran out.

PET image acquisition and analysis

^{18}F-FDG PET was performed at baseline and 6 months after surgery to assess the metabolic changes of brain function [32,33]. A

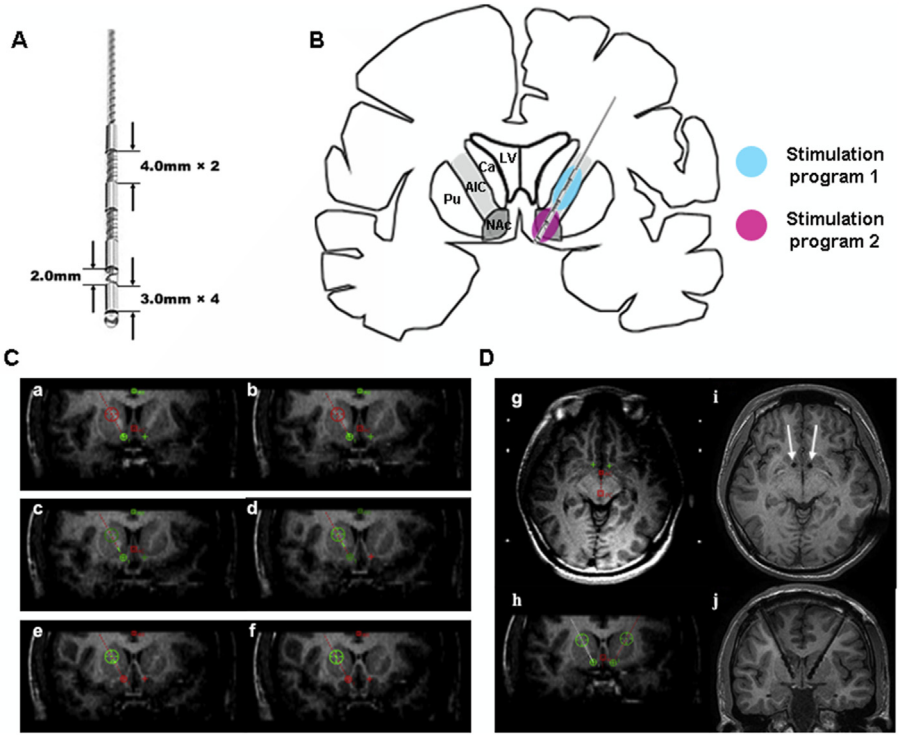

Fig. 1. Deep brain stimulation with electrodes designed for simultaneous stimulation of the NAc and ALIC. A: Customized electrode (1.27 mm in diameter) consisting of 4 stimulation contacts (3.0 mm in length), which were spaced by 2.0, 4.0 and 4.0 mm respectively. B: A schematic drawing of the implanted electrode's location. The electrode can deliver stimulation with one group of parameters through the two ventral contacts (NAc), while delivering stimulation with different parameters through the two dorsal contacts (ALIC). C: A trajectory of electrode implantation through the ALIC into the NAc was designed using the Leksell surgical planning system in conjunction with brain images from a 3.0T T1-weighted MRI. Images a-f represent coronal sections of the selected brain targets. The coordinates of the NAc (green or red crosses) were first identified (a), and then extended into the ALIC (large green or red circles with crosses) layer by layer (b–f). D: The trajectories of electrodes were planned preoperatively (green crosses in g, white and red dotted lines in h) using 3.0T T1-weighted MRI images and verified postoperatively (white arrows in i, black electrodes in j) using 1.5T T1-weighted MRI images. Ca: the head of the caudate nucleus, ALIC: anterior limb of the internal capsule, LV: lateral ventricle, NAc: nucleus accumbens, Pu: putamen. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

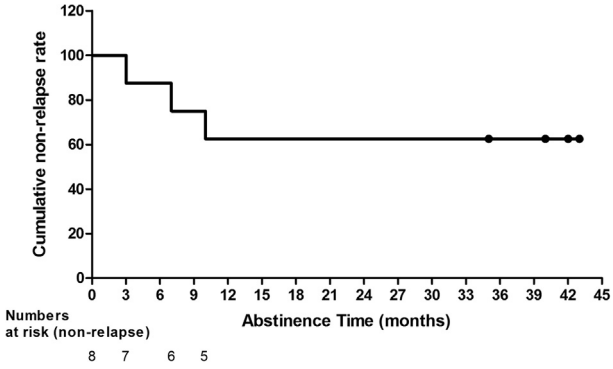

Fig. 2. Cumulative abstinence rate. Seven subjects maintained abstinence for more than six months, and five subjects remained abstinent throughout the entire follow-up period of 40.6 ± 3.36 months.

description of the detailed procedure and statistical analysis is discussed in the Supplemental section.

