Heliyon 9 (2023) e14411

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Could deep brain stimulation be a possible solution for acquired hypothalamic obesity?

Amber R. Dassen [a], Jiska van Schaik [a,b], Pepijn van den Munckhof [c], P.R. Schuurman [c], Eelco W. Hoving [d], Hanneke M. van Santen [a,b,*]

[a] Department of Pediatric Endocrinology, Wilhelmina Children's Hospital, Utrecht, the Netherlands
[b] Department of Pediatric Oncology, Princess Máxima Center, Utrecht, the Netherlands
[c] Department of Neuro-Surgery, Amsterdam UMC, Amsterdam, the Netherlands
[d] Department of Neuro-Surgery, Princess Máxima Center, Utrecht, the Netherlands

ARTICLE INFO

Keywords:
Deep brain stimulation
Craniopharyngioma
Prader-Willi syndrome
Hypothalamic obesity
Nucleus accumbens

ABSTRACT

Objective: Hypothalamic dysfunction may result in morbid obesity as a consequence of decreased energy expenditure, decreased feelings of satiety, and increased fat storage. In patients with hypothalamic dysfunction, neurobehavioral dysfunction is also often present. Currently, no effective treatment has been found for hypothalamic obesity (HO). We hypothesize that deep brain stimulation (DBS) may be an effective treatment for patients with hypothalamic dysfunction, aiming to treat HO as well as the neurobehavioral dysfunction.

Methods: A systematic search was conducted in the PubMed, EMBASE and Cochrane Library databases for studies published until May 2022 reporting on DBS for the treatment of HO.

Results: Three studies met the predetermined inclusion criteria, with in total six patients treated with DBS for HO, of which five patients with Prader-Willi syndrome (PWS) and one patient with HO after treatment for craniopharyngioma (CP). Targets of DBS included the lateral hypothalamic area (LHA) and the nucleus accumbens (NAcc). In patients with PWS, LHA-DBS was associated with a mean increase of Body Mass Index (BMI) (+5.8%), with no change in hormonal levels, results of blood workup, sleep, or neuropsychological evaluation. In the patient with CP, NAcc-DBS was associated with a decrease in BMI (−8.7%) and a subjective increase in mental health, energy and willingness to act, and no feeling of increased appetite. No objective measurements on neurobehavioral function were reported. No severe adverse events were reported in these cases. Mild to moderate adverse events included hypomanic symptoms and infection. All patients with a described follow-up period ($n = 5$) were able to sustain the treatment for at least 6 months with few interruptions.

Conclusion: There is limited research reporting on DBS for HO. The effectiveness differed across studies and the evidence is limited. Although there may be potential for DBS treatment in the severe-refractory condition of HO in patients with CP, more research is needed for target selection and evaluation of effectiveness.

* Corresponding author. Department: Pediatric Endocrinology, Institute/University/Hospital, Wilhelmina Children's Hospital and Princess Máxima Center for Pediatric Oncology, Lundlaan 6, Utrecht, 3584 EA, the Netherlands.
E-mail address: H.M.vanSanten@umcutrecht.nl (H.M. van Santen).

https://doi.org/10.1016/j.heliyon.2023.e14411
Received 3 August 2022; Received in revised form 20 February 2023; Accepted 3 March 2023
Available online 9 March 2023

1. Introduction

When the hypothalamus is damaged, patients may develop hypothalamic obesity (HO) [1–5]. HO frequently arises in survivors of craniopharyngioma (CP) or other suprasellar tumors, due to tumor invasion in the hypothalamus or as a consequence of neurosurgical intervention or radiotherapy. An estimated two thirds of CP survivors encounter overweight or obesity, with 50% of all patients with CP belonging to the obese group [6–8]. Other etiologies of HO include inflammatory causes, trauma, and genetic syndromes, such as the Prader-Willi syndrome (PWS) [4,5]. HO brings upon a high rate of morbidity and mortality due to associated complications, such as metabolic syndrome and cardiovascular diseases, and may greatly disrupt quality of life [7,9–12]. Among CP patients cardiovascular mortality is estimated to be 3.2 to 3.6 times higher than in the general population due to the hypothalamic dysfunction [9,13].

HO is caused by a disruption of the energy homeostasis, which is regulated in specific hypothalamic nuclei [14,15]. These nuclei are found to be essential for balancing food intake and energy expenditure, of which the paraventricular nucleus, the ventromedial nucleus (VMH), the arcuate nucleus, the dorsomedial nucleus, the dorsal hypothalamic area, and the lateral hypothalamic area (LHA) are most commonly mentioned [14,16]. These nuclei work together to integrate peripheral hormones and nutrient-related signals and convert these signals into nervous system output [14,15,17,18]. In addition to the homeostatic regulation of feeding, there is the hedonic feeding circuitry, which is driven by the sensory perception or pleasure of eating [17]. This circuitry involves the mesolimbic dopamine system, running from the ventral tegmental area to the nucleus accumbens (NAcc). The brain structures involved are connected with the hypothalamic homeostatic feeding network [14,17]. Of note, higher order cognition in humans is also involved in the control of energy metabolism. Brain areas, as the amygdala, hippocampus, and prefrontal cortex, affect the processes described in the hypothalamus and mesolimbic system [15,18].

The dysregulation in metabolism is not the only factor contributing to the development of obesity in patients with hypothalamic dysfunction. In search for new treatments, an understanding of all clinical factors contributing to HO is important [18]. In a systematic review of Van Iersel et al. [18] for patients with acquired HO, these factors have been subdivided into six domains: psychosocial disorders, hyperphagia, sleep disturbances, decreased energy expenditure, hyperinsulinemia, and hypopituitarism. In particular, hyperphagia can be extreme and hard to control [18]. In 57% of patients with CP, neurobehavioral dysfunction is present [19]. The behavioral disorders can consist of disrupted impulse-control, aggressiveness, and episodic rage. Hyperphagia and neurobehavioral dysfunction combined can result in irresistible food cravings, overeating, and food stealing [20]. The symptoms of neurobehavioral dysfunction in these patients show similarities with those seen in patients with obsessive-compulsive disorders (OCD). Moreover, some of the patients with hypothalamic dysfunction and HO also show non-food related compulsive behavior, such as compulsive buying [21]. Also, in PWS obsessive-compulsive behavior is often observed and these patients show some overlap with patients with OCD in functional brain imaging alterations [22].

