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Long-term functional outcomes improved with deep brain stimulation in patients with disorders of consciousness

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ABSTRACT

Background Deep brain stimulation (DBS) has been preliminarily applied to treat patients with disorders of consciousness (DoCs). The study aimed to determine whether DBS was effective for treating patients with DoC and identify factors related to patients' outcomes.

Methods Data from 365 patients with DoCs who were consecutively admitted from 15 July 2011 to 31 December 2021 were retrospectively analysed. Multivariate regression and subgroup analysis were performed to adjust for potential confounders. The primary outcome was improvement in consciousness at 1 year.

Results An overall improvement in consciousness at 1 year was achieved in 32.4% (12/37) of the DBS group compared with 4.3% (14/328) of the conservative group. After full adjustment, DBS significantly improved consciousness at 1 year (adjusted OR 11.90, 95% CI 3.65–38.46, p<0.001). There was a significant treatment×follow up interaction (H=14.99, p<0.001). DBS had significantly better effects in patients with minimally conscious state (MCS) compared with patients with vegetative state/unresponsive wakefulness syndrome (p for interaction <0.001). A nomogram based on age, state of consciousness, pathogeny and duration of DoCs indicated excellent predictive performance (c-index=0.882).

Conclusions DBS was associated with better outcomes in patients with DoC, and the effect was likely to be significantly greater in patients with MCS. DBS should be cautiously evaluated by nomogram preoperatively, and randomised controlled trials are still needed.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Disorders of consciousness (DoCs) impose heavy medical and economic burdens on families and society. Deep brain stimulation (DBS) may be an effective treatment for these patients.

WHAT THIS STUDY ADDS

⇒ DBS significantly improved patient consciousness at 1 year, and enhanced therapeutic effects were found in patients with minimally conscious state. We constructed a nomogram based on age, state of consciousness, and pathogeny and duration of DoCs; this nomogram showed excellent predictive performance as a clinical tool.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ DBS is likely to be effective for treating DoCs and should be cautiously evaluated by nomogram preoperatively.

INTRODUCTION

Disorders of consciousness (DoCs) are neuropsychiatric disturbances in arousal and awareness that are commonly caused by trauma, stroke or anoxia.[1–3] DoCs encompass comas (unconscious), vegetative state/unresponsive wakefulness syndrome (VS/UWS; awake yet unresponsive) and minimally conscious state (MCS; inconsistent but clearly discernible behavioural evidence of self-awareness or environmental awareness).[4 5] Such conditions present challenges for clinicians, as the overall possibility of spontaneous recovery is low.[6 7] Efforts have been made to identify whether neuromodulation therapy facilitates recovery; however, evidence is limited.[4 8 9]

Deep brain stimulation (DBS), as a potential promising neuromodulatory technique, involves implanting electrodes that can electrically stimulate specific structures of deep brain regions and modify abnormal neural pathways; this treatment has been widely applied for patients with Parkinson's disease, epilepsy and other psychiatric diseases.[10–12] In 2007, Schiff *et al* reported treating a patient with traumatic brain injury with DBS of the central thalamic nuclei and observed behavioural improvements.[13] Since then, only seven studies of DBS including 46 patients with DoC have been published, and the results are inconsistent due to small sample sizes and missing control groups.[13–19] Thus, the existing data are limited, and the factors that may influence the long-term effects of DBS remain unclear. In this study, we consecutively enrolled patients with DoCs who received DBS or conservative treatment in our department and summarised the results of follow-ups. Additionally, we analysed the factors related to the long-term effects of DBS in patients with DoC and discussed the potential basis for preoperative screening to provide evidence for precision treatment options for patients with DoCs.

MATERIALS AND METHODS

Study participants

We recruited 421 consecutive patients who were admitted to the Departments of Disorders of Consciousness at the People's Liberation Army General Hospital and Beijing Tiantan Hospital, Capital Medical University, from 15 July 2011 to 31 December 2021. The inclusion criteria were as follows: patients who (1) were diagnosed with a DoC according to their score on the JFK Coma Recovery Scale-Revised (CRS-R)[20]; (2) had a duration of DoC >3 months; and (3) family or surrogates provided written informed consent. The exclusion criteria were as follows: patients with (1) sudden DoCs caused by gradual deterioration of neurological function or (2) progressive improvement or deterioration of consciousness for more than four consecutive weeks. After application of the inclusion and exclusion criteria, 365 patients who underwent follow-up were included. The patient recruitment flow chart is shown in online supplemental figure S1. The treatment options, possible risks of treatment and the nature of DBS for DoCs were explained to each patient's legal representative and/or close relatives, as these patients were unable to understand or legally provide their consent. The caregivers were offered an informed consent form that followed the internationally adopted ethical standards for the performance of clinical treatment and research (the Declaration of Helsinki). Once their caregivers provided written informed consent, the patients were enrolled in the study.

Data collection and outcomes

Data on demographic characteristics, clinical features and radiological examinations were extracted from the electronic medical record system. Demographic characteristics included age, sex, pathogeny and duration of DoCs at admission. Clinical features included state of consciousness. Radiological examinations include MRI, electroencephalography (EEG), the mismatch negativity (MMN) and CT. Outpatient follow-up was performed 6 months and 1 year after discharge, and patients' Glasgow Outcome Scale (GOS) score, CRS-R score and radiological examinations were recorded. Improvement in consciousness was defined improvement of more than 3 points on the CRS-R; the primary outcome of the study was improvement in consciousness at 1 year. Secondary outcomes included improvement in consciousness at 6 months and emergence from unconsciousness, defined as a GOS score >2 at 6 months and 1 year.

