FACULTAD DE MEDICINA
UNIVERSIDAD DE CANTABRIA

GRADO EN MEDICINA

TRABAJO FIN DE GRADO

Depende la eficacia de la estimulación cerebral profunda en la Anorexia Nerviosa de la area cerebral estimulada: Una revisión sistemática y metanálisis de datos de participantes individuales

Does the Efficacy of Deep Brain Stimulation in Anorexia Nervosa depend on the targeted zone: A systematic review and meta-analysis of individual participant data

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Santander, 5 de Junio **20** 22

Acknowledgements

First and foremost, I would like to thank my wife Thaísa. Your constant presence in my life has given me the love and support to get to this point today. I would also like to thank the Faculty of Medicine at the University of Cantabria for giving me the opportunity to undertake my studies at this esteemed university. I will be forever indebted to this wonderful place that has permitted me to become a doctor. My gratitude also goes out to my esteemed supervisor Dr. Alvaro Diaz Martinez for his invaluable insight, and guidance to complete this work. Additionally, I am thankful to Dr. Emilio Garro Martínez for his supervision throughout the project. Last but not least, I would like to thank my parents, Jim and Joan Weinrauch, for the lifetime of love and support you have given me. I am proud of the man I have become and that's all thanks to both of you.

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Abstract:

Background: Deep brain stimulation (DBS), an effective treatment in other psychiatric disorders, is beginning to emerge as an option in anorexia nervosa (AN). Few studies exist on this novel application of DBS, and none have compared the efficacy of different stimulation targets for AN.

Methods: Prisma guidelines were followed to conduct a systematic review and individual patient data meta-analysis. The outcomes measured were postoperative Body Mass Index, YBOCS, and HAMD, which were all analyzed using ANCOVA to look for differences between DBS stimulation targets in AN.

Results: 11 studies were included in the systematic review and 6 provided individual-patient data to be included in the meta-analysis (n= 10 for subcallosal cingulate (SCC), and n= 16 for nucleus accumbens (NAc)). No significant difference in Postoperative BMI was found between SCC or NAc stimulation (p=0.50251). The psychological improvement was significantly different for both YBOCS (0.041811) and HAMD (0.048007) with SCC stimulation shown to be superior to NAc stimulation.

Conclusion: The existing evidence shows both SCC and NAc to be promising DBS targets for AN. Despite no difference found in BMI between them, greater psychological benefits were found for SCC stimulation. Therefore, SCC stimulation should be prioritized over NAc stimulation for future investigations.

Key Words: Deep brain stimulation, Anorexia nervosa, Subcallosal Cingulate, Nucleus Accumbens, Individual patient data Meta-analysis

Resumen:

Introducción: La estimulación cerebral profunda (DBS), un tratamiento efectivo en otros trastornos psiquiátricos, comienza a emerger como una opción en la anorexia nerviosa (AN). Existen pocos estudios sobre esta nueva aplicación de DBS, y ninguno ha comparado la eficacia de diferentes zonas de estimulación de para la AN.

Métodos: Se siguieron las pautas de Prisma para realizar una revisión sistemática y un metaanálisis de datos de pacientes individuales. Los resultados medidos fueron el índice de masa corporal posoperatorio, YBOCS y HAMD, que se analizaron mediante ANCOVA para buscar diferencias entre las zonas de estimulación en AN.

Resultados: 11 estudios se incluyeron en la revisión sistemática y 6 proporcionaron datos de pacientes individuales para incluirlos en el metaanálisis (n = 10 para giro cingulado subcalloso (SCC) y n = 16 para núcleo accumbens (NAc)). No se encontraron diferencias significativas en el IMC posoperatorio entre la estimulación de la zona de SCC o NAc (p = 0,50251). La mejora psicológica fue significativamente diferente tanto para YBOCS (0,041811) como para HAMD (0,048007) y se demostró que la estimulación de la zona de SCC es superior a la estimulación de NAc.

Conclusión: La evidencia existente muestra que tanto SCC como NAc son zonas de estimulación prometedores de DBS para AN. A pesar de que no se encontraron diferencias en el IMC entre ellos, se encontraron mayores beneficios psicológicos para la estimulación SCC. Por lo tanto, la estimulación SCC debe priorizarse sobre la estimulación NAc para futuras investigaciones.

Palabras clave: Estimulación cerebral profunda, Anorexia nerviosa, Giro cingulado subcalloso, Núcleo accumbens, Metaanálisis de datos de pacientes individuales

Title: Does the Efficacy of Deep Brain Stimulation in Anorexia Nervosa depend on the targeted zone: A systematic review and meta-analysis of individual participant data

1. Introduction

According to the DSM-5, anorexia nervosa, is defined an eating disorder with severe restriction of food intake which leads to significantly low body weight for the patient's age, sex, and height together with an intense fear of gaining weight and distorted view of themselves [1]. This is a worldwide problem with lifetime prevalence rates up to 4% in women and 0.3% in men [2], [3], [4]. Anorexia nervosa is notoriously difficult to treat with no specific pharmacological therapies, limiting therapeutic options to only structured care and psychotherapy which result in a failure to produce remission in approximately 50% of patients [5], [6]. This frequent failure of conventional therapy is important as anorexia presents a high risk for morbidity with chronic malnutrition leading to disorders of the gastrointestinal system, liver, heart, and bones [5]. Furthermore, the mortality for patients suffering from anorexia is the highest of all psychiatric illnesses. A recent meta-analysis on the standardized mortality rate found patients suffering from anorexia nervosa were 6 times more likely to die than an individual of the same age in the general population [3].

Due to the inability of current treatment options to successfully control anorexia nervosa in 50% of patients, researchers have sought new approaches to this relevant problem. Beginning with the work of Kaye and colleagues [7], researchers began to develop models of the atypical processing of information derived from the visceral, somatic, and autonomic systems in patients with anorexia nervosa. These advancements were possible due to new imaging studies identifying aberrant brain circuits specific to patients with anorexia and thus thought to be implied in the pathogenesis. This identification coupled with the success of Deep Brain Stimulation (DBS) in the treatment of obsessive-compulsive disorder (OCD) led to investigations on DBS for refractory anorexia nervosa patients [8]. Research groups have particularly focused on two main targets, the subcallosal cingulate (SCC) and the nucleus accumbens (NAc) when attempting to revert anorexia with DBS. The subcallosal cingulate (SCC) began to be targeted by the group led by Lipsman [9] due to the SCC being both structurally and functionally key in modulating emotional response. Functional neuroimaging performed by this group showed dysfunction in the SCC and its efferents that were consistent with the clinical manifestations of anorexia. Thus, implying that this brain circuitry's aberrant emotional response is the predominant driving factor of anorexia. Furthermore, the previous use of DBS in the SCC in major depressive disorder showed this to be a safe and effective target. The nucleus accumbens (NAc) identification as a DBS target for Anorexia largely stemmed from the clinical success of targeting the NAc with DBS [10] in OCD. investigators identified the analogous dysfunctional neurocircuitry and symptomatology of anorexia and OCD, and hypothesized that the NAc could be a viable DBS target in anorexia. Other targets, also implicated in the limbic system, have been reported in case reports but have been utilized on a very limited basis.