Currently, no therapy has been convincingly proven to be effective for HO, and hence new treatment options should be explored [18,23]. Lifestyle interventions and pharmacotherapy have not shown satisfying results and were either not effective or were only able to stabilize or marginally reduce the body mass index (BMI) increase in most cases [18,23]. Bariatric surgery appeared most effective, but has a high rate of relapse on the long term and has its ethical concerns among children [16,18,23]. Deep brain stimulation (DBS) is a treatment that has been explored for obesity, as well as for patients with OCD and treatment-resistant neurobehavioral disorders. For this reason, we hypothesize that DBS may be worth exploring for as treatment solution for acquired HO.

A DBS device consists of a subcutaneously placed pulse generator (on the chest wall) connected to electrodes implanted in specific targets within the brain. After DBS implantation, clinicians use a computer to communicate with the implantable pulse generator transcutaneously to set the stimulation parameters. The characteristics of the electric current such as pulse width, frequency, and amplitude, can be adjusted to each individual. The mechanism of action of DBS is not completely understood. The electrodes produce electrical impulses that can affect certain cells and chemicals within the brain. In theory, the electric current generated is thought to depolarize axons, which can lead to excitation or inhibition of neurons in the targeted area [24]. In this way, the pathological activity leading to the respective disorder can be counteracted.

There is a small number of adult cases in which DBS has been used as a treatment for obesity [17,25]. In these cases ($n = 16$), DBS was shown to be potentially effective with a reduction of body weight in almost half of the individuals ($n = 7$) with mostly minor side effects [17]. As opposed to DBS for obesity, DBS for OCD has been widely applied to patients already. It has been shown to be an effective therapy for treatment-resistant OCD and is generally well tolerated [26]. For other treatment-resistant neurobehavioral disorders, such as addiction, anorexia nervosa, and aggressiveness, disorders that show similarities in expressed behavior when compared to HO, DBS has been used as experimental therapy with limited, but promising results [27,28]. We aimed to perform a systematic search to examine the effect of DBS on HO in patients with congenital or acquired hypothalamic dysfunction.

2. Methods

A systematic search was performed in three databases: PubMed, Embase, and Cochrane Central. Search terms concerning the domain (HO) and determinant (DBS) of the research question were identified and synonyms were included. An overview of the search strategy can be found in Supplemental Table 1. Inclusion criteria involved the use of DBS and human participants with hypothalamic dysfunction resulting in HO. Duplicates found in the complete search were removed manually. Title and abstract screening was performed by two reviewers (AD and JvS) independently using Rayyan. Discussion between the reviewers took place whenever there were discrepancies in the inclusion or exclusion of articles. If no consensus was reached, a third reviewer (HvS) was consulted. References of relevant articles and reviews found during screening were studied for possible inclusion. Of the included full text papers, data was extracted. Risk of bias assessment was performed using the Cochrane risk of bias assessment tool for RCTs if applicable. For

nonrandomized studies, the Risk of Bias in Nonrandomized Studies of Interventions tool was used [29]. Uncontrolled observational studies and case reports/series were a priori considered to be at very serious risk of bias. Due to the low number of retrieved studies, no meta-analysis was performed, but results were descriptively summarized.

3. Results

3.1. Study selection

In total, 197 papers could be identified through the database search by May 2022 with two additional records identified through backward tracking of references of the identified articles (see flow diagram in Fig. 1). After duplicate removal, 127 papers were screened on title and abstract, leaving 18 articles for a full-text screening. Full-text papers were excluded for the following reason: the patient population did not fit the domain (n = 15), mostly because there was no description of hypothalamic damage and/or dysfunction in the patients. Finally, three studies were included.

3.2. Study characteristics

The identified studies included one non-randomized trial and two case reports, with in total a population of six patients. The population in these studies consisted of patients with HO, due to either PWS or CP. Age at DBS ranged between 18 and 28 years, median BMI was 35.1 kg/m^2, and median follow-up time was 6.0 months [range: 6.0 – 14.0] (n = 5). DBS had been targeted to the LHA (n = 5) or the NAcc (n = 1). Overall, of six patients, only the patient who developed HO after CP treatment lost weight. A description of the studies and their outcomes on BMI, hyperphagia, food-related behavior, and adverse events can be found in Table 1.

3.3. Effect of DBS on BMI in patients with hypothalamic obesity

Franco et al. [30] included four patients, aged 18–28 years, with PWS and severe obesity in an open-label non-randomized clinical trial for DBS to the LHA bilaterally. All patients suffered from psychiatric comorbidities, including skin picking, aggressive behavior,