Statistical analysis

Repeated measures analysis of variance was used to determine significant differences between the means of psychometric test scores before and after DBS. Data was analyzed using SPSS (SPSS inc.V.19). A p value of less than 0.05 was considered statistically significant.

Role of the funding source

This study was sponsored by Suzhou Sceneray Co. Ltd, China and supported by the National Natural Science Foundation of China (Grant No. 81301179; 81401104; 81671366). The sponsor had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit the manuscript for publication.

Results

Patients' demographic data

Eight patients (seven male, one female) that met the DSM-V criteria for the diagnosis of drug addiction voluntarily enrolled in this trial (Table 1). All patients had received multiple medical and behavioral treatments, but were not able to maintain long-term abstinence. All of the patients used drugs heavily (mean gram amount of heroin used in a day was 0.51 ± 0.19 g), and all patients repeatedly relapsed (mean number of attempts to abstain was 6.5 ± 2.8, Table 1) after receiving a variety of relapse-prevention treatments, including methadone maintenance treatment (all patients) and compulsive detoxification (three patients). Other drugs that patients had abused include methamphetamine in one patient, diphenoxylate in one patient, opium in three patients, and marijuana in one patient. In the one to six months prior to enrollment, patients had ceased to abuse the non-heroin drugs. No other treatments, either psychosocial or pharmacological therapy, were used on the patients after they underwent surgery.

Contact optimization

Electrode contacts were numbered 0, 1, 2, 3 for the left hemisphere (ventral to dorsal) and similarly 4, 5, 6, 7 for the right

Table 1
Demographic data.

n	Gender (M/F)	Education (years)	Marital status	Age at surgery	Age at onset of drug use	Duration of drug use (years)	Pre-treatments	Number of abstinence	Average gram per drug use (g)	Average gram per day (g)	Routes of drug use	Duration of longest abstinence (months)	Ever used drugs	Comorbid symptoms[a]
1	M	12	married	38	21	17	Metha	9	0.3	0.9	snorting	3	none	De
2	M	9	married	30	12	18	Metha, CD	10	0.2	0.5	iv	6	–	none
3	M	9	single	22	19	3	Metha	3	0.3	0.3	iv	5	MA	OCD
4	F	12	married	50	25	25	Metha	5	0.2	0.6	snorting	1	OP	OCD
5	M	12	married	37	25	12	Metha, CD	10	0.2	0.4	iv	5	OP、Mari	De、OCD
6	M	12	divorce	39	25	14	Metha,	4	0.2	0.6	iv	4	OP	none
7	M	11	married	26	20	6	Metha, CD	6	0.1	0.4	iv	6	DP	OCD
8	M	6	married	30	24	6	Metha,	5	0.2	0.4	snorting	8	–	De、OCD
Mean (SD)		10.4 (2.2)		34 (8.8)	21.4 (4.5)	12.6 (7.4)		6.5 (2.8)	0.21 (0.06)	0.51 (0.19)		4.75 (2.12)		

F:femal, M:male, n:number, SD:standard deviation, CD:compulsory detoxification, Metha:methadone, iv:intravenous injection, MA:methamphetamine, DP:diphenoxylate, OP:opium, Mari:marijuana, De:depression, OCD:obsessive compulsive disorder.
[a] Obtained from the results of scale ratting.

Table 2
Acute responses of the patients to DBS.

Acute responses to DBS	Patients							
	No.1[a]	No.2[a]	No.3[a]	No.4[a]	No.5[b]	No.6[b]	No.7[a]	No.8[a]
Self-reported changes								
mood/affective elevation	+	+		+			+	+
feeling happy		+						
energetic/increment in vigor	+	+	+				+	
sudden brightening of the room	+							
difficulty in falling asleep	+	+	+	+			+	+
transient palpitation				+				
dizziness	+	+	+	+			+	+
feeling warm		+					+	
decreased craving for drug use	+	+	+	+			+	+
Objective observations								
smile/laughter	+	+	+	+			+	+
talkativeness	+	+						
increased voice	+							
increased motor activity	+	+		+			+	
yawn/sigh							+	
agitation/irritability	+		+					
sweating							+	

+ having such a reaction.
[a] Patients in response to DBS.
[b] patients no response to DBS.