Both the subcallosal cingulate and nucleus accumbens have produced positive initial results in non-sham-controlled studies, with almost all trials leading to increases in average body mass index in Anorexic patients. Although this is promising, it should

be noted that few studies with minimal patients have been conducted as of date. This is due to the costs, equipment, and expertise required being limiting factors. Furthermore, a meta-analysis of the efficacy of DBS in Parkinson's disease, which is a very well-established indication of DBS, has shown to be dependent on the target chosen to stimulate [11]. Therefore, it is crucial to identify the DBS target, the SCC or the NAc, most likely to be successful in improving the body mass index in anorexic patients, prior to DBS's implication in larger sham-controlled clinical trials. This meta-analysis of individual participant data will aim to answer this question; if DBS for anorexia patients has shown to be more effective in raising body mass index when implanted in the subcallosal cingulate or the nucleus accumbens.

1.1 Objectives

1.1.1 Primary Objective - Body Mass Index

Determine if Patients diagnosed with Anorexia Nervosa, using the Diagnostic and Statistical Manual of Mental Disorders (DSM), who undergo treatment with Deep Brain stimulation (DBS) have differences in their Postoperative Body Mass index, depending on the location of the target zone of the DBS. The outcome to measure is the change from baseline of the patient's Body Mass Index at the latest follow-up, minimum 1 month.

1.1.2 Secondary objective - Yale–Brown obsessive-compulsive scale

Determine if Patients diagnosed with Anorexia Nervosa, using the Diagnostic and Statistical Manual of Mental Disorders (DSM), who undergo treatment with Deep Brain stimulation (DBS) have differences in the improvement of their symptoms of obsessions and compulsions, depending on the location of the target zone of the DBS. The outcome to measure is the change from baseline of the patient's Yale–Brown obsessive-compulsive scale (YBOCS) at the latest follow up, minimum 1 month.

1.1.3 Secondary objective - Hamilton depression rating scale

Determine if Patients diagnosed with Anorexia Nervosa, using the Diagnostic and Statistical Manual of Mental Disorders (DSM), who undergo treatment with Deep Brain stimulation (DBS) have differences in the improvement of their affect symptomatology, depending on the location of the target zone of the DBS. The outcome to measure is the change from baseline of the patient's Hamilton depression rating scale (HAMD) at the latest follow-up, minimum 1 month.

1.2 Literature review of the pathophysiology of Anorexia Nervosa

Anorexia nervosa is not triggered by a single abnormality in the brain circuitry and instead involves various alterations leading to the clinical manifestations. Imaging technologies such as FDG PET, single-photon emission computed tomography (SPECT), functional MRI (fMRI), and Diffusion magnetic resonance imaging (dMRI) with subsequent tractography, measuring structural connections in the brain, have demonstrated dysfunctional cerebral pathways implicated in sensory processing and reward mechanisms [5], [12]. The consensus among researchers is that the main implicated areas are the limbic system, prefrontal cortex, and cingulate cortex [5], [12]. Individual studies have found specific alterations including overactivation of the insula,

amygdala, hippocampus, hypothalamus, orbitofrontal, and anterior cingulate cortices in response to images of food using fMRI [12], [13]. Further studies that have explored this overactivation found specific hyperactivity of the hypothalamus, orbitofrontal cortex, and the amygdala in response to conscious eating while unconscious calorie intake did not elicit said hyperactivity. This suggests an overactivation of the fear circuitry in response to food stimuli which override hunger signals thus contributing to the food avoidance seen in anorexic patients [14]. These results support the hypothesized model for food avoidance of Castro and colleagues [15] which is derived from animal studies. When animals were unstressed rostral accumbal dopamine D1 receptors, mediating desire and thus being appetite enhancing were activated. Meanwhile, when placed in stressful situation, caudal nucleus accumbens D1 and D2 receptors were activated leading to dread and, producing fearful defensive food avoidance. Based on these findings, coupled with neuroimaging studies showing overactivation of the frontal cortex, this group believes that a fear of weight gain generated in AN patients' frontal cortex invokes a dopamine D1 and D2 receptor-mediated response in the NAc, triggering dread and avoidance. Furthermore, due to it connectivity this subsequently influences the hypothalamus through a Dopamine D1 response to suppress hunger signals leading to food avoidance. The model, Figure 1, which indicates overactivation of these key areas has been supported by various imaging studies in anorexic patients [5], [14], [15].

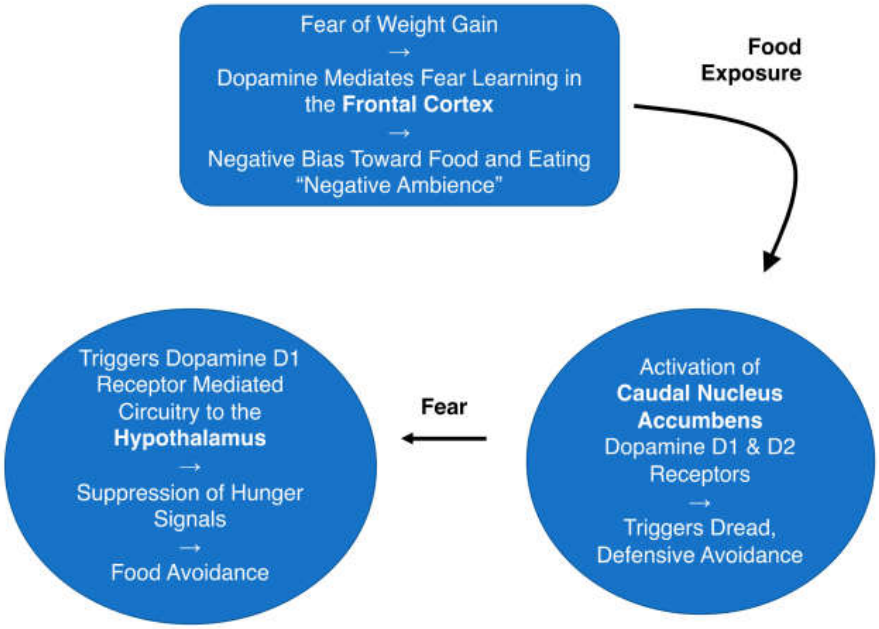

Figure 1. *Castro et al's hypothesized model for Anorexia Nervosa food avoidance. Reproduced from [14] and [15].*