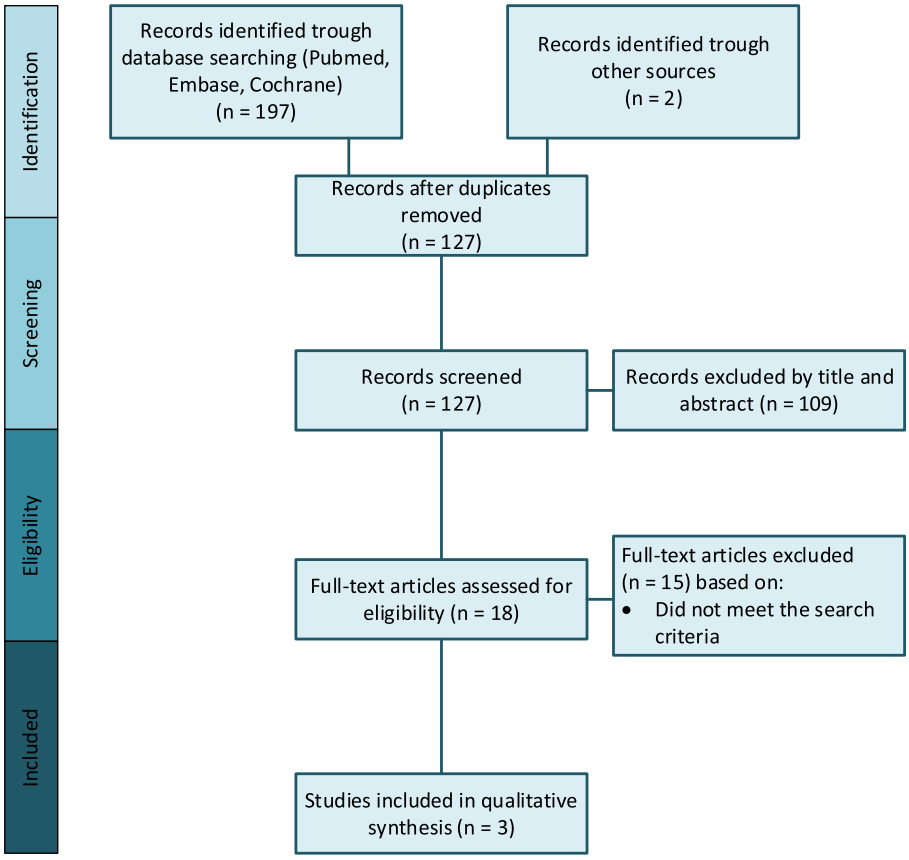

Fig. 1. Flowchart of study selection for deep brain stimulation in hypothalamic obesity. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The Prisma Statement.

Table 1
Descriptive characteristics of studies applying deep brain stimulation in hypothalamic obesity.

References	Study population	N	Age [range] (y)	DBS target	DBS parameters	Total follow-up duration	Main results	Adverse events (N)
Franco et al., 2018[29]	PWS with severe obesity	4	[18-28]	LHA (bilateral)	Low frequency: 3 mA, 210 μsec, 40 Hz High frequency: 2 mA, 91 μsec, 130 Hz	DBS off period: 4 – 5.5 months LFS: 1 month HFS: 1 month Follow-up with HFS or LFS: 6 months	- Mean +9.6% increase in weight (compared to baseline) - Mean +5.8% increase in BMI (compared to baseline) - Mean 0% change in calorimetry compared with baseline. Individual changes from 6 months of follow-up compared to baseline (weight/BMI): - ID 1: +2.9%/−7.1% - ID 2: +28.2%/+28.3% - ID 3: +3.7%/+3.7% - ID 4: +7.0%/+6.8% - Hormonal levels, results of blood workup, sleep studies, and neuropsychological evaluation remained unchanged.	Manic symptoms (2), infections (2), priapism (1)
Talakoub et al., 2017[30]	PWS with severe obesity	1	19	LHA (bilateral)	Low frequency: 3 V, 90 μsec, 8 Hz	N/A	The patient experienced a sensation of fullness, but continued craving for food. No change in pattern/amount of food consumption.	N/A
Harat et al., 2016[31]	CP-patient with severe obesity	1	19	NAcc (bilateral)	Low frequency: 3.75 mA, 208 μsec, 30 Hz	14 months	−8.7% BMI, −8.9% weight. Patient reported feeling better, more energy and willingness to act. No increased appetite nor increased need for food.	None

Abbreviations: PWS = Prader-Willi syndrome CP = craniopharyngioma; LHA = lateral hypothalamic area; NAcc = nucleus accumbens; BMI = body mass index; LFS = low frequency stimulation; HFS = high frequency stimulation; N/A = not available.

and hypomania. These comorbidities were reported as being well controlled with medication. Two of the patients were noted to have hyperphagia. At the start of the stimulation period, the parameters (amplitude, pulse width, and frequency) were titrated for one to two months, based on hunger or weight changes. Following titration, DBS was turned off for 1–2 months. Thereafter, first low frequency stimulation (LFS) (3 mA, 210 μsec, 40 Hz) and then high frequency stimulation (HFS) (2 mA, 91 μsec, 130 Hz) were applied for one month each with a 15 days wash-out period in between. After these phases, the optimal settings were selected for each patient dependent on subjective reports by caregivers (no standardized methods were reported). A six month period of chronic DBS followed with these preferred settings, which consisted of HFS for patient 1 and LFS for the other three patients. By the end of the follow-up, one of the participants had a decrease in BMI of −7.1%, the other three participants had an increase in BMI of +3.7%, +6.8%, and +28.3%. Pre-operative BMI and weight trends were not described, only anthropometric data from the start of the trial until after the period of surgery + titration + DBS off phase (first 4.0 – 5.5 months, reported as 'DBS off'), the LFS phase, the HFS phase, and six months of follow-up are available. Patient 1 had an increase in weight compared to baseline during these phases of: +0.4% (DBS off), +0.7% (LFS), +0.4% (HFS), and +2.9% (six months of follow-up). However, BMI decreased during these phases from 56 kg/m^2 to eventually 52.0 kg/m^2 (−7.2%). Patient 2 had an increase in weight with +13.2%, +6.7%, +16.7%, +28.2% (all compared to baseline), respectively. Her BMI fluctuated in a similar pattern. Patient 3 increased in weight in the DBS off period with +1.7%, and in the LFS phase with +3.4%, and remained stable in the HFS and six months of follow-up phase (both +3.7% compared to baseline) with similar changes in BMI. The last patient increased in weight with +3.4%, +1.3%, +5.2%, and +7.0%, respectively compared to baseline. Aside from the DBS off period, her BMI changed according to her weight. The calorimetry changes reported ranged from −5.6% to +6.7% at 6 months follow-up compared to baseline. Franco et al. concluded that at 6 months of follow-up of chronic DBS, patients had a mean of +9.6% [range: 3.7% – 28.2%] increase in weight, +5.8% [range −7.1% – 28.3%] increase in BMI, +8.4% [range: 0.7% – 19.4%] increase in abdominal circumference, +4.2% [range: 2.3% – 15.6%] increase in neck circumference, +5.3% [range 2.9% – 8.0%] increase in the percentage of body fat, and 0% [range: 5.6 – 6.7%] change in calorimetry compared to baseline. In addition, no changes in hormonal levels, results of blood workup, sleep studies, and neuropsychological evaluations were reported. However, in the supplementary data, changes in some blood parameters can be observed, including an increase in FSH (+21.7 U/L) and LH (+5.9 U/L) in patient 1, a reduction in testosterone of 70 ng/dL in patient 3 (had a similar hormonal variability pre-trial), an increase in prolactin of 67.2 ng/ml in patient 4, increased cholesterol (+17 mg/dL) and low-density lipoprotein (+36 mg/dL) in patient 3, a decrease of cholesterol in patient 2 (−48 mg/dL) and 4 (−38 mg/dL), and a decrease of low-density lipoprotein in patient 4 (−39 mg/dL). Outcomes regarding food-related behavior, hyperphagia, or neurobehavioral function were not reported.