Table 3
The abstinence results of follow-up.

No.	Duration of abstinence (months)	Had a job preoperatively	Had a job postoperatively	Weight (Kg)			Frequency of sexual activity (/month)			Others
				Baseline	24 months	Change	Baseline	24 months	Change	
1[a]	43	Y	Y	60	69	9	1	12	11	His wife got pregnant at 2 months post-operatively and had delivered a healthy baby.
2[a]	43	N	Y[c]	57	62.5	5.5	0.5	8	7.5	
3[a]	42	N	Y[d]	60	68	8	–	–	–	He got married at 4 months and his wife got pregnant at 6 months post-operatively and had delivered a healthy baby.
4[a]	40	N	N	64	60	−4	4	6	2	
5^	10	N	Y-N[e]	65	64	−1	2	4	2	
6[b]	3	N	–	–	–	–	–	–	–	
7[a]	35	N	Y[c]	101	104	3	1	10	9	
8^	7	N	N	60	58	−2	2	2	0	

No. number, Y: yes, N: no.
[a] These patients kept abstinence at least 24 months postoperatively.
^ These patients kept abstinence above 6 months postoperatively, but relapsed after then.
[b] This patient was lost follow-up at 3 months postoperatively, he changed his address and phone number and was out of contact.
[c] These patients found full-time jobs and gone back to society at 6 months postoperatively.
[d] This patient found part-time job at 6 months postoperatively.
[e] This patient found part-time job at 6 months postoperatively, but lost it after relapsed.

hemisphere. For NAc stimulation, both contacts (0- and 1-in the left brain, 4- and 5- in the right brain) were chosen and set as the cathode, with IPG as the anode (C+) in all patients (Supplemental Table 3). For ALIC stimulation, the most dorsal contacts (3-, 7-) were set as the cathode in 3 subjects (No. 1, 2, 3), while in the other 5 subjects (No. 4, 5, 6, 7, 8) the second dorsal contacts (2-, 6-) were set as the cathode. No contact changes were performed during chronic stimulation. The final optimized stimulation parameters were NAc: 2.2–2.8 V, 180–240 μs, 145 Hz; ALIC: 1.5–2.4 V, 150–240 μs, 185 Hz (Supplemental Table 3).

Primary outcomes

Seven patients had follow-up for at least 24 months, while one patient (No. 6) was lost to follow-up at three months following surgery due to losing contact with him (Table 3). Five of the seven patients (No. 1, 2, 3, 4 and 7) maintained abstinence throughout their final follow-up (40.6 ± 3.36 months), although no stimulation was performed after 24 months due to the battery running out of power. The two remaining patients (No.5 and 8) relapsed at 10 and 7 months, respectively. Despite increasing the programming parameters, both patients were not able to keep abstinent. The subject lost to follow-up was conservatively assumed to have relapsed, giving an abstinence rate of 62.5% at 24 months post-surgery (5/8; Fig. 2). Of note, all seven patients preferred the devices to be left in their bodies after the battery running out for two reasons: (1) If a relapse occurred, stimulation could be restarted after changing the battery; (2) To avoid the possible surgical risks inherent in the operation to explant the devices.

Acute responses to DBS

The acute responses of patients to DBS are summarized in Table 2. These reactions occurred when the NAc and ALIC were stimulated simultaneously and were classified as subjective changes reported by patients and objective changes observed by

investigators. Six patients (No. 1, 2, 3, 4, 7 and 8) manifested both subjective and objective changes upon DBS. Among the subjective changes, "mood/affective elevation" and "energetic/increment in vigor" occurred the most frequently. The corresponding objective reactions, "smile/laughter" and "increased motor activity" also were most commonly identified. Dizziness was also reported by the six patients when the stimulation intensities were high enough (greater than 5 V). These reactions happened seconds to minutes after the IPG was turned "on." Moreover, these same reactions weakened immediately after IPG was turned "off." In addition, all six patients reported "difficulty in falling asleep" (inability to sleep until several hours later than usual) during the first one to three nights after turning the IPG on. After a few days of stimulation and parameter optimization, all six patients returned to baseline sleeping habits. All six patients described "Decreased cravings for drug use" during this acute period (Supplemental Table 2). However, five maintained abstinent and one relapsed. Therefore, the relationship between acute craving responses to DBS and the chronic effect of DBS in preventing relapse needs further investigation. Other subjective changes occurring in at least one patient included "feeling happy," "sudden brightening of the room," "transient palpitation," and "feeling warm." The reported objective reactions included "talkativeness," "increased voice," "yawn/sigh," "agitation/irritability" and "sweating." At the same time, the patients became desensitized to some of the acute responses to DBS, such as "difficulty in falling asleep," "dizziness," "agitation," and "sweating." Two patients (No.5 and 6) reported no overt acute changes even when the stimulation parameters were set at very high intensity (7 V). Notably, neither of the two patients remained abstinent at the one-year follow-up.

