



## Habenula deep brain stimulation for refractory bipolar disorder

### Background

Bipolar disorder (BD) is a mood disorder associated with significant morbidity and mortality. In many cases, BD can be managed with pharmacotherapy, psychological therapy, or electroconvulsive therapy [1]. For some afflicted patients, however, BD is a chronic and severely disabling condition that is resistant to the aforementioned treatments. Deep brain stimulation (DBS) offers a safe and effective neurosurgical treatment for otherwise refractory movement disorders and obsessive-compulsive disorder [2,3]. Here, we describe the first case of refractory BP treated effectively with DBS of the habenula (HB).

The HB is an epithalamic structure that regulates serotonergic raphe nucleus activity and modulates dopaminergic midbrain functions [4]. The HB is believed to play a crucial role in sleep, rewarding and aversive stimulus events, including pain, stress, and fear-provoking stimuli. Given its role in arousal and mood regulation, HB dysfunction has been implicated in the pathophysiology of depression [4,5]. In line with this hypothesis, experimental ablation of the habenula in animal models of depression alleviates depressive-like behavior [5]. Moreover, initial treatment studies indicate that DBS targeting the major afferent bundle (stria medullaris) of the lateral HB is effective in refractory depression [6]. Accordingly, we hypothesized that HB-DBS would be similarly effective in managing medically intractable BD as this stimulation potentially avoids triggering manic states, consistent with its role in negative reward processing.

### Patient information

The present case involves a 41-year-old male patient who was diagnosed with Bipolar I disorder. The patient had experienced a manic episode, a remission, and multiple depressive episodes over an illness course of about 21 years. During the past 4 years, he suffered from severe depression symptoms that could no longer be alleviated with available treatments, including multiple pharmacotherapies, electroconvulsive therapy, and several hospitalizations, which resulted in substantial functional impairment (e.g., long-term disability from work). The patient gave informed consent before participating in the clinical trial, which was approved by Ruijin Hospital Ethics Board and registered in clinicaltrials.gov(NCT03254017). Resting state functional magnetic resonance imaging (fMRI) scans (pre-surgery and multiple points post-surgery) were compared to data from 21 healthy controls.

### Surgical procedure

High-resolution magnetic resonance imaging (MRI, 3.0 T; General Electric Company; USA) and Leksell SurgiPlan (Elekta,

Stockholm, Sweden) were used for targeting, we obtained T1 maps, proton spin density maps, R2\* maps, and quantitative susceptibility maps. From high resolution T1-weighted images, we were able to delineate the habenula clearly in the axial view. Both quadripolar DBS electrodes (model 3387; Medtronic, Minneapolis, MN, USA) were implanted under general anaesthesia; the pulse generator (37603 SC, Medtronic) was implanted subclavicularly under general anaesthesia.

### Results

#### Clinical outcome

Following HB-DBS at high frequency (C+3-, C+11-, 3.0V, 120µs, 130Hz, Medtronic Activa PC), the patient showed a significant clinical improvement (46% decreased depression score) at 3-month follow-up, but his clinical state subsequently worsened, despite parameter adjustments (Table 1). Seven months post-surgery, DBS was turned off (single-blind), which resulted in an unexpected yet significant and rapid (within 24 hours) clinical improvement. As a result, the patient was able to return to part-time work. Eight months post-surgery, HB-DBS at a lower frequency (1+0-, 8+9- 2V, 60µs, 60Hz) was initiated (single-blind) in an effort to maintain the clinical benefits achieved. Within one day after the onset of low-frequency DBS, the patient showed minor but enduring additional clinical improvements, with enhanced energy preceding improvements of depression and anxiety. Furthermore, the patient's sleep and quality of life, as well as his physical, social, and occupational (e.g., resuming full-time work) functioning, all showed marked progressive improvements during the 4-month period of low-frequency HB-DBS treatment. Low-frequency HB-DBS did not impact the patient's cognitive functions, except slightly improving visual processing speed, planning, and set shifting. HB-DBS did not induce hypomania or adverse side effects, except blurred vision which was reversible. Lead placement with respect to HB, electric fields, and estimated volumes of tissue activated for the stimulation settings at different time points post-implantation are presented in Supplementary Fig. 1.