FDG PET imaging studies hypermetabolism in the subcallosal cingulate, left insula, frontal lobe, amygdala, and hippocampus, while showing marked hypometabolism in the parietal and prefrontal lobes thus impacting reward control but also the cognitive control of appetite [12], [13], [16], [17]. This hypoactivity in the parietal lobe has a clinical correlation to the disease's manifestation in distorted body image perception in anorexic patients as the parietal lobe is vital to the visuospatial processing and thus

our construction of self-body image [5], [16]. Furthermore, the subcallosal and subgenual cingulate abnormality can help explain the affective disorders often displayed in anorexic patients as this region is also implicated in major depressive disorder, and OCD [5]. Finally, Wu et al [16] showed the importance of serotonin 5-HT1A and 5-HT1B abnormalities in anorexic patients with their abnormal function in anorexic patients leading to the dysregulation of appetite, mood, and impulse control. As of today, there is no current consensus on the most appropriate DBS target for anorexia due to the various circuits implied in the pathogenesis. Saying that, all current trials aiming to treat anorexia nervosa with deep brain stimulation have focused on 2 key areas; the subcallosal cingulate and the nucleus accumbens due to these areas not only being involved in reward pathways but also important links between the limbic and cortical systems [13], [17]. Furthermore, case reports of improvement in anorexia symptomatology when patients were treated with DBS for a comorbid psychiatric illness, have shown the subgenual cingulate cortex, ventral capsule/ventral striatum, and stria terminalis/medial forebrain bundle (MFB) as potential targets for future trials [5]. Finally, in patients with Parkinson's disease treated with DBS researchers have noted changes in their BMI and eating habits when DBS was placed in the internal globus pallidus, and Subthalamic nucleus to treat the movement disorder [4].

2. Methodology

A systematic review and meta-analysis of individual participant data with a qualitative analysis of the individual studies and quantitative analysis using an Analysis of covariance (ANCOVA). This design will permit the control of covariants while determining if there is a statistically significant difference in the body mass index (BMI), Yale–Brown obsessive-compulsive scale (YBOCS), and Hamilton depression rating scale (HAMD) depending on the location of the deep brain stimulation.

2.1 Search Design of Identifying studies

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines were followed to conduct this meta-analysis. An extensive literature search of the databases of; PubMed/Medline, SciELO, and PsycNET was conducted to include all publications in English, Spanish, or Portuguese, published up until September 2021 which included a combination of the search terms: "deep brain stimulation" or "DBS" and "anorexia" (((deep brain stimulation) OR (DBS)) AND (anorexia)) along with the subsequent translations for Spanish (((estimulación cerebral profunda) O (ECP)) Y (anorexia)) and Portuguese (((estimulação cerebral profunda) OR (ECP)) AND (anorexia)).

2.2 Study Selection process

Using the aforementioned search databases and terms, 94 articles were identified. An initial screening on the articles title and abstract was conducted applying the following exclusion criteria; duplicate articles, publications that were not trials or case reports, or were not conducted using human subjects. Following exclusion, the 19 remaining articles' eligibility was assessed based on the inclusion criteria at the study level; Study participants were clinically confirmed to have Anorexia Nervosa, DBS was the primary treatment intervention, and the researcher reported pretreatment and posttreatment body mass index (BMI). The finalized process concluded with 11 studies included in **Figure 2** below.