JFK CRS-R scores and follow-up

The CRS-R was used to assess the level of consciousness of each patient. Scores on this scale may vary from 0 to 23, and six subscores are used to quantify auditory, visual, motor and verbal functions as well as communication and arousal. CRS-R scores at admission were obtained through repeated assessments (minimum of five assessments within 2 weeks) prior to DBS to avoid fluctuations of consciousness. The scale was applied by trained professional raters, who recorded the highest of the scores as the consciousness level at admission. CRS-R scores were regularly determined at each follow-up, after surgery and before discharge (once a week). During the COVID-19 pandemic, we scored patients through video calls to collect follow-up data. We did the video assessment with video software (PINS, China) under the supervision of a certificated doctor. Patient port: JOINPINS (PINS) software+patient program controller C702 (also 701 or 802); doctor port: remote program system (PINS). Patients with DoC are mostly in rehabilitation centres with bedside doctors.

Neuroradiological and electrophysiological evaluation

MRI and resting-state functional MRI (fMRI) were performed using a 3.0 T MRI scanner (HD750, GE, USA) to evaluate brain atrophy and damage to critical brain regions and to calculate brain network activation and connectivity (https://github.com/realmsong504/pDOC). Preoperative EEG data were collected from all patients for at least 2 hours using an EEG recording device (BrainAmp 64 MRplus, Brain Products, Germany); subsequently, a trained senior clinician scored the EEG data according to the Synek grading scale.

Surgical indications

The general indications for DBS surgery were as follows: (1) no large-area skull defects, no skull repair or shunt pump placement; (2) no major complications or contraindications to surgery; and (3) structurally intact bilateral thalamus. We also explored whether patients who were highly recommended for DBS according to the criteria had a better outcome than patients who were weakly recommended after receiving DBS. Notably, these criteria were not used to select among treatment options in these patients. Therefore, patients who received DBS underwent preoperative MRI, EEG and MMN wave examination as previously reported.[21–24] Briefly, patients who met more than two of the following criteria were considered highly recommended: (1) focal brain damage <30%, (2) probability of emergence from unconsciousness >30% according to the prolonged DoC analysis tool,[25] (3) MMN wave >1[26] and (4) Synek grade <3.[27]

DBS surgical approach and stimulation protocol

Regarding development of the preoperative plan, the surgical path was designed to avoid the lateral ventricles. Patients were mounted with a stereotactic instrument base ring under general anaesthesia. Axial, coronal and sagittal T1-weighted MRI sequences were performed after the installation of the Leksell G head frame (Elekta, Sweden), with a scan thickness of 2 mm. The electronic atlas of thalamic nuclei in the assisted surgical planning system is superimposed to improve the accuracy of intraoperative positioning.

Further, all the T1-weighted MR images were processed using the CIVET pipeline (https://www.bic.mni.mcgill.ca/ServicesSoftware/CIVET), developed at the Montreal Neurological Institute (MNI) for morphometric analyses of human MR images.[28] First, the images were corrected for non-uniformity artefacts using the N3 algorithms. The individual structural MR images were then transformed into the standardised MNI space using linear and non-linear transformations by registering to a standard brain imaging template (International Consortium for Brain Mapping 152). Second, the CM/Pf nuclei extracted from Morel's histological thalamus atlas in the MNI space were selected as region of interest (ROI) and registered to native T1 space by reversing the transformation parameters.

As for the imaging features of the enrolled patients, the length of the anterior commissure-posterior commissure (AC-PC) line was (24.6 ± 3.2) mm. The anatomical coordinates of centre median-parafascicular (CM-Pf) were: 7.8–9.7 mm behind the midpoint of the AC-PC line, 8.8–10.5 mm from the AC-PC line (4.5–5.5 mm from the ventricular wall) and 0–1.5 mm downward from the AC-PC plane. An electrode (3387, Medtronic, USA or L302, PINS) was implanted into the CM-Pf complex. During the operation, the microelectrodes recorded that the discharge activity of the single cells in the CM-Pf was significantly lower than that of the surrounding nuclei, almost in a silent state, which can assist in judging the location of the target. When making a preoperative surgical plan, avoid the lateral ventricle when planning the path. The implantable pulse generator (IPG, G102RZ) was placed at the midpoint of an imaginary line between the subclavian and anterior axillary lines and the middle sternal line. Postoperative CT or MRI scans were performed to confirm the implantation location.

The IPGs were activated 7 days after surgery, when the wound healed and the local oedema caused by the puncture subsided. Periodic electrical stimulation was administered to the brains of patients. The main source of stimulation was monopolar with a frequency of 100 Hz, 120 µs and 1.0–4.0 V. Stimulation was provided continuously from 08:00 to 20:00 hours with a 15 min on/off cycle (15 mins on, 15 mins off).[29]

Statistical analysis

SPSS V.25 (IBM), Prism V.8 (GraphPad Software, USA) and R V.4.2.1 (USA) were used for statistical analyses. The normality of data distribution was evaluated using the Kolmogorov-Smirnov test. For continuous variables, normally distributed data are presented as the mean±SD and compared using a t-test; non-normally distributed data are presented as the median (IQR) and compared using the Wilcoxon rank-sum test. The χ^2 test was used to compare categorical variables. Repeated measures data that were not normally distributed were analysed using the Scheirer-Ray-Hare test. A two-tailed p value <0.05 was considered to indicate statistical significance.