#### Functional MRI

The fMRI data were analyzed using dynamic functional connectivity and leading eigenvector dynamics analysis [7], which assigns each fMRI timepoint into functional connectivity states using a k-means clustering algorithm. We used k = 5 for a good tradeoff between reliability and specificity (Supplementary Fig. 2). Off DBS (pre-operative and at 8 and 9 months) dynamic functional

**Table 1**

Clinical outcome measures.

DBS status	Pre-op	HFS	HFS	HFS	HFS	OFF	LFS	LFS
Rating Scale	Baseline	2 wk	3 mo	6 mo	7 mo	8 mo	9 mo	12 mo
<b>HDRS</b>	24	17	13	24	21	5	3	1
<b>MADRS</b>	28	26	16	42	30	5	1	0
<b>HARS</b>	15	13	12	19	18	4	2	2
<b>YMRS</b>	0	0	0	0	0	0	0	0
<b>PSQI</b>	16	13	15	15	18	11	9	9
<b>COGSTATE</b>								
Psychomotor function	2.44	2.62	2.68			2.75	2.63	2.56
Attention	2.66	2.79	2.82			2.80	2.77	2.73
Visual learning	1.04	1.16	1.07			1.02	1.19	1.08
Speed of visual processing	0.73	1.16	1.03			1.23	1.06	1.00
Working Memory	2.81	3.02	3.01			3.07	3.02	2.84
Planning	60	28	48			24	34	48
Set Shifting	53	44	58			34	54	14
<b>SF-36</b>								
Physical Functioning	75	70	80	60	90	95	90	90
Role-physical	0	0	25	0	0	100	100	100
Body Pain	60	54	54	50	54	74	74	74
General Health	25	40	50	30	30	67	77	72
Vitality	35	40	40	30	35	75	80	80
Social Functioning	12.5	50	37.5	25	12.5	87.5	87.5	87.5
Role-emotional	0.0	0.0	33.3	0.0	33.3	100.0	100	100
Mental Health	52.0	40.0	48.0	44.0	36.0	64.0	68	72
Reported Health Transition	50.0	75.0	75.0	0.0	25.0	75.0	100	75
<b>SDS</b>								
Work/School	9	7	8	10	8	3	2	2
Social Life	9	8	8	10	8	4	2	2
Family Life/Home Responsibilities	9	7	8	10	8	3	2	3
Day Lost	7	7	5	7	6	2	0	1
Days Unproductive	7	7	4	7	4	1	0	0

Abbreviations: DBS:deep brain stimulation; Pre-op:pre-operative; HFS:high frequency stimulation; OFF:Off DBS; LFS:low frequency stimulation.

HDRS:17-item Hamilton Depression Rating Scale; HARS: Hamilton Anxiety Rating Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; YMRS:Young mania rating scale; PSQI: Pittsburgh sleep quality index; SF-36: Short Form Health Survey (Quality of Life); SDS: Sheehan Disability Scale.

Psychomotor function: Detection Test and Attention: Identification Test (mean of log10 transformed reaction times for correct responses); Visual learning: One Card Learning Test (arcsine transformation of square root for proportion correct responses); Speed of Visual processing: Groton Maze Chasing Test (total correct moves per second); Working memory: One Back Test (mean of log10 transformed reaction times for correct responses); Planning: Groton Maze Learning Test and Set Shifting (total number of errors).

connectivity showed greater probability in states characterized by negative correlations between default mode network, striatum, amygdala and somatosensory cortex and positive correlations between lateral prefrontal-parietal networks relative to healthy controls. In our patient, only high frequency (and not low frequency) DBS seemed to be associated with widespread negative correlations, although this effect was not significant.