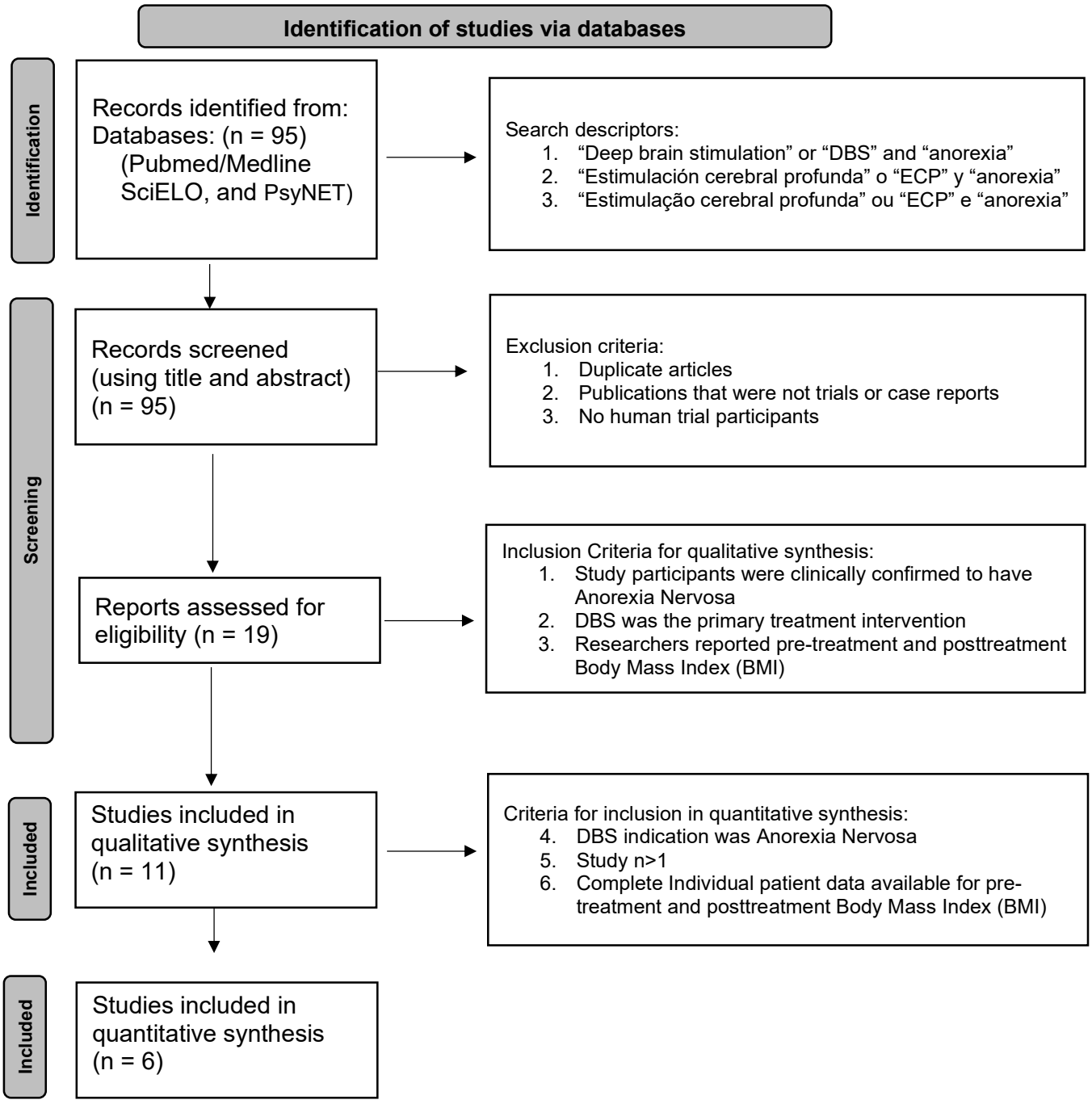

Figure 2. *Flowchart of study selection and data collection process*

2.3 Data Collection process

The study design led to the inclusion of 11 studies in the qualitative analysis. Of these 11 studies, 8 satisfied the inclusion criteria of the DBS indication being anorexia nervosa, and the study including more than 1 patient (n>1). Of these 8 studies, 6 provided the individual patient data directly in the original publication. Thus, in these 6

studies no follow up with the author was required. Authors of the 2 studies that did not provide such data were contacted with a request for the data. This request was not fulfilled and thus these 2 studies did not comply with the inclusion criteria of providing complete Individual patient data for pre-treatment and posttreatment body mass index (BMI). Therefore, they were not included in the quantitative analysis.

2.4 Data analysis method

The study's statistical analysis was conducted using an Analysis of covariance (ANCOVA), which is a combination of an analysis of variance (ANOVA) with the principles of regression. ANCOVA permits the study to analyze the effects of two separate categorical variables, (the deep brain stimulation targets of the subcallosal cingulate and nucleus accumbens) on a continuous dependent variable (the postoperative body mass index (BMI) for the primary outcome), controlling the effects of another variable (the preoperative body mass index (BMI) for the primary outcome), which covaries with our dependent variable. The ANCOVA analysis will also be applied for the secondary outcomes with the Hamilton depression rating scale (HAMD) and Yale–Brown obsessive-compulsive scale (YBOCS) both preoperatively and postoperatively being used in the same fashion as the BMI as described above.

2.5 Risk of Bias Quality assessment

The quality of the 11 publications comprising the qualitative analysis, the majority of which were non-randomized without a control group, w assessed utilizing the appropriate Joanna Briggs institute (JBI) critical appraisal tools for each study. The JBI appraisal includes 9 yes or no questions which aim to determine the methodological quality of each study, as well as verify the author's consciousness of potential bias in their study. In this work the JBI appraisal was carried out by the research group, with the results displayed in **Table 1**. The % of yes responses, the ideal publication would have 100%, for each publication was determined. Based on these results of the risk assessment, it was determined that no study needed to be excluded due to a poor JBI (<50%) appraisal. (Annexes #1-11)

Table 1. Joanna Briggs Institute Critical Appraisal results for studies meeting inclusion criteria. *Type* A = Case Report, B = Quasi-Experimental Studies (Non-controlled non-randomized one group pre-post-test). Responses: Y= Yes, N= No, X = Not Applicable, U = Unclear, N/A = Does not Apply.*

Publication	Type*	1	2	3	4	5	6	7	8	9	%	Exclude study?
Israel et al., 2010	A	Y	N	Y	Y	Y	Y	N	Y	N/A	75%	No
Wu et al., 2013	B	Y	Y	X	N	N	Y	Y	U	N	57%	No
McLaughlin et al., 2013	A	Y	N	Y	Y	Y	Y	N	Y	N/A	75%	No
Lipsman et al., 2013	B	Y	Y	X	N	Y	Y	Y	U	N	71%	No
Zhang et al., 2013	B	Y	N	U	Y	U	N	Y	U	Y	60%	No
Wang et al., 2013	B	Y	Y	X	N	N	Y	Y	U	Y	63%	No
Lipsman et al., 2017	B	Y	Y	X	N	Y	Y	Y	U	Y	75%	No
Blomstetdt et al., 2017	A	N	N	Y	Y	Y	Y	N	Y	N/A	63%	No
Manuelli et al., 2019	A	Y	Y	Y	Y	Y	Y	N	Y	N/A	88%	No
Liu et al., 2020	B	Y	Y	X	N	N	Y	Y	N	Y	63%	No
Villalba et al., 2020	B	Y	Y	X	N	Y	Y	Y	N	Y	75%	No

3. Results

3.1 Results of qualitative synthesis

3.1.1 Subcallosal cingulate open trials

The subcallosal cingulate (SCC) through numerous afferents is an important link in a vast network including portions of the cortex, the limbic system, thalamus, hypothalamus, and brainstem [18]. Thus, researchers identified this area as a potential DBS target due to its role in reward processing, emotional response, and affect regulation [17].

Two groups of researchers, one from Spain and the other from Canada, have implanted DBS electrodes in the SCC with mixed results [13], [19], [20], [21]. Both groups of researchers used Body Mass Index (BMI) as the primary outcome to determine the effectiveness of the DBS. Secondary outcomes that were in common between the research groups included the Hamilton Depression Rating Scale (HAMD17), the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), and the Yale-Brown-Cornell Eating Disorders Scale (YBC-EDS). While both measured anxiety, the Spanish group chose to utilize the Hamilton Anxiety Rating Scale (HAM-A) while the Canadian group opted for the Beck anxiety inventory (BAI).