RESULTS

Study population

We included 365 patients with DoCs who met the inclusion criteria and underwent follow-up; 37 of these patients (10.1%) received DBS. Patients with DoCs were further categorised according to their state of consciousness: 123 out of 365 (33.7%) patients were in an MCS and 242 out of 365 patients (66.3%) were in a VS/UWS (online supplemental table S1). In this cohort, 253 (69.3%) patients were male, and the median age was 49.0 (35.0–58.0) years. No significant differences in terms of age (Wilcoxon rank-sum test, p=0.431) or sex (χ^2 test, p=0.349) were observed between the DBS and conservative treatment groups. Regarding pathogeny, there were 136 trauma cases (37.3%), 164 stroke cases (44.9%) and 65 anoxia cases (17.8%); no significant difference was found in terms of state of consciousness of these patients (χ^2 test, p=0.080). Regarding the duration of DoCs, the DBS group had significantly more patients with shorter durations (25, 67.6%) than the conservative treatment group (40, 12.2%) (χ^2 test, p<0.001). Regarding the prevalence of MCS, there were 13 (35.1%) patients with MCS in the DBS group and 110 (33.5%) patients with MCS in the conservative treatment group; this difference was not significant (χ^2 test, p=0.856).

Data from the 37 patients who received DBS were further analysed according to demographic characteristics and state of consciousness (online supplemental table S2). The median age in the DBS group was 35.0 (26.0–48.5) years among patients with MCS and 49.5 (41.0–59.8) years among patients with VS/UWS; thus, the ages significantly differed (χ^2 test, p=0.002). The sex distribution was not significantly different between the MCS and VS/UWS subgroups (χ^2 test, p=0.288). In the VS/UWS subgroup, significantly more patients had DoC caused by stroke (15, 62.5%) compared with that caused by trauma (2, 8.3%) (χ^2 test, p=0.025). The VS/UWS subgroup also contained more patients with a 3–5 months' duration of DoC (21, 87.5%) than the MCS subgroup (4, 30.8%, χ^2 test, p=0.002). Regarding the recommendation criteria, both subgroups contained eight patients who were highly recommended for DBS; no significant group difference was found (χ^2 test, p=0.098).

Clinical characteristics of patients with DoC according to their outcome

To determine whether DBS was an effective treatment for patients with DoC, we first aimed to determine the proportion of patients who exhibited improvements in consciousness according to changes in their CRS-R scores. After follow-up for 1 year, 26 of the 365 overall patients (7.1%), regardless

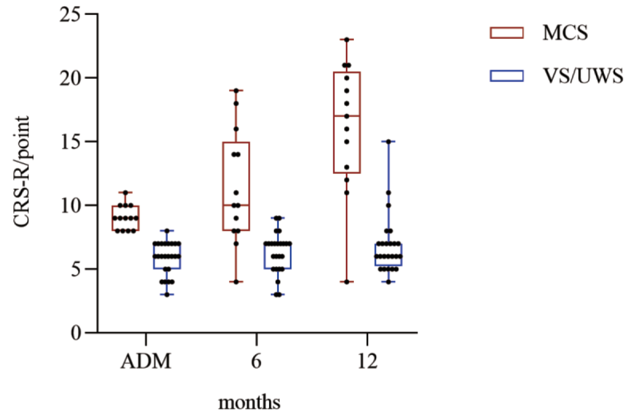
Table 1 Clinical characteristics of patients with DoC according to their outcome

Variable	Outcome Improved (n=26)	Unchanged/died (n=339)	P value
Age, years, median (IQR)	36.5 (26.0–55.5)	49.0 (36.0–58.0)	0.078
Sex (%)			0.992
Male	18 (69.2)	235 (69.3)	
Female	8 (30.8)	104 (30.7)	
State of consciousness (%)			<0.001*
MCS	18 (69.2)	105 (31.0)	
VS/UWS	8 (30.8)	234 (69.0)	
Pathogeny (%)			0.375
Anoxia	2 (7.7)	63 (18.6)	
Stroke	13 (50.0)	151 (44.5)	
Trauma	11 (42.3)	125 (36.9)	
Duration at admission (%)			0.006*
3–5 months	8 (30.8)	57 (16.8)	
6–11 months	8 (30.8)	49 (14.5)	
≥12 months	10 (38.5)	233 (68.7)	
Treatment (%)			<0.001*
DBS	12 (46.2)	25 (7.4)	
Conservative	14 (53.8)	314 (92.6)	

*P<0.05, significant difference.
DBS, deep brain stimulation; DoC, disorder of consciousness; MCS, minimally conscious state; VS/UWS, vegetative state/unresponsive wakefulness syndrome.

of whether they received DBS or conservative treatment, exhibited improvements in consciousness (table 1). While the median age in the improved group was slightly younger (36.5 (26.0–55.5)) than that in the unchanged group (49.0 (36.0–58.0)), this difference was not significant (Wilcoxon rank-sum test, p=0.078), nor were there significant differences in the sex distribution (χ^2 test, p=0.992). The improved and unchanged groups did not differ in pathogeny (χ^2 test, p=0.375). Regarding state of consciousness, significantly more patients were initially diagnosed with MCS in the improved group (18, 69.2%) than in the unchanged group (105, 31.0%, χ^2 test, p<0.001). We also found more patients with durations of DoC greater than 12 months in the unchanged group (233, 68.7%) than in the improved group (10, 38.5%, χ^2 test, p=0.006). In general, DBS appears to improve patient outcomes: significantly more patients improved at 1 year if they received DBS (32.4% (12/37) vs 4.3% (14/328), χ^2 test, p<0.001), and when emergence from unconsciousness was assessed by GOS scores, consistently more patients emerged from unconsciousness if they received DBS (χ^2 test, p<0.001). In patients who received DBS, those who improved had a significantly lower mean age (33.9±12.9 years) than those who remained unchanged (50.3±10.3 years, independent samples t-test, p<0.001), as shown in online supplemental table S3. Ten (83.3%) patients were diagnosed with MCS in the improved group and three (12.0%) were diagnosed with MCS in the unchanged group; this difference was significant (χ^2 test, p<0.001). Significantly more patients exhibited DoC induced by trauma (6, 50.0%) compared with anoxia (8.3%) in the improved group (χ^2 test, p=0.010). Additionally, significantly more patients were highly recommended for DBS according to the criteria in the improved group (9, 75.0%) compared with the unchanged group (7, 28.0%, χ^2 test, p=0.012). Notably, we did not find a significant difference in the duration of DoCs between the improved and unchanged groups, in contrast to findings in the whole sample (χ^2 test, p=0.286).