## Discussion and conclusion

Our case highlights the safety and proof-of-concept of HB-DBS for BD. Although placebo effects cannot be ruled out, the patient was blind to parameter changes and did not respond to previous treatments. Intriguingly, high frequency DBS alone showed limited efficacy, but this treatment in combination with the switch to Off DBS appeared to produce a marked clinical improvement. This observation highlights the role of modulating stimulation patterns in influencing habituation or resetting effects. Critically, low-frequency DBS was effective in our case of BD, which has also been observed for axial symptoms in Parkinson's disease [8,9]. Also, low-frequency (10 Hz) DBS has been found to decrease abnormal nucleus accumbens sensitization in rodent cocaine addiction models [10]. DBS clinical effects seem to be frequency-dependent and synaptically-mediated [11]. We postulate that low-frequency or "high frequency to Off" HB-DBS might induce physiological signals relevant to HB function and mood regulation in BD.

Commonly serendipitous observations in the DBS literature have led to crucial insights. Our first observation should be verified because the present study was not experimentally well controlled. Specifically, it remains to be elucidated whether low-frequency HB-DBS alone produced the clinical benefits to our patient or whether the preceding sequence of events (high-frequency HB-DBS followed by DBS off) also played a role. Notwithstanding our study limitations, the present data warrant initiation of additional clinical studies to determine whether the application of HB-DBS should be expanded to include the treatment of severe and otherwise intractable cases of BD.

## Disclosures

Dr. Bomin Sun received research support from PINS and SceneRay (donated devices); Dr. Chencheng Zhang has received honoraria and travel expenses from the Deep Brain Stimulation industry (Medtronic, PINS, SceneRay). The other authors have no conflicts.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brs.2019.05.010>.