Talakoub et al. [31] also studied DBS to the LHA in a patient with PWS, aged 19 years, with severe obesity (BMI: 33 kg/m^2). Based on local field potentials recorded during experiments with food related pictures in a hungry and sated state, the patient received low frequency DBS in the range of alpha rhythms measured at the hypothalamus when sated (3 V, 90 μsec, 8 Hz). During stimulation, the patient described a sensation of fullness, while having a continued craving for food. No differences in the pattern or amount of food

consumed were noticed during stimulation. Follow-up time or duration of the stimulation were not reported, neither were changes in BMI, neuropsychological assessments, or adverse events.

The third identified study by Harat et al. [32], performed DBS to the NAcc bilaterally in a 19-year old woman with HO after CP. The patient had a BMI of 52.9 kg/m^2 at baseline and was experiencing weight gain. The authors described her as "craving for food like an addict for drugs", probably referring to the severe hyperphagia, as observed in patients with HO. Parameter adjustments of the device eventually led to stimulation of 3.75 mA, 208 μsec, and 30 Hz, classified as low-frequency DBS. At the end of the 14 months follow-up the patient had a BMI of 48.3 kg/m^2, hence a change in BMI of −4.6 kg/m^2. The absolute weight loss was 13.4 kg over the 14 months. Her BMI fluctuated during the study to a lowest point of 46.2 kg/m^2 at three months follow-up. The authors reported that the stimulation pacemaker was accidentally switched off at times, which potentially caused the fluctuations in weight. Considering the patients behavior and emotional state, the patient subjectively reported to feel better, to have more energy and willingness to act, and to have no feelings of increased appetite. No objective measurements on neurobehavioral function were reported.

3.4. Adverse events

In the study by Franco et al. [30], adverse events of DBS included hypomanic symptoms in two patients and two cases of infection. For the hypomanic symptoms, one patient improved after turning off the DBS, and the other one required an increase in medication. Concerning the infections, one patient suffered from a postoperative skin infection, which was adequately treated with antibiotics. Another patient developed an infection over the connector site seven months after surgery, which was likely to be due to skin picking. One patient received preoperative testosterone injections for hypogonadism, which lead to an episode of priapism during the study. In the study of Talakoub et al. [31], no adverse events were reported. In the study of Harat et al. [32], no major adverse events were reported. During episodes of weight gain in the study, the patient reported a slight increase on the Beck Depression Inventory, which the authors described as not significant. The patient had a history of mild depression, as supported by the neuropsychological test before electrode implantation. Cognitive performance as assessed by neuropsychological testing stayed intact during DBS stimulation.

4. Discussion

Due to the severe impact that hypothalamic dysfunction may have on the quality of life of patients, and the fact that no effective treatment is yet available, new treatment strategies must be considered. DBS may be an interesting new treatment for HO, as well as for the neuropsychological behavioral problems in patients with (acquired) hypothalamic dysfunction. We aimed to summarize all literature, however, we found the reports on DBS performed in patients with HO to be extremely scarce. The three studies included in our review showed varying results and included only low patient numbers. The adverse events seem to be limited with four non-severe adverse events and five out of five patients with follow-up data sustaining treatment for at least 6 months. Taking the impact of HO and the severity of the condition into consideration, safety of DBS seems reasonable. It can be argued whether the observed weight increase in the patients with PWS in the study of Franco et al. [30] should be regarded as adverse event. This should be evaluated in the context of possible weight fluctuations before starting DBS treatment, which, unfortunately, was not taken into account. Regarding the effectiveness of DBS, results are questionable, especially for patients with PWS. Only in the single case of NAcc-DBS in a patient with CP, a reduction in weight was observed [32], and for such patients the effectivity of DBS may be worthwhile further exploring. Overall, due to the limited number of reports, we must be careful to draw conclusions. Larger studies are needed to evaluate the safety and effectivity of DBS as treatment for HO.