The Canadian group led by Lipsman published first in 2013 in a study of 6 patients, with a mean age of 38 years old, with refractory Anorexia who underwent DBS in the SCC with a bilateral stimulation at 130 Hz between 5–7 V. The results obtained by this study showed an overall BMI increase of 13.7 to 16.6 kg/m2, with 3 of the 6 patients showing increased BMI at up to 9 months post-implantation [19]. Furthermore, the study concluded that DBS in the SCC led to improvements in depression in 4 of 6 patients (>50% reduction in HAMD17), in obsessions and compulsions in 3 of 6 patients (>35% reduction in Y-BOCS), and reductions in YBC-EDS and BAI in 3 of 6 patients. These clinical improvements were also explored using FDG PET which showed reversal of the pathological metabolic changes seen in anorexic patients. These changes included a decrease in cerebral glucose metabolism in the SCC, anterior cingulate, and insula. Meanwhile, an increase in glucose metabolism was found in the parietal lobe as seen in **Figure 3**. In relation to adverse events, the only serious reverse event in the authors' consideration was a seizure, with the procedure being deemed safe and well tolerated by the researchers [19]. Due to these positive results, Lipsman et al [21] conducted a second trial using the same stimulation parameters enrolling 16 patients which reproduced the results of the first trial showing an overall BMI increase of 13.8 to 17.4 kg/m2 while also improving the secondary outcomes (HAMD17, Y-BCOS, YBC-EDS, BAI) in the group overall and showing the same normalization of cerebral glucose metabolism post-DBS in FDG PET.

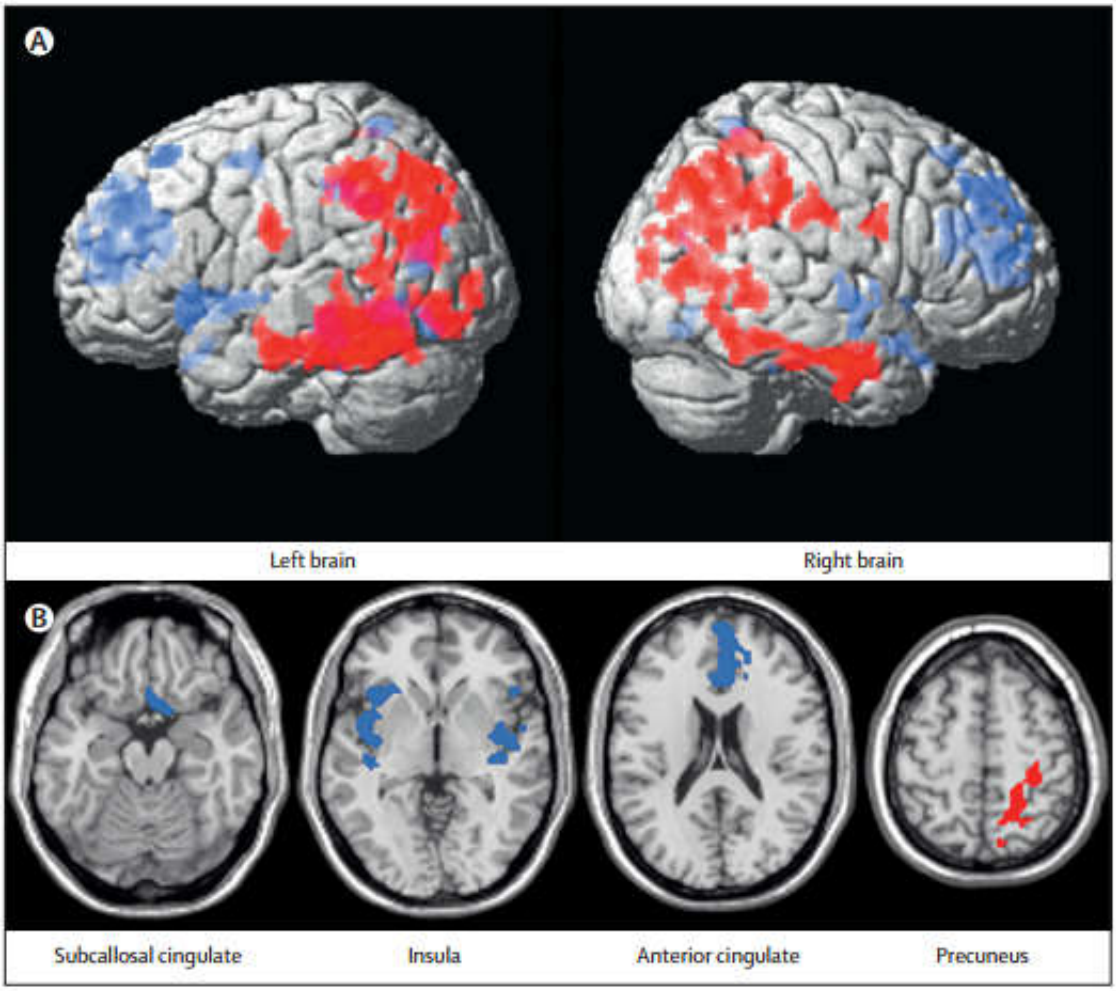

Figure 3. *6-month postop PET scans of composite data for the 6 patients treated with DBS of SCC reproduced from the 2013 study by Lipsman et al [21] compared with their composite baseline. Blue indicates a zone of statistically significant decrease in glucose metabolism while red indicates a zone of statistically significant increase in glucose metabolism.*

The Spanish group led by Dr. Gloria Villalba Martínez used DBS in 8 patients with anorexia subdividing the group into patients based on psychiatric comorbidities. Patients with comorbid affective disorders received electrode implantation in the SCC, while those with the comorbidity of anxiety received implantation in the nucleus accumbens (NAc) [17]. The group receiving Bilateral SCC DBS at 130 Hz, 5 mA started with an average BMI of 12.95 increasing to 14.25 at the 6-month follow-up. Of these 4 patients, 3 were considered responders using a 10% increase in BMI as the cut-off value to define treatment response. Despite this increase, statistical tests revealed no significant difference (p = 0.84) between mean preoperative and postoperative (month 6) BMI. Furthermore, contrasting the 2 studies by Lipsman et all this study determined that only depression (HAMD17) and obsession-compulsion (YBOCS) showed improvement while anxiety (HAM-A) and eating disorder (YBC-EDS) did not show a significant difference. The authors concluded the lack of response in this trial may be due to the small sample size, preliminary findings of only 6-month

follow-up data available, and the population study selection being limited to treatment-resistant, chronic patients with a minimal preoperative BMI of 13.