Furthermore, we examined the effect of the interaction between state of consciousness (MCS vs VS/UWS) and follow-up period (6 months vs 1 year) on improvement in patients who received DBS (figure 1). We observed a statistically significant difference in the improvement in consciousness between patients with MCS and VS/UWS who underwent DBS (Scheirer-Ray-Hare test, H=5.86, p=0.016). The treatment (DBS vs conservative) × follow up period interaction had a significant effect on the improvement in consciousness (Scheirer-Ray-Hare test, H=6.31, p=0.043). We also found a significant effect of the treatment×follow up interaction on the outcome differences (Scheirer-Ray-Hare test, treatment, H=18.56, p<0.001; follow-up, H=20.56, p<0.001; treatment×follow up interaction, H=14.99, p<0.001).



	Df	Sum Sq	H	P value
group	1	5368	5.86	0.016
time	2	18326	20.00	<0.001
group:time	2	5781	6.31	0.043
Residuals	105	71354		

Figure 1 Improvement in CRS-R scores over time in DBS patients according to state of consciousness. CRS-R scores gradually increased over time, with patients with MCS exhibiting the fastest improvement. P<0.05 indicates a significant difference. ADM, admission; CRS-R, Coma Recovery Scale-Revised; DBS, deep brain stimulation; MCS, minimally conscious state; VS/UWS, vegetative state/unresponsive wakefulness syndrome.

Analysis of primary and secondary outcomes

Regarding the primary outcome, after adjusting for age, sex, state of consciousness, pathogeny and duration of DoC, DBS was significantly associated with the improvement in consciousness at 1 year (DBS: 12/37 (32.4%) vs conservative treatment: 14/328 (4.3%); logistic analysis, absolute difference: 10.75 (4.50 to 25.64); adjusted OR (aOR): 11.90 (3.65–38.46), p<0.001; table 2).

Regarding the secondary outcomes, after full adjustment in the multivariate regression, the significant association of DBS and improvement in consciousness at 6 months persisted (DBS: 5/37 (13.5%) vs conservative treatment: 10/328 (3.0%); logistic analysis, absolute difference: 4.98 (1.60 to 15.38); aOR: 4.48 (1.11–18.18), p=0.036; table 2). DBS was significantly associated with better GOS scores at 1 year (χ^2 test, p<0.001) as well as emergence from unconsciousness at 1 year (DBS: 14/37 (37.8%) vs conservative treatment: 44/328 (13.4%); logistic analysis, absolute difference: 3.92 (1.88 to 8.20); aOR: 6.62 (2.28–19.23), p=0.001). The results suggest DBS is associated with better outcomes in patients with DoC.

Subgroup analysis within patients who received DBS

After establishing that DBS led to improved overall patients' outcomes, we next investigated in whom would particularly benefit from DBS. Subgroup analysis was performed with the outcome of the improvement of consciousness at 1 year (figure 2). The therapeutic effects of DBS among subgroups of patients did not significantly vary according to age (p for interaction=0.078), sex (p for interaction=0.299), pathogeny (p for interaction=0.070) or duration of DoCs (p for interaction=0.880). The therapeutic effects of DBS significantly differed according to state of consciousness (MCS: aOR=55.56 (10.31–333.33); VS/UWS: aOR=6.76 (0.97–47.62); p value for interaction: 0.033). Consistent with this finding, the GOS scores (χ^2 test, p<0.001) and likelihood of emergence from

Table 2 Univariate and multivariate analyses of primary and secondary outcomes

Outcome	DBS group (n=37)	Conservative group (n=328)	Absolute difference (95% CI)	Adjusted OR* (95% CI)	P value
Primary outcome					
Improvement in consciousness at 1 year, n/total (%)	12/37 (32.4)	14/328 (4.3)	10.75 (4.50–25.64)	11.90 (3.65–38.46)	<0.001
Secondary outcomes					
Improvement in consciousness at 6 months, n/total (%)	5/37 (13.5)	10/328 (3.0)	4.98 (1.60–15.38)	4.48 (1.11–18.18)	0.036
GOS score at 1 year, n/total (%)					<0.001
1	1/37 (0.0)	0/328 (0.0)			
2	22/37 (59.5)	284/328 (86.6)			
3	8/37 (21.6)	39/328 (11.9)			
4	3/37 (8.1)	5/328 (1.5)			
5	3/37 (8.1)	0 (0.0)			
Emergence from unconsciousness at 1 year, n/total (%)	14/37 (37.8)	44/328 (13.4)	3.92 (1.88–8.20)	6.62 (2.28–19.23)	0.001

P values <0.05 indicate significant differences.
*Adjusted for patient age, sex, diagnosis, pathogeny and duration of disorders of consciousness (DoCs).
DBS, deep brain stimulation; GOS, Glasgow Outcome Scale.

