



## Deep brain stimulation of the ventral anterior limb of the capsula interna in patients with treatment-refractory anorexia nervosa



### Keywords:

Anorexia nervosa  
 Deep brain stimulation  
 Treatment-refractory  
 Body mass index  
 Neurosurgery  
 Clinical trial

Dear editor,

Anorexia nervosa (AN) is a severe and often chronic psychiatric disorder with high morbidity and mortality [1]. Pilot studies and cases showed mixed but promising effects of deep brain stimulation (DBS) as a last-resort treatment option for life-threatening treatment-refractory AN [2,3].

The present study (N = 4) is the first to target DBS in AN at the ventral anterior limb of the capsula interna (vALIC), part of the reward circuitry. vALIC-DBS showed strong and long-lasting effects in obsessive-compulsive disorder (OCD). We hypothesized that, due to the clinical and neurobiological similarities between AN and OCD, vALIC-DBS may exert comparable effects in treatment-refractory AN. We included a sample of patients with exceptionally severe AN. Although challenging, they reflect the prototypical patients that may be eligible for DBS as a last resort treatment option [4].

Inclusion criteria included primary diagnosis of AN, a Body Mass Index (BMI) < 15, a Global Assessment of Function score (GAF-score) of 45 or less for  $\geq 2$  years [5], an illness duration of  $\geq 10$  years and a lack of response to  $\geq 2$  typical modes of treatment including  $\geq 1$  inpatient treatment of hospitalization.

We conducted bilateral stereotactic implantation of DBS electrodes in the vALIC.

In accordance with our DBS studies [6] the study comprised four sequential phases: preoperative (T-1), surgery (T0), optimization (3–9 months; T1-T2) and maintenance phase (12 months; T2-T4) (Supplement 1, methods and statistical analysis). During the study the patients received standard medical and psychiatric care, comprised of regular visits with a nurse-practitioner and a psychiatrist. No major psychopharmacological adjustments were made.

Primary outcome measures were 1) change in body mass index (BMI), 2) change in Yale-Brown-Cornell Eating Disorder Scale (YBC-EDS)-score [7] and 3) change in Eating Disorder Quality of Life (ED-QOL)-score [8]. We established side effects and safety through frequent and intensive monitoring by a psychiatrist, including

checks of vital parameters, standard laboratory assessments and ECG. All patients were assessed using (self-report) questionnaires.

Four female patients were enrolled between 2016 and 2020. Patients had a mean age of 39 years (SD = 10) and illness duration of 21 years (SD = 3). Average baseline BMI was 12.5 (SD = 1.0) kg/m<sup>2</sup>, indicating extremely severe AN.

Monopolar DBS at the middle two contacts was switched on at T1 (pulse width 90  $\mu$ s, frequency 130 ms) at a mean voltage of 3.0 V (2.5–3.5 V). The mean voltages at T2, T3 and T4 were respectively 3.8 V (3.0–5.0 V), 3.8 V (3.0–4.5 V) and 3.8 V (2.7–4.8 V). Adjustment of the stimulation intensity occurred in steps of 0.5 V, later fine-tuning in steps of 0.1 V. Pulse width and frequency remained unchanged during the study.

BMI increased substantially and significantly at the end of follow-up (5.32 kg/m<sup>2</sup>; +42.8%; P = .017) (Fig. 1).

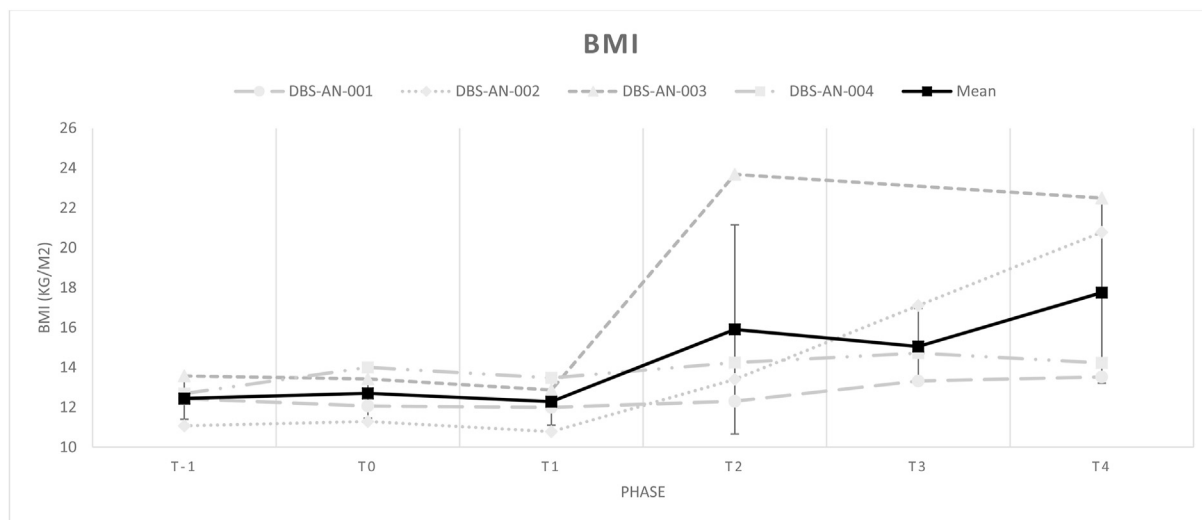
The score on the YBC-EDS showed a significant improvement over time (–23.9%; P = .012). This effect was driven by significant decreases in the *Preoccupation* and *Rituals* subscales (–16.2%; P = .026, and –31.1%; P = .001, respectively). This corresponded with the secondary outcome EDE-Q, which showed significant improvements on the subscales *Restraint* and *Eating Concern* (P = .039 and P = .024, respectively). The HAM-D and HAM-A showed additional significant improvements (–36.7% and –47.9%, respectively).