The patient with CP receiving NAcc-DBS with promising results, showed a decrease in her BMI during DBS treatment, but her BMI was far from normalized by the end of the 14-months of follow-up [32]. Importantly however, she experienced a positive change in emotional state, attitude, and appetite. Oppositely, during LHA-DBS performed in patients with PWS by Franco et al. [30], DBS led to an increase in mean BMI, although no comparison was made with velocity of BMI increase before DBS. Besides, only weight and BMI changes after each phase (DBS off, LFS, HFS, and six months of follow-up) compared to baseline were reported and these changes were not corrected for the duration of each phase. It must, however, be noted that patient 1, the only patient with high-frequency DBS during the 6-months chronic stimulation, had a decrease in BMI in all phases. In contradiction, her weight increased during this time. This suggests incorrect measurements or that this patient grew in length during the trial period and had a relatively better BMI by the end of the follow-up. Patient 2 had a decrease in velocity of BMI increase during the trial period (calculated from the available data: average BMI increase of 0.8 – 1.1 kg/m^2 per month in the DBS off phase, and average increase of 0.6 kg/m^2 per month in the follow-up phase). Patient 3 had a stable BMI in the HFS period and the six months of chronic DBS phase. Patient 2 and 3 both had a decrease in calorimetry outcome. A possible effect in these patients may thus have been present, although this was not described as such by the authors. Further studies should take change in velocity of BMI increase into account, describe the effects on patient level, and correct for the duration between anthropometric measurements. In addition, Franco et al. [30] performed measurements on blood parameters and hormone levels, in which they did not find significant consistent changes. When reading the raw data, some individual changes appear. However, with data of only four patients and many other factors that can influence this data, such as menstrual cycle, time of day when blood was taken, and activity, no conclusions can be drawn. In the single patient with PWS receiving LHA-DBS by Talakoub et al. [31] no BMI records were reported, but the patient experienced an increased sensation of fullness, while still craving for food. Unfortunately, the three studies reported in our review, did not objectively measure food intake, hyperphagia, or neurobehavorial function. It remains largely unclear whether the weight changes observed were the result of a lower caloric intake, a higher metabolic rate, more physical activity, or other factors. New studies should take objective measurements, using standardized questionnaires.

It may be questioned whether the results of DBS in the patient with CP may be compared to the results of the studies in patients with

PWS, because the etiology of HO associated with suprasellar tumors is different than in patients with PWS. PWS is a rare and complex disorder, with a genetic cause [33], resulting in different neurologic and endocrine challenges [33,34]. Children with PWS present with feeding difficulties in the first years of life, after which around the first 2–3 years weight gain occurs, with later on the development of hyperphagia and a lack of satiety around the age of eight years [33]. On the contrary, HO in patients with suprasellar tumors arises due to direct damage caused by the tumor or its treatment. Hence, HO in these patients arises later in life and the problem can be localized to a particular brain area. It may be hypothesized that this difference in etiology makes patients with a history of suprasellar tumors with HO more suitable for DBS therapy than patients with PWS. The second important difference between the studies are the DBS targets that have been used; in the patients with PWS, the LHA was chosen for stimulation, while in the patient with CP, the NAcc was used as DBS-target. Interestingly, a small study on functional magnetic resonance imaging in patients with CP showed higher activation in the insula, NAcc, and medial orbitofrontal cortex in response to food images after food intake, while controls showed suppression of activation in these areas [35].

In this review, only patients with PWS were described with LHA-DBS, while it might be worthwhile exploring LHA-DBS in patients with CP with HO, since they have a specific locus that is damaged. Also based on clinical experience with DBS in other disorders, the site of the dysfunctioning area might be a promising DBS target for acquired HO. However, it is important to realize that the anatomy of the hypothalamic region in patients with CP may not be intact and for this reason a hypothalamic target may be hard to identify. In these cases, targets outside the hypothalamic region may be preferred, such as the NAcc/ALIC. In patients with general obesity or other neurobehavioral disorders, such as OCD and addiction, some positive effects have been found when targeting this specific area with DBS [17,26–28,36–39]. Therefore, further research focusing on optimal target selection is needed.

DBS has also been described as optional treatment for general obesity, but as previously mentioned, just in a very selected group of patients. Although etiology differs between HO and general obesity, there are indications that hypothalamic inflammation and the thereby caused distortion in neuronal signaling in homeostatic regulation may play a role in general obesity [40]. This hypothalamic inflammation has been shown to be triggered by a high fat diet and can precede the excessive weight gain seen in obesity [40], thus providing a theoretic framework for targeting the dysregulated neuronal circuits using interventions as DBS [17]. In recent review papers, 10 general obesity cases were described, who received DBS targeted to either the VMH, the LHA, or the NAcc [17,25]. Eight of these patients experienced weight loss during DBS therapy. DBS to the VMH was performed in two patients using different parameters of the stimulation (frequency, pulse width, amplitude) [17]. In one of the cases, bilateral low-frequency DBS resulted in weight loss (12 kg/5 months) and decreased food cravings [41]. However, due to sleeping problems this patient regained the weight after switching the DBS off at night. The other patient with VMH-DBS had a panic attack during electrode implantation, which lead to cessation of the treatment [42]. In three cases of general obesity, who received bilateral high-frequency DBS targeted to the LHA, body weight reduced during the trial in two out of three patients (18.1 kg and 26.7 kg reduction). In the third patient, binge eating behaviors reduced after 35 months of follow-up [43]. DBS targeting the NAcc has been conducted in five cases with obesity, which were reported in two separate case reports and one small clinical trial [44–46]. The treatment with bilateral high-frequency NAcc-DBS seemed to be effective in all cases, since all had a decrease in body weight, ranging from approximately 32 kg to 45 kg weight loss. However, two patients did not finish the trial of Rezai et al. [46]: one patient requested removal of the device after 13 months follow-up (the reason was not reported), the other patient died by suicide after 27 months of follow-up. Both incidents were reported as not being related to the trial. All three patients in this specific trial had psychiatric comorbidities and experienced major stressors during the study. In these general obesity cases DBS was found to have mostly minor side effects, often disappearing by changing the settings of the stimulator. However, the reported psychiatric exacerbations draw attention to the fact that patient selection and monitoring should be carefully performed regarding psychiatric comorbidities.

Taking the results in HO and non-HO patients together, we conclude that DBS targeted to the hypothalamus or the NAcc may be effective in patients without PWS. Nevertheless, only limited conclusions can be drawn from the described studies, since they included different populations with various comorbidities, different DBS settings, varying follow-up periods, and confounding factors, such as a simultaneous lifestyle interventions.