	Underwent treatment No./Total No.	Adjusted odds ratio (95% CI)	P for interaction
All patients	37/365	13.07 (4.84 - 35.34)	
Age			
≤40years	14/126	55.56 (9.43 - 333.33)	0.078
>40 years	23/239	5.24 (1.04 - 26.32)	
Sex			
Male	23/253	18.52 (5.62 - 58.82)	0.299
Female	14/112	5.75 (0.65 - 50.00)	
Pathogeny			
Trauma	8/136	83.33 (9.52 - 1000.00)	0.070
Non-trauma	29/229	10.31 (2.51 - 41.67)	
Duration			
≤5	25/209	12.20 (3.05 - 50.00)	0.880
> 6	12/156	12.99 (2.79 - 333.33)	
Diagnosis			
MCS	13/123	55.56 (10.31 - 333.33)	0.033
VS/UWS	24/242	6.76 (0.97 - 47.62)	

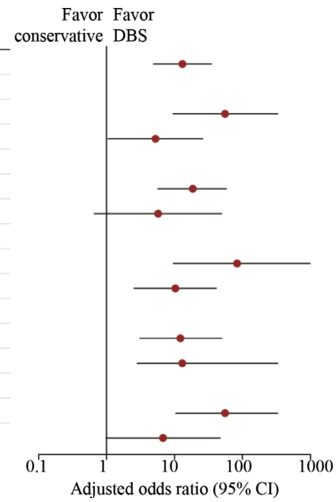


Figure 2 Subgroup analysis for the improvement in consciousness at 1 year using multivariate regression analysis adjusted for age, sex, pathogeny, duration of disorders of consciousness (DoCs) and state of consciousness. P<0.05 indicates a significant difference. DBS, deep brain stimulation; MCS, minimally conscious state; VS/UWS, vegetative state/unresponsive wakefulness syndrome.

unconsciousness (χ^2 test, p<0.001) were significantly better in patients with MCS than in patients with VS/UWS in the DBS group (online supplemental table S4).

Analysis of related factors and nomogram of the therapeutic effects of DBS

We further analysed the potential factors associated with therapeutic effects of DBS in patients with DoCs; the results are shown in table 3. After adjusting for all covariates, state of consciousness was the only factor that was significantly associated with the therapeutic effect of DBS (MCS: 10/12 (83.3%) vs VS/UWS: 2/24 (8.3%); logistic analysis, aOR: 68.400 (1.460–3203.834), p=0.031).

We also constructed a nomogram based on potential related factors, including age, state of consciousness, and pathogeny and duration of DoC. The nomogram achieved a c-index of 0.882, which is shown in figure 3. We also generated calibration curves for the nomogram, which are shown in online supplemental figure S2. The mean absolute error of the nomogram was 0.079. Then, we performed the Hosmer-Lemeshow goodness-of-fit test, which suggested that the model was well calibrated (χ2=5.435, p=0.710). The results suggest that the nomogram has an excellent predictive performance.

Table 3 Logistic analysis of factors related to improvement in consciousness after DBS

	Multivariate analysis	
Variable	**OR (95% CI)**	**P value**
Age	0.893 (0.743–1.072)	0.224
Sex, female	0.232 (0.006–8.393)	0.425
State of consciousness, MCS	68.400 (1.460–3203.834)	0.031
Pathogeny		
Anoxia	*	*
Stroke	16.988 (0.171–1683.366)	0.227
Trauma	29.939 (0.209–4287.686)	0.180
Duration of DoCs at admission	0.512 (0.041–6.313)	0.601
Recommendation criteria, highly recommended	0.104 (0.005–2.006)	0.134

*P<0.05, significantly different.
DBS, deep brain stimulation; DoCs, disorders of consciousness; MCS, minimally conscious state.

Effect of DBS on CRS-R subscale scores

In general, DBS significantly improved scores on the six subscales, namely audio (p=0.009), visual (p=0.004), motor (p<0.001) and verbal functions (p=0.001), as well as communication (p<0.001) and arousal (p<0.001) (Wilcoxon rank-sum test, figure 4A). In patients with MCS, similar results were found (table 4); significant improvements were observed in the audio (p<0.001), visual (p=0.005) and motor functions (p<0.001), as well as communication (p<0.001) and arousal (p<0.001); there was a small but significant difference in verbal function scores (p=0.001) (Wilcoxon rank-sum test, figure 4B). However, in patients with VS/UWS who received DBS, only the subscales of communication (p=0.006) and arousal (p=0.005) showed significant score improvement (Wilcoxon rank-sum test).

DISCUSSION

In this study, we found an overall improvement in consciousness at 1 year was achieved in 32.4% (12/37) of the DBS group compared with 4.3% (14/328) of the conservative group. DBS had significantly better effects