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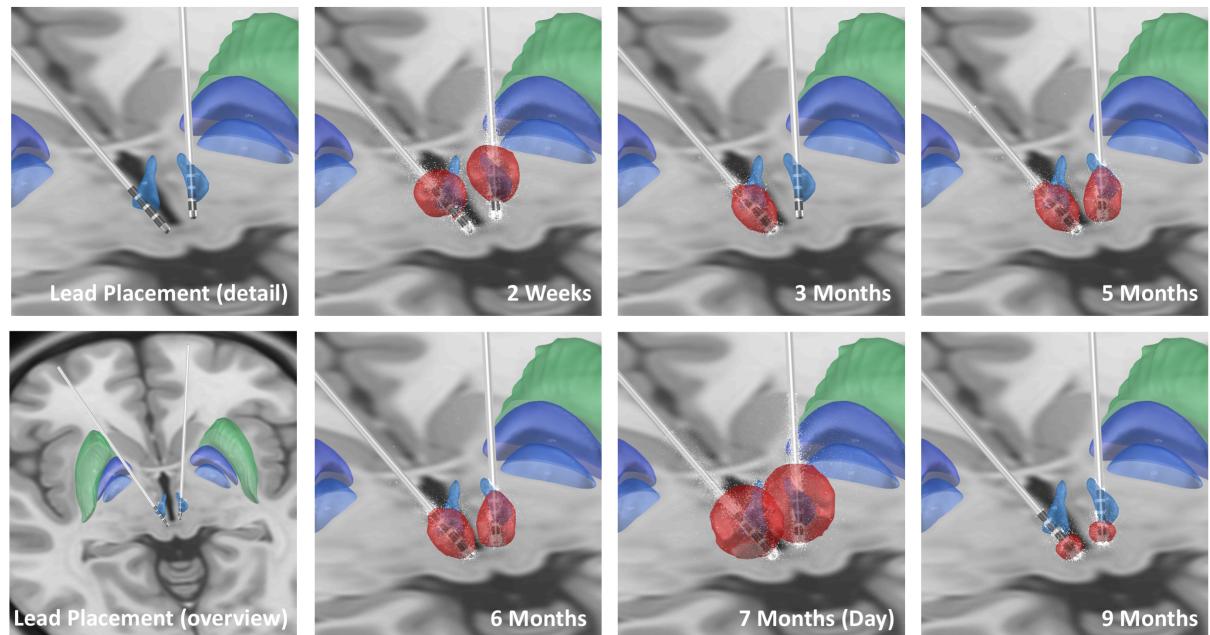
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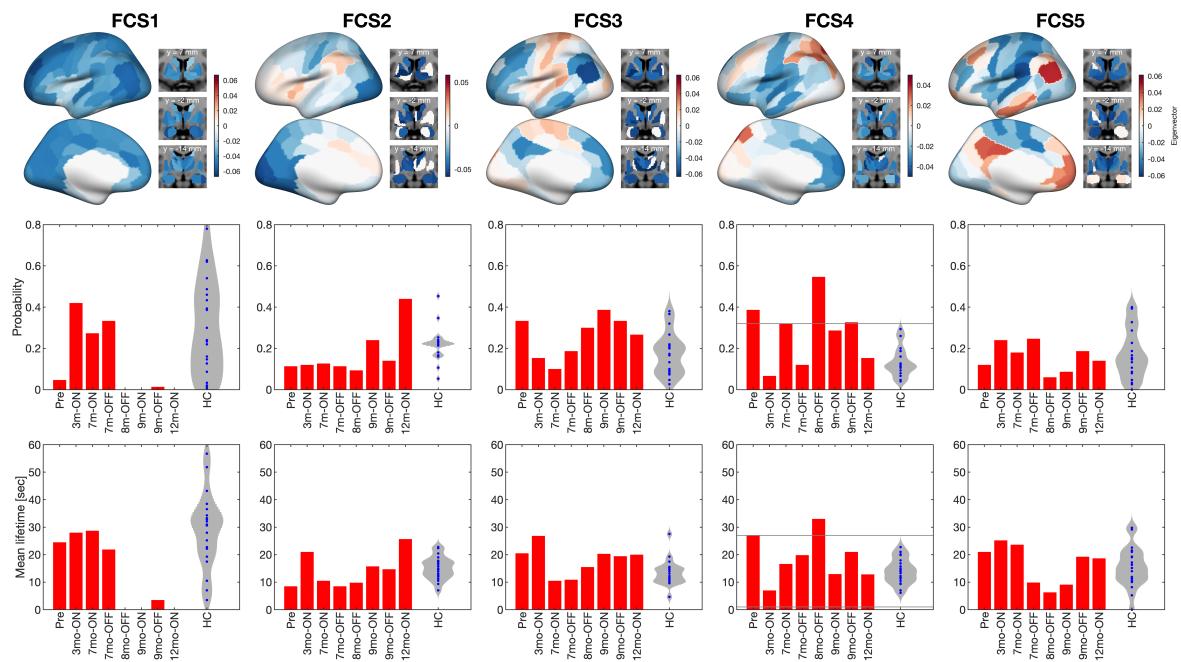
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Supplementary Figure 1. Left column: Demonstration of lead placement with respect to HN (blue), GP and Putamen shown additionally for orientation. Other columns: Electric fields (white dots) and estimated volumes of tissue activated (red) for the stimulation settings at different time points post implantation.



Supplementary Figure 2. The resting state dynamic functional connectivity pre- and post- habenula deep brain stimulation in a bipolar patient and healthy controls.