The Canadian group recently published in 2021 a long-term follow-up of 15 of the original 22 patients from their 2 trials with results less promising than the early indications [20]. Although the group did find an increase in BMI of 14.0kg/m2 at baseline to 16.3 (p=0.003) at 3 years of DBS in the SCC it should be noted that only 3/15 patients returned to a physiologic weight (≥18.5kg/m²), while 2/15 remained with a weight <16kg/m2, and the remaining patients showed improvement without a full recovery. Furthermore, in the secondary outcomes of YBCOS, YBC-EDS, HAMD, and BAI all patients showed significant improvement (P<0.025) at the one-year mark yet interestingly at the 3-year follow-up only approximately 50% of the patients maintained this psychometric improvement, Figure 4. The researchers speculated that the reasoning for the less promising results at this long-term follow-up contrasting with their initial results may be due to; differing sensitivity, both between patients and in patients waning over time to DBS, heterogenous simultaneous conventional psychiatric pharmacotherapy amongst the group, and slight differences in exact electrode location. Despite less promising results in both the follow-up study by the Canadian group and early results from the Spanish group, the SCC overall has been shown to be an effective DBS target for Anorexia Nervosa and its related comorbidities such as depression and anxiety [17], [19], [20], [21].

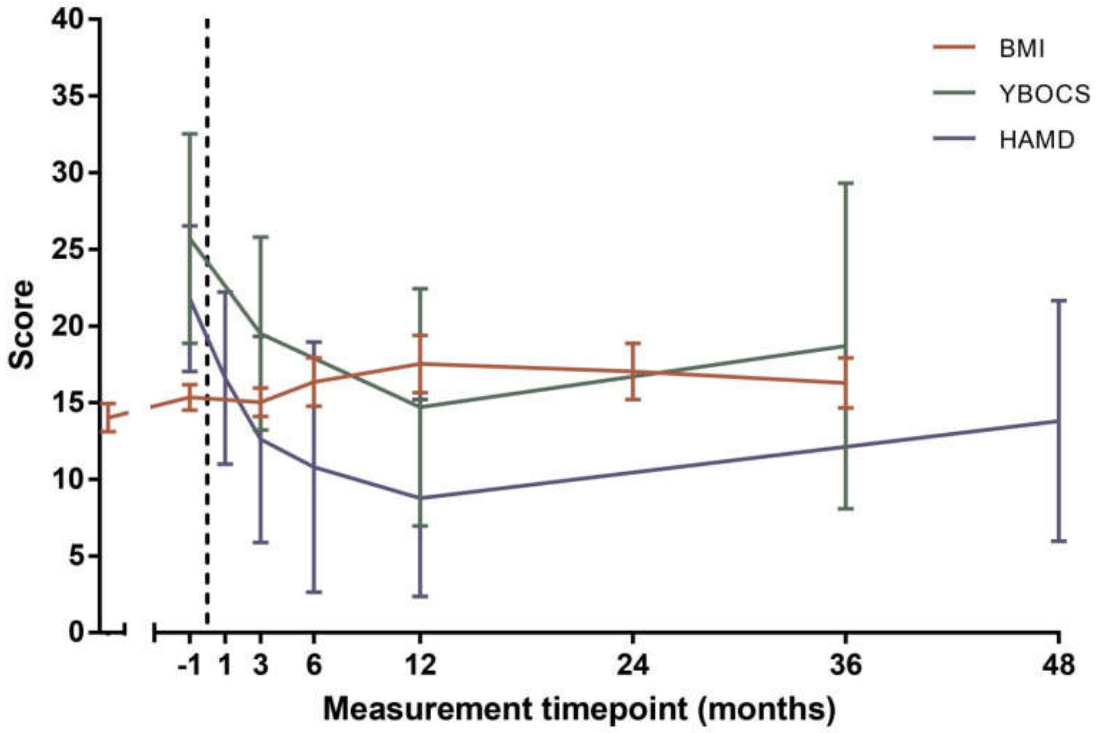

Figure 4. *Long term follow-up results from the Canadian group's SCC DBS patients (reproduced from [20]) showing diminishing effects on body mass index (BMI), Yale-brown obsessive-compulsive (YBOCS) score, and Hamilton depression scale (HAMD)*

3.1.2 Nucleus Accumbens open trials

The nucleus accumbens (NAc) is the main component of the ventral striatum and thus an important part of the cortico-striato-thalamo-cortical circuitry of the reward system. Furthermore, the NAc plays a part in the limbic-motor connection as well as regulating motivational and emotional processes [22]. The NAc subdivides into the rostral nucleus accumbens shell with D1 dopamine receptors, which when stimulated increase eating, and a caudal portion with dopamine D1 and D2 receptors, which when stimulated increases avoidance behavior and fear. In anorexic patients elevated D1 and D2 response leads to a higher vulnerability of fear conditioning and avoidance. Furthermore, this dopamine response is skewed to female patients thus helping explain the large difference in prevalence between the sexes [22]. This has prompted various groups to explore the possibility of the NAc as a suitable target for DBS.

The first study with DBS of the NAc was performed in Shanghai as reported by Wu and colleagues [16] and consisted of 4 female adolescent patients with severe refractory Anorexia Nervosa receiving bilateral DBS at 180 Hz, 6 V. The average BMI of this group pretreatment was 11.9 Kg/m2, and all presented psychiatric comorbidities: three with OCD (Y-BOCS average of 20) and one with generalized anxiety disorder (HAM-A of 19). The group underwent the neurosurgical procedure at different times (2007-2011) and thus the follow-up times varied but had an average of over 3 years. This work reported an average increase in BMI from 11.9 kg/m2 at baseline to 19.6 kg/m2 at follow-up. Furthermore, the group used the Y-BCOS and HAM-A scores as secondary outcomes and saw a drastic reduction in both with the Y-BCOS reduced to 1.7 overall and the HAM-A to 2. Finally, differing from the studies involving the SCC as a DBS target this group also included the return to normality of menstrual cycles as a secondary outcome with all 4 participants reporting a reversal of the preoperative amenorrhea in an average of 6.8 months postop [16].

This Shanghai group, based on the positive results of their initial trial, continued performing NAc DBS only slightly changing the stimulation parameters to 160 Hz, 2.5V. They published a report of a 2-year follow-up of their 28 patients with refractory anorexia nervosa operated between 2010 and 2015. The group maintained the primary and secondary outcomes reporting an improvement of BMI from 13.01 kg/m2 at baseline to 17.73 kg/m2, a Y-BOCS of 20.46 at baseline to 13.04, a HAM-A of 21.39 at baseline to 12.63, and a HAM-D of 26.93 at baseline to 15.93 as seen in **Figure 5**.