Cravings

The severity of craving for drugs was 7.6 ± 1.34 at baseline (assessed via the VAS score), which decreased to 1.4 ± 1.1 at the 3-month follow-up, and reached 0.8 ± 0.84 in abstinent patients ($p < 0.001$) at the 24-month follow-up (Table 4). In the two relapsed patients, the VAS scores at baseline were high, then declined significantly at 3-month follow-up while remaining abstinent, but returned to the preoperative level at 12 months when they had relapsed, after which they remained at this level through 24 months (Table 4).

Quality of life

After DBS treatment, the majority of abstinent patients obtained jobs (full/part-time), gained weight and increased the frequency of sexual activity (Table 3). In addition, one patient (No. 3) got married and two patients' wives (No. 1 and 3) became pregnant. By contrast, no obvious changes were observed in the relapsed patients.

The SF−36 is a 36-item questionnaire that measures the quality of life across eight emotional and physical subscales (Supplemental Table 4). At baseline, the total SF−36 score of the abstinent subjects was 504.9 ± 145.1, after which it increased to 704.3 ± 65.5 at the 6-month follow-up, and 704.0 ± 73.6 at 24 months ($p = 0.001$), indicating an improved overall health condition after DBS (Table 4). The body pain ($p = 0.001$) and general health ($p < 0.001$) scores increased significantly after DBS (Supplemental Table 4). In addition, the role-emotional scores also increased after six months of DBS treatment (Supplemental Table 4). In the relapsed patients, the total scores also increased from 392.6 ± 87.8 at baseline to 633.6 ± 51.5 at 6-month follow-up. However, the scores decreased to baseline levels after they relapsed (Table 4).

Psychometric assessments

The mean pre-implantation HDRS score of the abstinent subjects was 12.4 ± 6.2, which decreased to 2.4 ± 2.1 at 6-month follow-up and 3.4 ± 2.2 at 24 months ($p = 0.001$), indicating improved mood after DBS (Table 4). Although the HDRS scores of the two relapsed patients also decreased at 6-month follow-up, it increased to nearly the preoperative level after they relapsed (Table 4). More interestingly, the two relapsed patients had much higher HDRS scores than the abstinent patients at each time point. This suggests that a normal mood after DBS is beneficial for relapse prevention.

The mean baseline Y-BOCS score for abstinent subjects was 21.4 ± 10.9, which decreased to 7.2 ± 5.6 at 3-month follow-up and 3.8 ± 2.2 at 24 months ($p < 0.001$), indicating less thoughts about heroin and drug seeking after DBS (Table 4). Similar to the effect of DBS on the HDRS scores, the Y-BOCS scores of the two relapsed patients trended towards decreasing to normal followed by increasing to preoperative levels before and after they relapsed, respectively.

SCL−90 is a self-reported questionnaire developed to screen for psychological symptoms on nine subscales (Supplemental Table 5).

Table 4
Psychometric results.