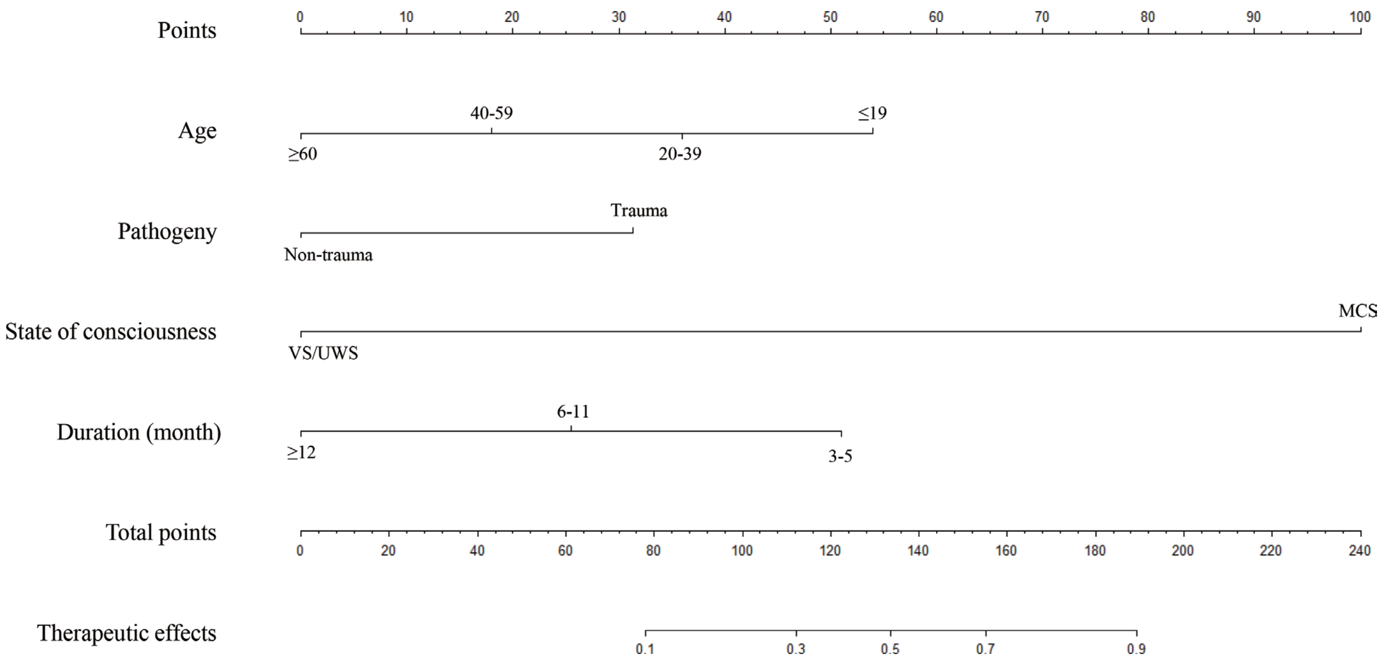


Figure 3 Nomogram of long-term outcome in patients with disorders of consciousness (DoCs) receiving deep brain stimulation (DBS). The pathogeny was classified as trauma or non-trauma (including stroke and anoxia). The therapeutic effect indicates the possibility of improvement in consciousness after receiving DBS in patients with DoCs; this probability ranged from 0 (unchanged/died) to 1 (effective). MCS, minimally conscious state; VS/UWS, vegetative state/unresponsive wakefulness syndrome.

in patients with MCS compared with patients with VS/UWS (p for interaction <0.001). We proposed the first nomogram to predict the therapeutic effects of DBS, and found that DBS was significantly associated with better long-term patient outcome and may represent a viable treatment option for patients with DoC, especially patients with MCS, as all six CRS-R subscales exhibited improvement after receiving DBS. To our knowledge, this study represents a novel comprehensive analysis of DBS in patients with DoCs.

DoCs are states of altered arousal, ranging from coma to unconsciousness, that occur after brain injury. Patients with DoCs have received a wide array of pharmacological and non-pharmacological treatments. To date, only amantadine administration has demonstrated benefits in a randomised placebo-controlled trial; this medication

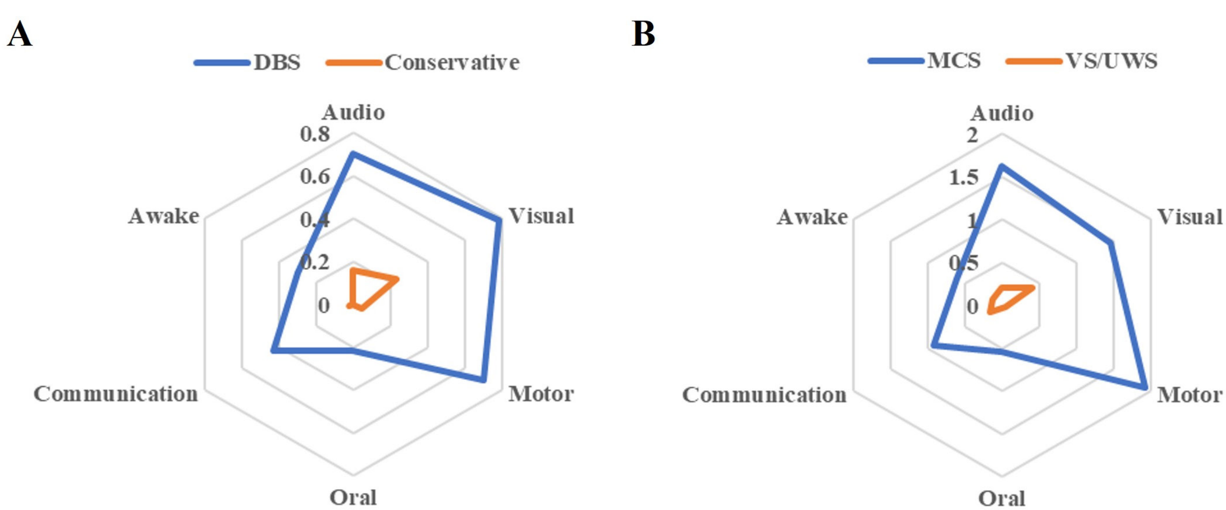


Figure 4 Radar chart for improvement in Coma Recovery Scale-Revised (CRS-R) subscores. (A) Deep brain stimulation (DBS) group and conservative group in overall patients. The blue line represents the DBS treatment group and the orange line represents the conservative treatment group. (B) Patients with minimally conscious state (MCS) and vegetative state/unresponsive wakefulness syndrome (VS/UWS) underwent DBS treatment. The blue line represents the MCS group and the orange line represents the VS/UWS group.