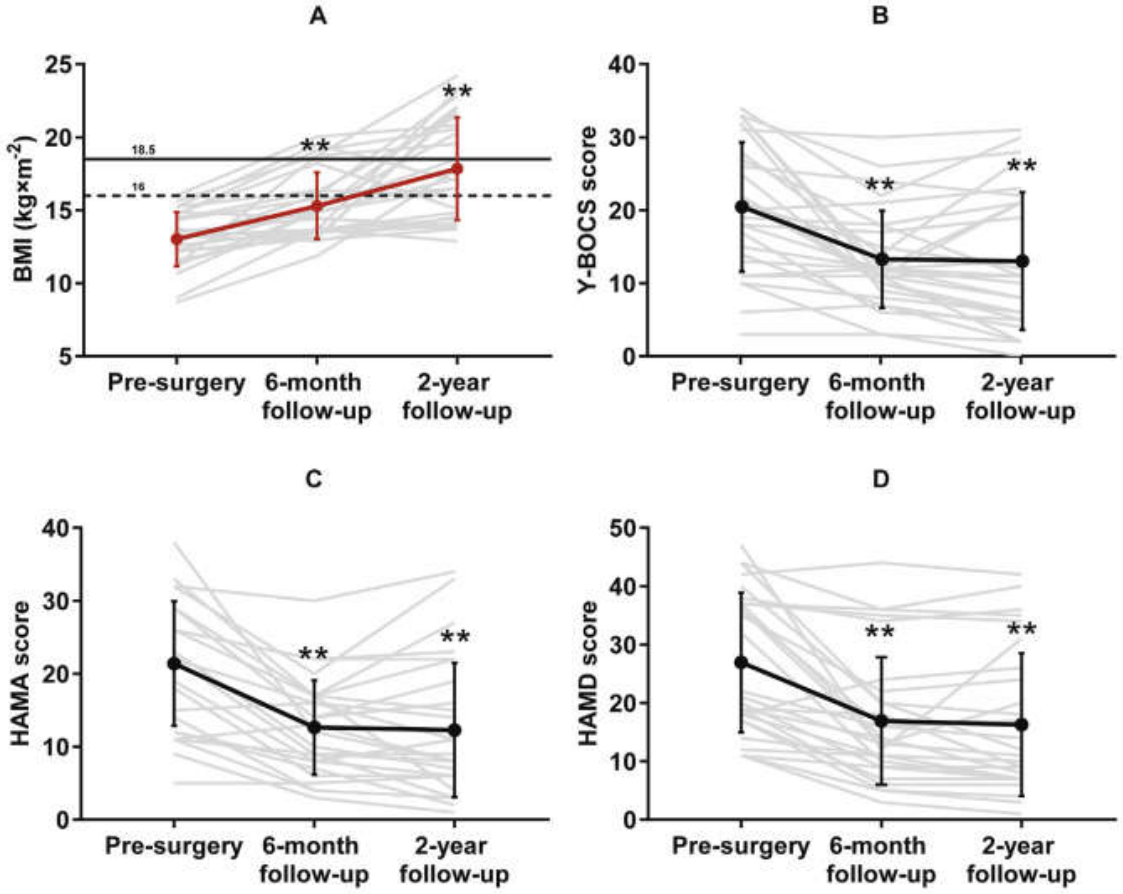

Figure 5. *Results of the NAc DBS from the Shanghai group reported at baseline, 6-month, and 2-year follow-ups. Individuals from the study are displayed in gray while black points represent the mean values and black bars are the 95% confidence intervals, respectively (**: p < 0.001) (reproduced from [23])*

Another Chinese group [24] also aimed to treat refractory anorexia nervosa patients with neurosurgery focusing on the NAc. This group used stereotactic radio frequency ablation in 6 patients and DBS in 2 patients. The patients, aged 28 and 18, receiving bilateral DBS at 135-180 Hz and 2.5-3.8 V in the NAc showed an improvement of BMI from 13.1 kg/m2 at baseline to 19.4 kg/m2 at a 1-year follow-up. Furthermore, this group reported anxiety (HAM-A), depression (HAM-D), and obsessive-compulsion (Y-BCOS) changes with statistically significant improvements in both patients receiving NAc DBS. This work reported that the 6 patients undergoing stereotactic radiofrequency ablation of the NAc presented the same benefits as the 2 DBS patients with no difference between these subgroups. This finding supplies further evidence implicating the NAc in anorexia nervosa pathophysiology.

Zhang et al., [25] also used DBS in the NAc but different to the other groups coupled this with pre- and post-operatory 18F-FDG PET to study glucose metabolism. The work compared these metabolic imaging findings in anorexic patients to age-matched healthy controls. Results, through statistical parametric mapping, demonstrated that the frontal lobe, limbic lobe (specifically the hippocampus and amygdala), lentiform nucleus, left insula, and left subcallosal gyrus presented hypermetabolism, **Figure 6**.