	Baseline	3 months	6 months	12 months	24 months	Repeated measures ANOVA[b]		
						Mauchly P[a]	F	p
VAS								
Non-relapsed	7.6 (1.34)	1.4 (1.14)	0.6 (0.89)	0.4 (0.55)	0.8 (0.84)	0.234	52.742	<0.001
Relapsed	7.5 (0.71)	2 (1.14)	1.5 (0.71)	8.0 (1.14)	7.0 (1.14)	–	–	–
HDRS-17								
Non-relapsed	12.4 (6.23)	3.6 (2.61)	2.4 (2.07)	3.8 (3.27)	3.4 (2.19)	0.278	7.96	.001
Relapsed	27.0 (7.07)	10.0 (1.41)	7.5 (2.12)	23.5 (12.02)	18.0 (4.24)	–	–	–
Y-BOCS								
Non-relapsed	21.4 (10.92)	7.2 (5.63)	4 (3.16)	3.2 (1.79)	3.8 (2.17)	0.192	14.193	<0.001
Relapsed	25.0 (4.24)	10.0 (1.41)	6.0 (1.41)	28.0 (1.41)	23.5 (2.12)	–	–	–
SF-36								
Non-relapsed	504.92 (145.09)	653.70 (123.73)	704.30 (65.51)	711.84 (83.97)	704.10 (73.61)	0.071	7.438	0.001
Relapsed	392.60 (87.82)	549.40 (76.51)	633.60 (51.48)	370.35 (128.48)	403.10 (46.81)	–	–	–
SCL-90								
Non-relapsed	1.72 (0.54)	1.36 (0.27)	1.16 (0.21)	1.18 (0.17)	1.22 (0.34)	0.066	2.743	.065
Relapsed	2.20 (0.31)	1.20 (0.26)	1.25 (0.13)	2.41 (0.59)	2.25 (1.00)	–	–	–

Data was Mean (SD), the number of non-relapsed patients was 5 and the relapsed was 2. SD: standard deviation.
VAS: visual analogue scale; HDRS-17: Hamilton depression rating scale - 17 version; Y-BOCS: Yale-Brown Obsessive Compulsive Scale; SF−36: Medical Outcomes Study 36-Item Short-Form Health Survey; SCL−90: symptom check list-90.
[a] P: Mauchly's test of sphericity.
[b] Repeated measures analysis of variance.

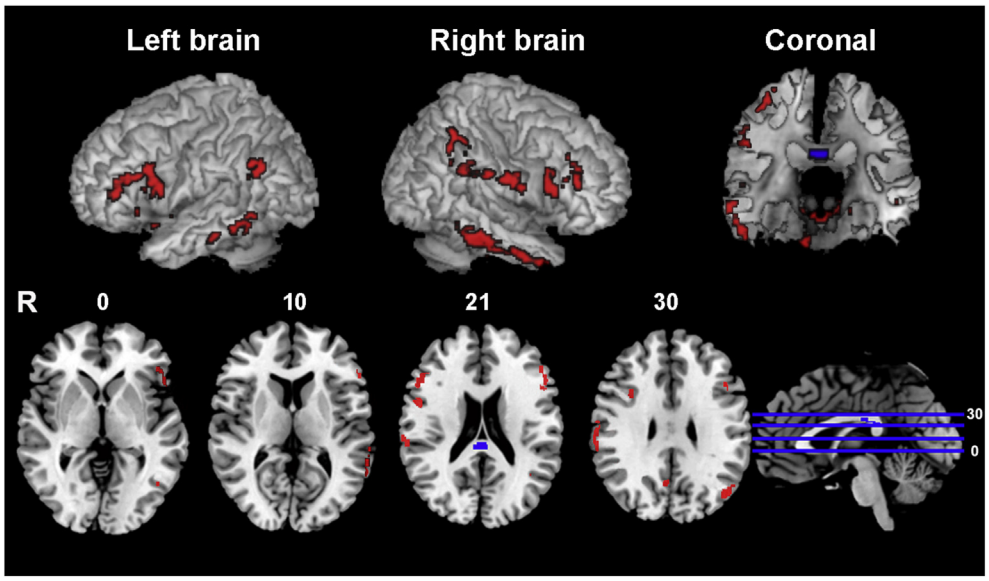

Fig. 3. PET scans after six months of deep brain stimulation (DBS) compared to baseline. The images are based on the composite data for 5 patients. Blue-colored areas denote significant decreases and red-colored areas signify increases in glucose metabolism after six months of DBS. Statistically significant voxel-wise results ($z > 2.73$, $p < 0.05$; uncorrected for multiple independent comparisons, cluster size greater than 50 voxels) are displayed on (above) a three-dimensional MRI rendering. (below) representative brain regions superimposed on MRI axial sections. R: right. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

The global severity index (GSI) of SCL–90 is the average rating over all 90 items, which reflects the overall psychological symptom status. At baseline, the GSI of the abstinent subjects was 1.7 ± 0.5 (Table 4). At 6 months, there was a decreasing trend in the abstinent patients (1.2 ± 0.2, $p = 0.065$). Furthermore, it is worth noting that the subscales of these patients were no different than the corresponding normal mean reference values (Supplemental Table 5). For the relapsed patients, GSI also presented a "decreasing-increasing" tendency, but none of the two patients at any time point reached the level of positive symptoms (Chinese norm group, 2.6 ± 0.6). However, the subscales of depression and anxiety exceeded the normal level at baseline and 24 months, after which they decreased to the corresponding normal level at 6 months while they were abstinent. This indicated a worse mood after the relapse, which was similar to the HDRS investigation.