The ED-QOL showed a significant improvement over time on the subscale *Physical Health* (P = .005) (Supplement 2, Table 1: results).

Evidently, there are points of discussion. The mean baseline BMI of our patients was extremely low (categorized as ‘very severe’ in the DSM-5), which on average improved at one year postoperatively to the DSM-5 category ‘mild’. The increase in BMI was primarily seen in two of four patients. The other two subjects showed only a mild increase in BMI. This response rate of 50% is comparable to other studies [2,3].

Improvement was also observed in psychological outcomes. Two out of four patients were categorized as responders ( $\geq 35\%$  decrease on the YBC-EDS). All patients reported a decrease in pre-occupations and rituals, experiencing them as less rewarding. There was a decrease in eating-related behavior like purging and caloric and body checking, and significant decrease in depression and anxiety symptoms, which have great clinical importance for AN-patients [9].

All patients reported a *subjective* improvement of their psychological state and quality of life. The majority of patients reported that eating disorder behavior and rituals have lost their rewarding properties, leaving the more room for healthier behavior. All



**Fig. 1.** Time course of DBS-induced BMI (fixed effects  $\pm$  SE).

Linear mixed model analyses showed a significant linear effect of time on BMI ( $43.16 \pm 15.96$ , CI 95% 9.07–77.25,  $t = 2.704$ ,  $P = .017$ ).

patients confirmed that they still would prefer DBS, even though their eating disorder did not reach complete remission.

There were no intraoperative adverse events in any of four patients. Nevertheless, 28 severe adverse events (SAE's) occurred, with two being probably and nine possibly related to the intervention. Probable related SAE's were (hypo)manic symptoms. Possible related SAE's consisted of self-destructive behavior (auto-intoxication, auto-mutilation and aggression). SAE's were mostly related to the severity of AN and its somatic complications rather than DBS ( $n = 11$ ).

The number of SAE's reflects the challenging nature of this study. Transient hypomanic and impulsive symptoms may be caused by downregulation of reward and emotion regulation circuitries due to DBS [4,10]. We hypothesize that vALIC-DBS inhibits positive reinforcement of ritualistic AN behavior making them useless as a coping strategy. Patients develop alternative coping strategies such as self-destructive behavior, explaining some of our (S) AE's. Three out of four patients showed improvement on coping and emotion regulation following psychotherapy.

DBS was provided open-label, therefore results might be influenced by placebo or other non-specific effects. These were however minimized due to the one-year follow-up period. Though the small sample size of this vALIC DBS study limits its power, it is deemed sufficient to answer basic research questions.

To the best of our knowledge, this is the first study of vALIC-DBS in AN. The results indicate that vALIC-DBS is a valid, safe and feasible last-resort intervention in treatment-refractory AN. Our findings pave the way for a follow-up study with a larger sample size.

### Trial registration

Registered in the Netherlands Trial Register (<https://www.trialregister.nl/trial/3322>): NL3322 (NTR3469).

### Declaration of competing interest

The authors declare that they have no competing interests.

### Acknowledgments

There was no funding for this study, there were no sponsors. RJTM is supported by an unrestricted ABC Talent Grant.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brs.2021.10.387>.

### References

- [1] Steinhausen HC. Outcome of eating disorders. *Child Adolesc Psychiatr Clin N Am* 2009;18(1):225–42.
- [2] Lipsman N, et al. Deep brain stimulation of the subcallosal cingulate for treatment-refractory anorexia nervosa: 1 year follow-up of an open-label trial. *Lancet Psychiatr* 2017;4(4):285–94.
- [3] Liu W, et al. Deep brain stimulation of the nucleus accumbens for treatment-refractory anorexia nervosa: a long-term follow-up study. *Brain Stimul* 2020;13(3):643–9.
- [4] Bergfeld IO, et al. Invasive and non-invasive neurostimulation for OCD. *Curr Top Behav Neurosci* 2021;49:399–436. [https://doi.org/10.1007/7854\\_2020\\_206](https://doi.org/10.1007/7854_2020_206).
- [5] Association AP. Diagnostic and statistical manual of mental disorders. fifth ed. 2013. Washington, DC.
- [6] Denys D, et al. Efficacy of deep brain stimulation of the ventral anterior limb of the internal capsule for refractory obsessive-compulsive disorder: a clinical cohort of 70 patients. *Am J Psychiatr* 2020;177(3):265–71. <https://doi.org/10.1176/appi.ajp.2019.19060656>.
- [7] Mazure CM, et al. The Yale-Brown-Cornell eating disorder scale: development, use, reliability and validity. *J Psychiatr Res* 1994;28(5):425–45.
- [8] Engel SG, et al. Development and psychometric validation of an eating disorder-specific health-related quality of life instrument. *Int J Eat Disord* 2006;39(1):62–71.
- [9] Hudson JL, et al. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. *Biol Psychiatr* 2007;61(3):348–58.
- [10] Figeo M, et al. Deep brain stimulation restores frontostriatal network activity in obsessive-compulsive disorder. *Nat Neurosci* 2013;16(4):386–7.

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1 October 2021  
Available online 20 October 2021