Repeated within-subject resting state scans were compared with 21 healthy controls (mean age:  $41.1 \pm 7.1$  years; 16 females; data plotted in violin plots) acquired on a 1.5-T Siemens Aera MR system. Dynamic functional connectivity was analyzed using the leading eigenvector dynamics analysis (LEiDA). Functional connectivity state (FCS), such as spatial weights (C, top row), probability (C, middle row), and mean lifetime (C, bottom row) are shown. The right temporo-parietal area was excluded from analysis due to susceptibility artifacts caused by DBS leads. A modified two-sample t-test was used ( $P < 0.05$  FDR). Two-tailed confidence interval of 95% is marked by grey and horizontal lines. PRE: Pre-surgery; 3 mo-ON: high frequency DBS; 7 mo-ON: high frequency DBS; 7 mo-OFF: DBS off for 24 hours; 8 mo-OFF: DBS off for 1 month; 9 mo-ON: low frequency DBS; 9 mo-OFF: DBS off for 24 hours; 12 mo-ON: low frequency DBS. All DBS manipulations were single-blind.



Electrode reconstruction methods description for “Habenula deep brain stimulation for refractory bipolar disorder”

Post-operative DBS lead analysis was carried out using LeadDBS software. DBS-Electrodes were automatically localized from post-operative CT in native and template space using the PaCER algorithm and localization was manually validated. Electric fields of the different stimulation settings at 2 weeks, 3 months, 5 months, 6, months, 7 months and 9 months after surgery were simulated using the Simbio/Fieldtrip Model described in. Note that VTAs are independent of the simulation frequency. However, different stimulation frequencies might induce different effects within the same VTA.

The post-operative CT was co-registered to the T1 MRI using a two-stage linear registration (rigid followed by affine) as implemented in the LeadDBS software [4] using the Advanced Normalization Tools (ANTs) [1]. Other MRI modalities were processed the same way.

All image acquisitions were then spatially normalized into MNI\_ICBM\_2009b\_NLIN\_ASYM space [5] based on preoperative acquisitions using the SyN registration approach implemented in ANTs [1]. Nonlinear normalisation into template space was achieved in five stages: After two linear (rigid followed by affine) steps, A nonlinear (whole brain) SyN-registration stage was followed by two nonlinear SyN-registrations that consecutively focused on the area of interest as defined by subcortical masks in [2].

DBS-Electrodes were automatically localized from postoperative CT in native and template space using the PaCER algorithm [3].

The automatic CT based DBS-Electrodes localisations was manually validated by blending reconstructed trajectories on post-operative acquisitions using a tool specifically provided for this in Lead-DBS software. The reconstructions were deemed very accurate and no manual changes to the localisations were made.

Electric fields of the stimulation where simulated using the Simbio/Fieldtrip Model described in [7] as implemented in LeadDBS. Volumes of Tissue Activated (VTA) for a the final stimulation settings using a pulse width of  $60\mu\text{s}$  were estimated using a conductivity threshold of  $0.24\text{V/mm}$ . This value reflects the threshold for  $60\mu\text{m}$  pulse width on axons of  $3\mu\text{m}$  diameter according to [6] and is close to the widely used general heuristic of  $0.20\text{V/mm}$  as suggested in [7]. Therefore the  $3\mu\text{m}$  diameter was selected as an illustrative example allowing comparisons between different contact and voltage settings.

The simulation of the DBS settings at 1 week, 3 months, 5 months, 7 months and 9 months post op, which used a significantly larger pulse width of  $90\mu\text{s}$ ,  $120\mu\text{s}$ ,  $130\mu\text{s}$ ,  $150\mu\text{s}$  and  $160\mu\text{s}$  were computed with thresholds of  $0.185\text{V/m}$ ,  $0.157\text{V/mm}$ ,  $0.147\text{V/mm}$   $0.134\text{V/mm}$  and  $0.128\text{V/mm}$  respectively. Settings for pulse widths above  $120\mu\text{s}$  where extrapolated from the data in [4] using an exponential regression model. Conductivities for white matter and grey matter where assumed at the default values of  $0.33\text{S/m}$  and  $0.14\text{S/m}$  as proposed in [7].

Note that VTAs are independent of the simulation frequency, i.e. the number of stimulation pulses delivered per second. However, different stimulation frequencies might induce different effects within the same VTA.

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