Adverse events

All patients tolerated the surgery and postoperative stimulation well. An intracranial hemorrhage (<3 ml) adjacent to the implanted electrode in the right hemisphere occurred in patient No. 4 (Supplemental Fig. 1), but the patient did not experience a neurological deficit. Other surgery-related adverse events included a fever in one patient and a headache in another, which all lasted no more than three days. Stimulation resulted in dizziness, agitation/irritability, sweating, and difficulty in falling asleep during the first night that DBS was turned on. However, all symptoms were reversible after the DBS was turned off. One patient reported a slight memory decline during chronic stimulation. There was no evidence of infection, lead dislodgment, seizure, motivation decline, muscle cramps, visual deficits, anxiety or suicidal ideation during surgery or stimulation.

PET results

Five patients (No.1, 2, 3, 4 and 5) completed two PET scans (one at baseline and one at 6 months after DBS). PET analysis showed that after 6 months of DBS the glucose metabolism changed in several brain structures. Increased glucose metabolism was found in the left anterior lobe of the cerebellum, left angular, both sides of the middle temporal gyrus, left inferior frontal gyrus, bilateral inferior frontal pars opercularis, right supramarginal gyrus and right precuneus. Decreased glucose metabolism was found in the right corpus callosum (Fig. 3, Supplemental Table 6).

Discussion

In this study, we found that bilateral deep brain stimulation of the NAc and the ALIC may be able to help patients remain abstinent from heroin. Five of eight patients maintained abstinence for more than three years, while they had relapsed within 6.5 months after previous treatments. Interestingly, these five patients continued to be abstinent one year after cessation of stimulation. No long-term adverse events occurred during this study. These results indicate that simultaneous DBS of the NAc and ALIC may be an effective and safe long-term measure for heroin prevention after detoxification.

Because the NAc is the central node of the reward circuit, it has been used as a target in several studies to treat addiction by DBS therapy, showing promising efficacy in preventing relapse. However, the sample sizes of these studies have been small. Another structure adjacent to the NAc, the ALIC, was also found to be significantly involved in the pathology of several psychiatric disorders, including addiction. Previous anatomical studies have concluded that a number of nerve fibers, including the fronto-pontine tract, anterior thalamic radiations (ATR), and especially the MFB, which link the core reward circuit, project from the VTA to numerous forebrain limbic structures such as NAc, medial hypothalamus and prefrontal cortex (PFC) [30,34]. These fibers pass through the ALIC, making it a promising target to treat addiction with neurostimulation. For example, in cocaine self-administrating rats, Levy et al. demonstrated that high-frequency (100 Hz) electric stimulation of MFB can significantly reduce cue-induced seeking behavior, suggesting that targeting the MFB may potentially prevent relapse [27]. In fact, MFB has been listed as the most promising target for neuromodulatory treatment of addiction [28]. Moreover, the anatomical proximity of the ALIC with the NAc makes it feasible

to stimulate these two structures simultaneously with a single lead. The present study used bilateral deep brain stimulation of the NAc and the ALIC/MFB to prevent relapse of detoxified heroin addicts, based on the findings that the two stimulated sites are both central components of the addiction circuitry. Due to the lack of control studies, we can not conclude that this type of multiple-site stimulation is superior to single-site stimulation. Although the evidence from movement disorders supports this inference, whether the combined multi-site stimulation has a more powerful efficacy for psychiatric disorders still needs to be clarified.

In the present study, bilateral DBS of the NAc and the ALIC induced acute responses in six of the eight patients, which was similar to the response rate seen in VC/VS DBS for OCD and TRD [31]. These positive responses can be explained by the affective influence of the NAc and MFB, both of which have been established to be structural correlates of positive affective excitement [29]. The two patients without an acute positive effect eventually relapsed, suggesting that the acute lack of benefit might be a predictor of a long-term outcome. As the acute benefits were different from the euphoric feelings elicited by drug use, we hypothesize that high-frequency stimulation does not act by replacing the desire to take drugs. However, not all of the patients who experienced acute positive responses remained abstinent, suggesting a need to further evaluate the precise relationship between acute response and efficacy.