DBS has given encouraging results for other neurobehavioral disorders and eating disorders. DBS is effectively used in selected patients with treatment-refractory OCD, using various brain targets: the anterior limb of the internal capsule (ALIC), subthalamic nucleus, NAcc/nucleus caudatus, ventral capsule/ventral striatum, and the bed nucleus of the stria terminalis [26,28]. New experimental targets for OCD include the inferior thalamic peduncle and the medial forebrain bundle [27]. There is limited evidence for DBS efficacy in addiction, with DBS targeted to the NAcc or ALIC inducing abstinence for several years in on average 50% of patients [27,28,36,37]. For aggressive behavior treatment, there seems to be potential for DBS of the posterior part or the posteromedial area of the hypothalamus, mainly in those with intellectual disability [27,47]. Considering anorexia nervosa, results of case series and small trials are encouraging. High frequency DBS to the ventral striatum and the NAcc, or solely to the subgenual cingulate cortex, have resulted in BMI increase (and improved psychiatric symptoms) in half of the patients [27,38,39]. DBS in bulimic disorders has only been used in a few cases, targeted to the LHA or the NAcc [38]. This resulted in two out of four cases in reduced binge eating. Overall, DBS has been considered to be a safe treatment of the described psychiatric disorders [17,26–28,36–38,47].

In summary, this review illustrates the scarcity of knowledge on DBS for (acquired) HO. DBS for patients with PWS showed low potential, however, DBS with hypothalamic targets as well as the NAcc/ALIC showed encouraging effects in acquired obesity and other neurobehavioral and eating disorders. Regarding the great morbidity and mortality in the most severe cases of HO and the lack of treatment possibilities, a future trial in which DBS treatment will be explored in patients with severely treatment-refractory acquired HO would be interesting. In such a trial, we would suggest a period of low-frequency DBS titration, a wash-out period, and a period of high-frequency DBS titration. Patients with relatively intact hypothalamic anatomy may be suitable to receive DBS targeted to the hypothalamus, while for patients where the hypothalamic areas cannot be identified the NAcc/ALIC could be used as DBS target. After

these initial phases, we would propose a longer follow-up period in which patient-tailored stimulation takes place. This set-up allows for selection of the optimal DBS settings for each individual participant and can give more insights on the effects of low and high frequency stimulation. During such a trial, in addition to DBS, a standardized lifestyle and cognitive-behavioral intervention should be initiated, as is standard of care in our medical centers, to optimize clinical outcomes of these patients.

5. Conclusion

This review summarized the data available on DBS treatment in patients with HO. The studies are scarce with only six cases described. No clear effect was observed of LHA-DBS in patients with PWS, although some effects on patient level may be questioned. In one patient with CP, NAcc-DBS was associated with weight loss and positive effects on mental health. The effects of the studies discussed above, together with the relative safety, and the information available from DBS in other (neurobehavioral) disorders, make it interesting to consider future studies in this patient group on the possible positive effects of DBS. There is an urgent need for new treatment options in patients with severe hypothalamic dysfunction, and perhaps a future solution may lay in offering DBS treatment to a selected group of patients.

Production notes

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

No data was used for the research described in the article.

Declaration of interest's statement

The authors declare no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e14411.

References

[1] H.L. Müller, G. Bruhnken, A. Emser, et al., Longitudinal study on quality of life in 102 survivors of childhood craniopharyngioma, Childs Nerv. Sys. 21 (11) (2005) 975–980. https://doi-org.proxy.library.uu.nl/10.1007/s00381-004-1124-y.

[2] R.H. Lustig, S.R. Post, K. Srivannaboon, et al., Risk factors for the development of obesity in children surviving brain tumors, J. Clin. Endocrinol. Metab. 88 (2) (2003) 611–616. https://doi-org.proxy.library.uu.nl/10.1210/jc.2002-021180.

[3] H.L. Müller, U. Gebhardt, A. Faldum, et al., Xanthogranuloma, Rathke's cyst, and childhood craniopharyngioma: results of prospective multinational studies of children and adolescents with rare sellar malformations, J. Clin. Endocrinol. Metab. 97 (11) (2012) 3935–3943. https://doi-org.proxy.library.uu.nl/10.1210/jc.2012-2069.

[4] A. Bereket, W. Kiess, R.H. Lustig, et al., Hypothalamic obesity in children, Obes. Rev. 13 (9) (2012) 780–798. https://doi-org.proxy.library.uu.nl/10.1111/j.1467-789X.2012.01004.x.

[5] I. Hochberg, Z. Hochberg, Expanding the definition of hypothalamic obesity, Obes. Rev. 11 (10) (2010) 709–721. https://doi-org.proxy.library.uu.nl/10.1111/j.1467-789X.2010.00727.x.

[6] K.W. Wang, A. Fleming, D.L. Johnston, et al., Overweight, obesity and adiposity in survivors of childhood brain tumours: a systematic review and meta-analysis, Clin. Obes. 8 (1) (2018) 55–67, https://doi.org/10.1111/cob.12224.

[7] S. Yano, M. Kudo, T. Hide, et al., Quality of life and clinical features of long-term survivors surgically treated for pediatric craniopharyngioma, World Neurosur.g 85 (2016) 153–162, https://doi.org/10.1016/j.wneu.2015.08.059.

[8] H.L. Müller, A. Emser, A. Faldum, et al., Longitudinal study on growth and body mass index before and after diagnosis of childhood craniopharyngioma, J. Clin. Endocrinol. Metab. 89 (7) (2004) 3298–3305. https://doi-org.proxy.library.uu.nl/10.1210/jc.2003-031751.