Table 4 Improvement in CRS-R subscale scores of patients with MCS who received DBS

Variable	All (n=123)	DBS group (n=13)	Conservative group (n=110)	P value
CRS-R subscale				
Audio	0 (0–1)	2 (0–2.5)	0 (−1 to 1)	<0.001
Visual	0 (0–1)	2 (0–2)	0 (0–1)	0.005
Motor	0 (−1 to 1)	2 (1–3.5)	0 (−1 to 1)	<0.001
Verbal	0 (0–0)	0 (0–1)	0 (0–0)	0.001
Communication	0 (0–0)	1 (0–1.5)	0 (0–0)	<0.001
Arousal	0 (0–0)	1 (0–1)	0 (0–0)	<0.001

P<0.05, significantly different.
CRS-R, Coma Recovery Scale-Revised; DBS, deep brain stimulation; MCS, minimally conscious state.

is recommended in the 2018 DoC guidelines.[4 30] Since the late 1960s, patients with severe brain injury have been sporadically treated with DBS.[31–33] However, as the concept of MCS had not yet been defined, some of the cases may have been misdiagnosed. In 2007, Schiff *et al* reported one patient with MCS who presented with coma for 6 years after brain injury; this patient was successfully awakened after DBS of the central thalamic nuclei. In their study, a parameter of 100 Hz, 4.0 V was used for stimulation, which is consistent with our study. Meanwhile, Dang *et al* studied nine patients with MCS who received 100 Hz DBS treatment, and proved 100 Hz DBS improved EEG functional connectivity and brain networks, indicating that the long-term use of DBS could improve the level of consciousness of patients with MCS. Therefore, we used 100 Hz for stimulation. Aspects of consciousness are based on two main components: wakefulness and awareness. Wakefulness refers to the patient's level of arousal and is assessed by observing eye opening. Awareness is related to subjective experiences and can be subdivided into awareness of the external world (ie, perception of the environment or 'consciousness') and 'awareness' of the internal world (ie, stimulus-independent thoughts such as mental imagery and inner speech or 'self-awareness'[34]). Behavioural changes refer to the behavioural manifestations of the external environment and self-response. In 2020, *Neuron* published a study in which the anaesthetised macaques were stimulated, and a specific frequency (50 Hz) effectively restored wakefulness and wakefulness-like nerve process. In 2022, Tasserie *et al* used anaesthesia to suppress the consciousness of non-human primates. During anaesthesia, central thalamus stimulation induced increasing fMRI activity in the prefrontal, parietal and cingulate cortices.[35] DBS restores two dimensions of consciousness, arousal and access to conscious content. Lemaire *et al* found that DBS improved visual and auditory processes and led to an increase in medial cortex activity.[19] Magrassi *et al* found that DBS promoted desynchronisation of the power spectrum of EEGs and increased CRS-R scores.[17] However, there is still a paucity of literature on the use of DBS in patients with DoC. Due to the ethical challenges of carrying out large, controlled studies in patients with DoC, the identified studies have been mostly limited to single-subject data and lack a sham control group. Thus, more research to evaluate the effectiveness of DBS for patients with DoC is urgently needed. In the present study, we included patients who underwent conservative treatment to compare its effects with that of DBS; we suggest that DBS may facilitate the recovery of patients with DoCs in a continuous manner. Notably, we found that patients with MCS had significantly better outcomes than patients with VS/UWS. Patients with MCS can follow certain commands[36 37]; therefore, global connectivity and vital circuits are preserved in these patients, providing a basis for subsequent functional recovery through the application of DBS. This may explain the superior outcome in patients with MCS, and patients in VS/UWS should be more rigorously evaluated either clinically or in future researches.

Regarding the underlying mechanisms of the effect of DBS, the relevance of the mesencephalic reticular formation to alertness was confirmed in earlier studies that stimulation of the mesencephalic reticular formation induced arousal-like desynchronisation of the EEG.[17 38] Moreover, a 'mesocircuit' model of forebrain dysfunction has been proposed as a potential mechanism underlying DoCs.[39] Neurons within the central thalamic nuclei regulate arousal in the forebrain and may play an important role in forebrain dysfunction after brain injury. Damage to the central thalamic nuclei often results in severe and persistent loss of consciousness. Thus, DBS targeting the central thalamic nuclei may compensate for a loss of arousal regulation normally controlled by the frontal lobe in the intact brain, and the excitatory output generated by DBS targeting the central thalamic nuclei may normalise cortico-striatal-thalamo-cortical function in patients with DoCs whose background synaptic activity is chronically downregulated following brain injury.[40 41] In the present study, the CM-Pf complex was selected as the DBS target in all 37 patients with DoC. As the central thalamic nuclei are approximately 7 mm in diameter and centrally located in the thalamus, three-dimensional brain map matching was used to select targets and guarantee the accuracy of electrode implantation, especially for patients with DoC with large changes in brain structure. The CM-Pf complex constitutes a major portion of the intralaminar thalamus and provides strong connections to several subcortical structures.[42 43] Previous studies have reported that the CM-Pf complex is a key structure in motor, associative-limbic and integrative circuits at the crossroads of the basal ganglia; Schiff captured its role by proposing the key participation of the central thalamic nuclei in arousal.[44 45] Thus, the CM-Pf complex lies at the intersection of motor function and arousal, making it an ideal target for brain stimulation. The proper selection and precise targeting of targets are key to the success of DBS. The anatomical coordinates of targets can be clarified by preoperative imaging, and the neural electrophysiological signals can be recorded intraoperatively by microelectrodes to clarify the target cells, ensuring surgical precision. DBS in treating DoCs differs from tremor control, which requires continuous stimulation to suppress abnormal movements. In terms of DoC treatment, DBS mainly plays a role in maintaining nerve excitability, and does not require continuous stimulation. On the contrary, continuous stimulation will lead to fatigue and decreased nerve excitability of patients, so we adopted the strategy of intermittent stimulation. According to our previous experience that based on several spinal cord stimulation clinical studies, we believe that 15 min on and 15 min off is a very effective strategy.[29]