Six of eight patients had psychological problems according to the HDRS and Y-BOCS evaluations at baseline. This was reflected by the “withdrawal/negative affect” stage after chronic drug exposure [5]. Interestingly, this discomfort was ameliorated with chronic stimulation. Moreover, the patients' cravings were decreased with stimulation. The abstinent patients also reported a better mood after DBS, while the relapsed patients reported a worse mood. Therefore, we hypothesized that DBS improves the negative emotional state associated with the motivational withdrawal syndrome in addiction, which may also be a possible factor that helps maintain abstinence. The two patients who relapsed and the patient who was lost to follow-up notably had the worst baseline quality of life and diagnoses of moderate depression. Even with chronic stimulation, their quality of life and depression were worse than those of the abstinent patients, although a partial improvement was noted during their period of abstinence. The patients who relapsed stated that they restarted using drugs when they saw their friends injecting heroin at a party. This was an intensive conditioned cue, which made them lose control. Based on the incentive-sensitization theory [6], our results suggest that NAc/ALIC-DBS may correct the abnormal incentive-salience attributed to drugs by restoring the function of mesocorticolimbic reward circuits.

To date, the exact mechanism of action of DBS is still unclear. However, there is wide consensus that DBS not only influences the local target, but also modulates neural network activity through direct or antidromic activation. Previous studies suggest that NAc DBS suppresses neuronal activity and alters local field potential (LFP) oscillation power and coherence within a network involving the medial frontal cortex, the orbitofrontal cortex (OFC), and the mediodorsal thalamus [35]. Neuroimaging studies of VC/VS DBS for OCD showed altered metabolism in the OFC, medial prefrontal cortex, amygdala/hippocampus, insula, and thalamus, which are also known to be involved in addiction [36]. Similarly, Heldmann et al. also reported that NAc DBS increased the activation of the paracingulate cortex, temporal poles, precuneus and hippocampus, which have been linked to behavioral control and decision-making [16]. Similarly, our PET investigations revealed that 6 months of combined NAc/ALIC stimulation increased the metabolism in the related brain regions, including the frontal (inferior frontal gyrus), temporal (middle temporal gyrus) and parietal (angular, precuneus and supramarginal gyri) lobes. Previous studies have demonstrated that the left inferior frontal gyrus and precuneus are critically involved in decision-making [37], while hypoactivation in the angular gyrus has been correlated with a deficit of self-concept in individuals who are addicted to games [38]. Our results indicate that functional changes in the PFC may be a crucial mechanism for relapse prevention due to NAc/ALIC stimulation, which affects PFC by direct or antidromic activation.

Taken together, we hypothesize that NAc/ALIC DBS normalizes the pathological state of addiction by correcting the abnormal incentive salience attributed to drugs, while simultaneously elevating the negative emotional state, enhancing the ability to self-identify, and improving inhibitory control and decision-making when facing temptation. These attributes may help in maintaining abstinence. This would subsequently reduce the likelihood of cue- and stress-induced relapse. Since the abstinent patients remained abstinent for over a year after cessation of stimulation, one hypothesis is that chronic stimulation may reverse or rebalance the neuroplasticity associated with addiction, which is consistent with long-term potentiation or long-term depression seen in animal studies [35,39].

However, this study does have a number of limitations. The sample size was only eight subjects and there were no control group. Therefore, a placebo effect cannot be excluded, and the degree of ongoing contact that our research team had with the participants during the follow-up phase could certainly influence or facilitate ongoing abstinence. Thus, a further double-blind trial with sham control is crucial. Nevertheless, compared to the duration of patients' abstinence after conventional treatments for which ongoing contact with the participants was also routine throughout the follow-up, the DBS treatment appears to be superior. In conclusion, simultaneous DBS of the NAc and ALIC appears to be a safe and potentially efficacious treatment for heroin addiction. Despite the promising evidence, randomized control trials are necessary prior to adopting it as a treatment paradigm.

Conclusion

Simultaneous DBS of NAc and ALIC appears to be safe, with few side effects, and produces beneficial long-term effects for preventing heroin relapse after detoxification.

Declaration of interests

Dr. Guodong Gao, Dr. Xuelian Wang, and Dr. Nan Li received consulting fee from Suzhou Sceneray Co. Ltd, China. The other authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2018.09.006.

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