[9] D.S. Olsson, E. Andersson, I. Bryngelsson, A.G. Nilsson, G. Johannsson, Excess mortality and morbidity in patients with craniopharyngioma, especially in patients with childhood onset: a population-based study in Sweden, J. Clin. Endocrinol. Metab. 100 (2) (2015) 467–474. https://doi-org.proxy.library.uu.nl/10.1210/jc.2014-3525.

[10] H. Holmer, B. Ekman, J. Björk, et al., Hypothalamic involvement predicts cardiovascular risk in adults with childhood onset craniopharyngioma on long-term GH therapy, Eur. J. Endocrinol. 161 (5) (2009) 671–679. https://doi-org.proxy.library.uu.nl/10.1530/EJE-09-0449.

[11] S. Srinivasan, G.D. Ogle, S.P. Garnett, J.N. Briody, J.W. Lee, C.T. Cowell, Features of the metabolic syndrome after childhood craniopharyngioma, J. Clin. Endocrinol. Metab. 89 (1) (2004) 81–86. https://doi-org.proxy.library.uu.nl/10.1210/jc.2003-030442.

[12] A.S. Sterkenburg, A. Hoffmann, U. Gebhardt, M. Warmuth-Metz, A.M.M. Daubenbüchel, H.L. Müller, Survival, hypothalamic obesity, and neuropsychological/psychosocial status after childhood-onset craniopharyngioma: newly reported long-term outcomes, Neuro Oncol. 17 (7) (2015) 1029–1038. https://doi-org.proxy.library.uu.nl/10.1093/neuonc/nov044.

[13] B. Bülow, R. Attewell, L. Hagmar, P. Malmström, C. Nordström, E.M. Erfurth, Postoperative prognosis in craniopharyngioma with respect to cardiovascular mortality, survival, and tumor recurrence, J. Clin. Endocrinol. Metab. 83 (11) (1998) 3897–3904. https://doi-org.proxy.library.uu.nl/10.1210/jcem.83.11.5240.

[14] G.J. Morton, T.H. Meek, M.W. Schwartz, Neurobiology of food intake in health and disease, Nat. Rev. Neurosci. 15 (6) (2014) 367–378. https://doi-org.proxy.library.uu.nl/10.1038/nrn3745.

[15] K. Timper, J.C. Brüning, Hypothalamic circuits regulating appetite and energy homeostasis: pathways to obesity, Dis. Model Mech. 10 (6) (2017) 679–689. https://doi-org.proxy.library.uu.nl/10.1242/dmm.026609.

[16] M.J. Abuzzahab, C.L. Roth, A.H. Shoemaker, Hypothalamic obesity: prologue and promise, Horm. Res. Paediatr. 91 (2) (2019) 128–136, https://doi.org/10.1159/000496564.

[17] D.A. Formolo, J.M. Gaspar, H.M. Melo, et al., Deep brain stimulation for obesity: a review and future directions, Front. Neurosci. 13 (2019) 323, https://doi.org/10.3389/fnins.2019.00323.

[18] L. Van Iersel, K.E. Brokke, R.A.H. Adan, L.C.M. Bulthuis, E.L.T. Van Den Akker, H.M. Van Santen, Pathophysiology and individualized treatment of hypothalamic obesity following craniopharyngioma and other suprasellar tumors: a systematic review, Endocr. Rev. 40 (1) (2019) 193–235. https://doi-org.proxy.library.uu.nl/10.1210/er.2018-00017.

[19] G. Zada, N. Kintz, M. Pulido, L. Amezcua, Prevalence of neurobehavioral, social, and emotional dysfunction in patients treated for childhood craniopharyngioma: a systematic literature review, PLoS One 8 (11) (2013), e76562, https://doi.org/10.1371/journal.pone.0076562.

[20] A. Skorzewska, S. Lal, J. Waserman, H. Guyda, Abnormal food-seeking behavior after surgery for craniopharyngioma, Neuropsychobiology 21 (1) (1989) 17–20, https://doi.org/10.1159/000118545.

[21] O. Iizuka, K. Suzuki, E. Mori, Severe amnesic syndrome and collecting behavior after surgery for craniopharyngioma, Cognit. Behav. Neurol. 20 (2) (2007) 126–130, https://doi.org/10.1097/WNN.0B013E31804C6FB8.

[22] J. Pujol, L. Blanco-Hinojo, S. Esteba-Castillo, et al., Anomalous basal ganglia connectivity and obsessive-compulsive behaviour in patients with Prader Willi syndrome, J. Psychiatry Neurosci. 41 (4) (2016) 261–271, https://doi.org/10.1503/jpn.140338.

[23] K.W. Wang, R. Chau, A. Fleming, et al., The effectiveness of interventions to treat hypothalamic obesity in survivors of childhood brain tumours: a systematic review, Obes. Rev. 18 (8) (2017) 899–914. https://doi-org.proxy.library.uu.nl/10.1111/obr.12534.

[24] D.J. Aum, T.S. Tierney, Deep brain stimulation: foundations and future trends, Front. Biosci. 23 (1) (2018) 162–182, https://doi.org/10.2741/4586.

[25] F.V. Gouveia, E. Silk, B. Davidson, et al., A systematic review on neuromodulation therapies for reducing body weight in patients with obesity, Obes. Rev. 22 (10) (2021), e13309. https://doi-org.proxy.library.uu.nl/10.1111/obr.13309.

[26] P. Vicheva, M. Butler, P. Shotbolt, Deep brain stimulation for obsessive-compulsive disorder: a systematic review of randomised controlled trials, Neurosci. Biobehav. Rev. 109 (2020) 129–138, https://doi.org/10.1016/j.neubiorev.2020.01.007.

[27] J.A. Beszłej, T. Wieczorek, A. Kobyłko, et al., Deep brain stimulation: new possibilities for the treatment of mental disorders, Psychiatr. Pol. 53 (4) (2019) 789–806, https://doi.org/10.12740/PP/OnlineFirst/103090.