We also compared the CRS-R and GOS before and after the patients received DBS, and found that the behaviour and consciousness level of the patients have improved significantly. CRS-R is more detailed in the behavioural improvement among patients with DoC, while GOS is a more feasible score to assess whether the patient emerged from unconsciousness, and the effect of DBS in patients with DoC is consistent. This inconsistency in subscale improvements highlights the need for more imaging studies to investigate the effects of DBS in patients with DoC and further clarify the underlying neural mechanism rather than allowing regional injury to guide future clinical directions.

In light of these mechanistic and clinical findings, factors related to the outcomes of DBS can be discussed. Nomogram is based on multifactor regression analysis, integrates multiple predictive indicators and then uses scaled line segments to draw on the same plane according to a certain ratio, so as to express the relationship between variables in the predictive model. The nomogram transforms the complex regression equation into a visual graph, making the results of the prediction model more readable and convenient for patient evaluation. It is precisely because of the intuitive and easy-to-understand characteristics of the nomogram that it has gradually received more and more attention and application in medical research and clinical practice. Although data are scarce, it is generally believed that patients with MCS have less damage to neurocircuitry than patients with VS/UWS, as their fMRI scans show more activated areas and increased connectivity, and patients with MCS have a better outcome. Of the 37 patients who received DBS in this study, 12 exhibited significant improvement after DBS, including two patients with VS/UWS and 10 patients with MCS. We explored whether the recommendation criteria used in spinal cord stimulation of patients with DoC[46] would also be feasible for DBS criteria; however, no significant difference was found regarding highly or weakly recommended patients for DBS. This lack of difference may be because these two neuromodulation techniques (spinal cord stimulation vs DBS) have different neural mechanisms; the specific differences merit further study in DoC patients.

The recovery of patients with DoC involves multiple mechanisms that alter global neuronal function as well as specific neural circuits.[47] According to our long-term follow-up, the therapeutic effect gradually decreased with increasing age, indicating that the high neuroplasticity and metabolic activity observed in childhood might decrease with age.[48–50] Patients with DoC induced by trauma had significantly better outcomes than patients with DoC induced by other causes, which may be a result of local deficits rather than the diffuse brain injuries commonly observed in response anoxia that affect the connectivity of the whole brain. Additionally, we found that a longer duration of DoC was associated with worse outcomes of DBS, suggesting that timely stimulation may help rescue the remaining circuits. Moreover, we constructed a nomogram that allows intuitive assessment of the impact of these factors on the therapeutic effect. The Hosmer-Lemeshow goodness-of-fit test revealed that the model was well calibrated, and the c-index indicated that these factors were excellent at predicting therapeutic effects. Use of a preoperative screening tool is crucial because patients with DoC and their families face clinical dilemmas regarding treatment decisions. In the future, adding more electrophysiological and imaging indicators to the model facilitates identification of patients suitable for DBS.

Limitations

This study is retrospective, and due to limitations in the study design, it is difficult to fully exclude confounding factors that may influence the therapeutic effect after DBS. Overall, continuous significant improvement was observed at different time points in patients who received DBS, suggesting that the results are reliable. At the time of inclusion, we only included patients with a disease course of more than 3 months and no progressive increase in consciousness for two consecutive weeks or more, so the possibility of spontaneous recovery was strictly excluded. In addition, we also performed neurophysiological test (MMN and Synek) for patients receiving DBS treatment and conservative treatment. Consistently, we found no significant difference in neurophysiological tests between DBS group and conservative group preoperatively, which indicate that the residual consciousness before treatment is similar. In this way, the selection bias was minimised. However, we have carefully studied the existing literatures, and found that the existing stimulation parameters have great heterogeneity, which brings difficulty for further systematic analysis. The effectiveness of DBS in the treatment of DoCs urgently requires an international multicentre well-designed prospective study, preferably a randomised controlled study, which may help to further clarify the effect of DBS in the treatment of DoCs. Subsequent studies should continue to increase the sample size and explore the mechanisms underlying these DBS-induced improvements.

CONCLUSION AND PROSPECTS

DBS was associated with improvements in consciousness in this cohort analysis; therefore, it represents a promising neuromodulation technique to promote the improvement in consciousness in patients with DoC. The DBS-induced improvements in patients with DoC lasted for a long time, and the therapeutic effect was significantly greater for patients with MCS than patients with VS/UWS. For patients with MCS, the six subscales of the CRS-R all exhibited improvement; in contrast, for patients with VS, DBS mainly improved communication and arousal. In conclusion, patients with DoC should be carefully evaluated before selecting DBS as the treatment option. Further closed-loop stimulation strategies may promote recovery along with modern electrophysiological and neuroimaging technologies.

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