[28] M. Ranjan, N. Ranjan, M. Deogaonkar, A. Rezai, Deep brain stimulation for refractory depression, obsessive-compulsive disorder and addiction, Neurol. India 68 (8) (2020) 282–287, https://doi.org/10.4103/0028-3886.302459.

[29] J.A. Sterne, M.A. Hernán, B.C. Reeves, et al., ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions, BMJ 355 (2016) i4919, https://doi.org/10.1136/bmj.i4919.

[30] R.R. Franco, E.T. Fonoff, P.G. Alvarenga, et al., Assessment of safety and outcome of lateral hypothalamic deep brain stimulation for obesity in a small series of patients with Prader-Willi Syndrome, JAMA Netw. Open 1 (7) (2018), e185275, https://doi.org/10.1001/jamanetworkopen.2018.5275.

[31] O. Talakoub, R.R. Paiva, M. Milosevic, et al., Lateral hypothalamic activity indicates hunger and satiety states in humans, Ann. Clin. Trans. Neur. 4 (12) (2017) 897–901. https://doi-org.proxy.library.uu.nl/10.1002/acn3.466.

[32] M. Harat, M. Rudaś, P. Zieliński, J. Birska, P. Sokal, Nucleus accumbens stimulation in pathological obesity, Neurol. Neurochir. Pol. 50 (3) (2016) 207–210, https://doi.org/10.1016/j.pjnns.2016.01.014.

[33] M.A.F. Gutierrez, M.D. Mendez, Prader-Willi Syndrome, StatPearls Publishing, 2020. *StatPearls [Internet]*.

[34] M.J. Khan, K. Gerasimidis, C.A. Edwards, M.G. Shaikh, Mechanisms of obesity in prader–Willi syndrome, Pediatr. Obes. 13 (1) (2018) 3–13. https://doi-org.proxy.library.uu.nl/10.1111/ijpo.12177.

[35] C.L. Roth, E. Aylward, O. Liang, N.M. Kleinhans, G. Pauley, E.A. Schur, Functional neuroimaging in craniopharyngioma: a useful tool to better understand hypothalamic obesity? Obesity facts 5 (2) (2012) 243–253, https://doi.org/10.1159/000338695.

[36] P.A. Navarro, T. Paranhos, E. Lovo, et al., Safety and feasibility of nucleus accumbens surgery for drug addiction: a systematic review, Neuromodulation 25 (2) (2022) 171–184. https://doi-org.proxy.library.uu.nl/10.1111/ner.13348.

[37] O. Hassan, S. Phan, N. Wiecks, C. Joaquin, V. Bondarenko, Outcomes of deep brain stimulation surgery for substance use disorder: a systematic review, Neurosurg. Rev. 44 (4) (2021) 1967–1976. https://doi-org.proxy.library.uu.nl/10.1007/s10143-020-01415-y.

[38] P. Duriez, R. Bou Khalil, Y. Chamoun, et al., Brain stimulation in eating disorders: state of the art and future perspectives, J. Clin. Med. 9 (8) (2020) 2358, https://doi.org/10.3390/jcm9082358.

[39] M.S. Oudijn, R. Mocking, R.R. Wijnker, et al., Deep brain stimulation of the ventral anterior limb of the capsula interna in patients with treatment-refractory anorexia nervosa, Brain Stimul. 14 (6) (2021) 1528–1530, https://doi.org/10.1016/j.brs.2021.10.387.

[40] J. Seong, J.Y. Kang, J.S. Sun, K.W. Kim, Hypothalamic inflammation and obesity: a mechanistic review, Arch Pharm. Res. (Seoul) 42 (5) (2019) 383–392, https://doi.org/10.1007/s12272-019-01138-9.

[41] C. Hamani, M.P. McAndrews, M. Cohn, et al., Memory enhancement induced by hypothalamic/fornix deep brain stimulation, Ann. Neurol. 63 (1) (2008) 119–123. https://doi-org.proxy.library.uu.nl/10.1002/ana.21295.

[42] W.B. Wilent, M.Y. Oh, C.M. Buetefisch, et al., Induction of panic attack by stimulation of the ventromedial hypothalamus: case report, J. Neurosurg. 112 (6) (2010) 1295–1298. https://doi-org.proxy.library.uu.nl/10.3171/2009.9.JNS09577.

[43] D.M. Whiting, N.D. Tomycz, J. Bailes, et al., Lateral hypothalamic area deep brain stimulation for refractory obesity: a pilot study with preliminary data on safety, body weight, and energy metabolism, J. Neurosurg. 119 (1) (2013) 56–63. https://doi-org.proxy.library.uu.nl/10.3171/2013.2.JNS12903.

[44] M. Mantione, W. Van De Brink, P.R. Schuurman, D. Denys, Smoking cessation and weight loss after chronic deep brain stimulation of the nucleus accumbens: therapeutic and research implications: case report, Neurosurgery 66 (1) (2010) E218. https://doi-org.proxy.library.uu.nl/10.1227/01.NEU.0000360570.40339.64.

[45] V.M. Tronnier, D. Rasche, V. Thorns, D. Alvarez-Fischer, T.F. Münte, B. Zurowski, Massive weight loss following deep brain stimulation of the nucleus accumbens in a depressed woman, Neurocase 24 (1) (2018) 49–53. https://doi-org.proxy.library.uu.nl/10.1080/13554794.2018.1431678.

[46] A.R. Rezai, V. Krishna, J. Bogner, et al., Letter: feasibility of nucleus accumbens deep brain stimulation for morbid, treatment-refractory obesity, Neurosurgery 82 (5) (2018) E136–E137. https://doi-org.proxy.library.uu.nl/10.1093/neuros/nyx630.

[47] C.V. Torres, G. Blasco, M.N. García, et al., Deep brain stimulation for aggressiveness: long-term follow-up and tractography study of the stimulated brain areas, J. Neurosurg. 134 (2) (2021) 366–375. https://doi-org.proxy.library.uu.nl/10.3171/2019.11.JNS192608.