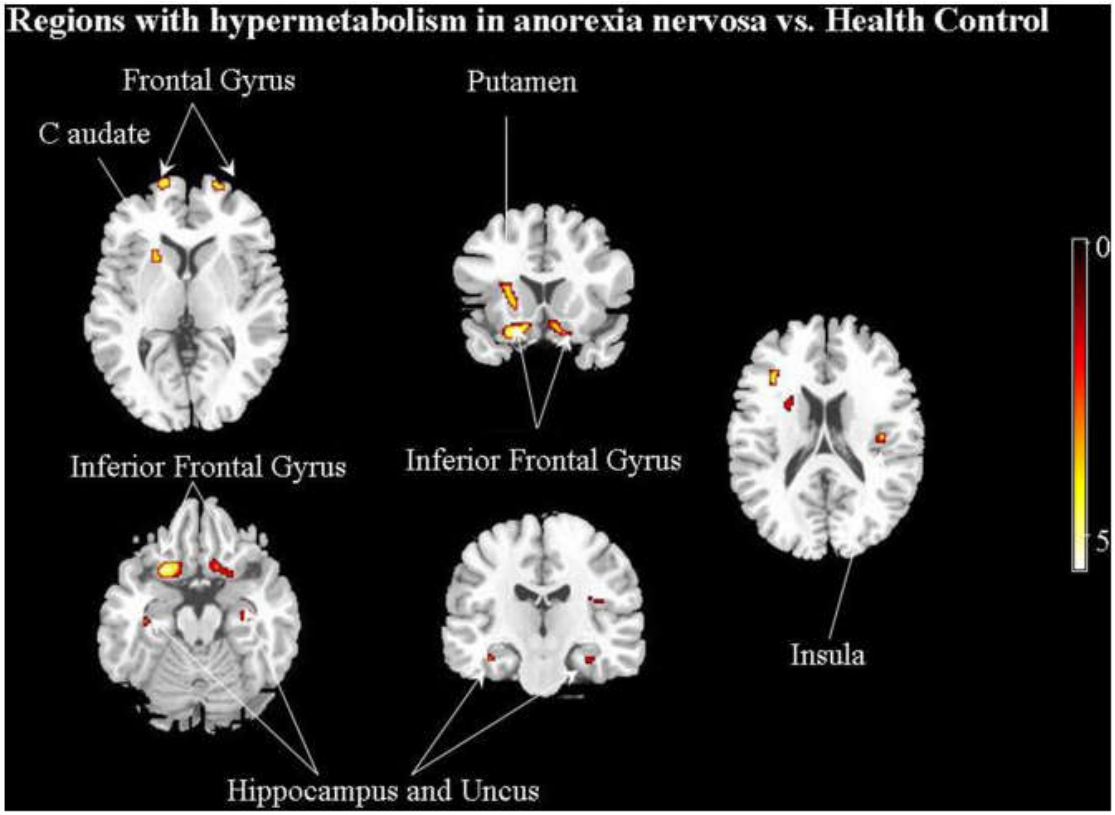

***Figure 6**. Reproduced from [25] showing the regions with hypermetabolism in anorexia patients vs healthy control subjects. Red regions indicate areas of relative hypermetabolism.*

On the other hand, the parietal lobe presented hypometabolism in anorexic patients preoperatively. Like the previous studies mentioned targeting the NAc, this group also reported an increase of baseline BMI, from 12.13 kg/m2 to 15.65 at the first follow-up. Furthermore, after DBS of the NAc the 4 patients showed decreased hypermetabolism in the frontal lobe, hippocampus, and lentiform nucleus at 6 months postop. This is promising as it shows that there was a correlation between the clinical response and underlying pathological brain circuitry when targeting the NAc in DBS.

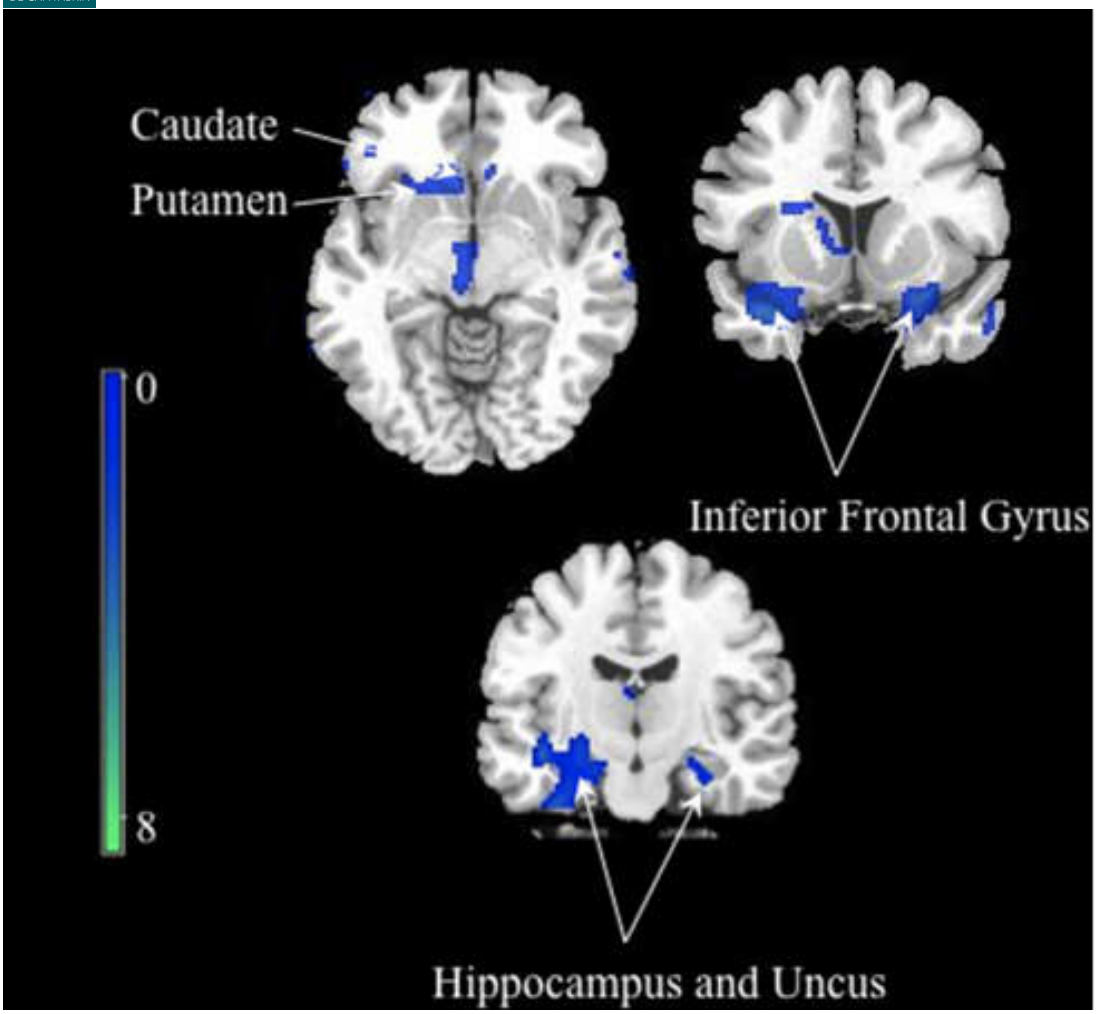

Figure 7. *PET images of zones of decreased glucose metabolism relative to the preoperative PET for patients receiving NAc DBS. Reproduced from [25].*

Contrasting these positive results, the Spanish group, Villalba Martínez et al [13], that used DBS in the SCC also performed bilateral DBS at 130 Hz, 5 Ma in the NAc, **Figure 8**, and did not find a statistically significant improvement in patient BMI for either group at the 6-month follow up. Furthermore, when the results were reanalyzed using a 10% increase in BMI as a positive result only 1 in 4 of the patients receiving DBS in the NAc showed response to the treatment. The major difference in the demographics of the Spanish group, with a mean age of 40.75 years, and the Chinese studies involving mainly adolescents and some young adults could be one explanation for the contrast in results. Furthermore, the previous studies of NAc DBS recruited patients with less severe anorexia nervosa and with a much shorter duration of the disease as well as higher BMIs prior to surgery all of which could help explain the lack of response in this Spanish group.

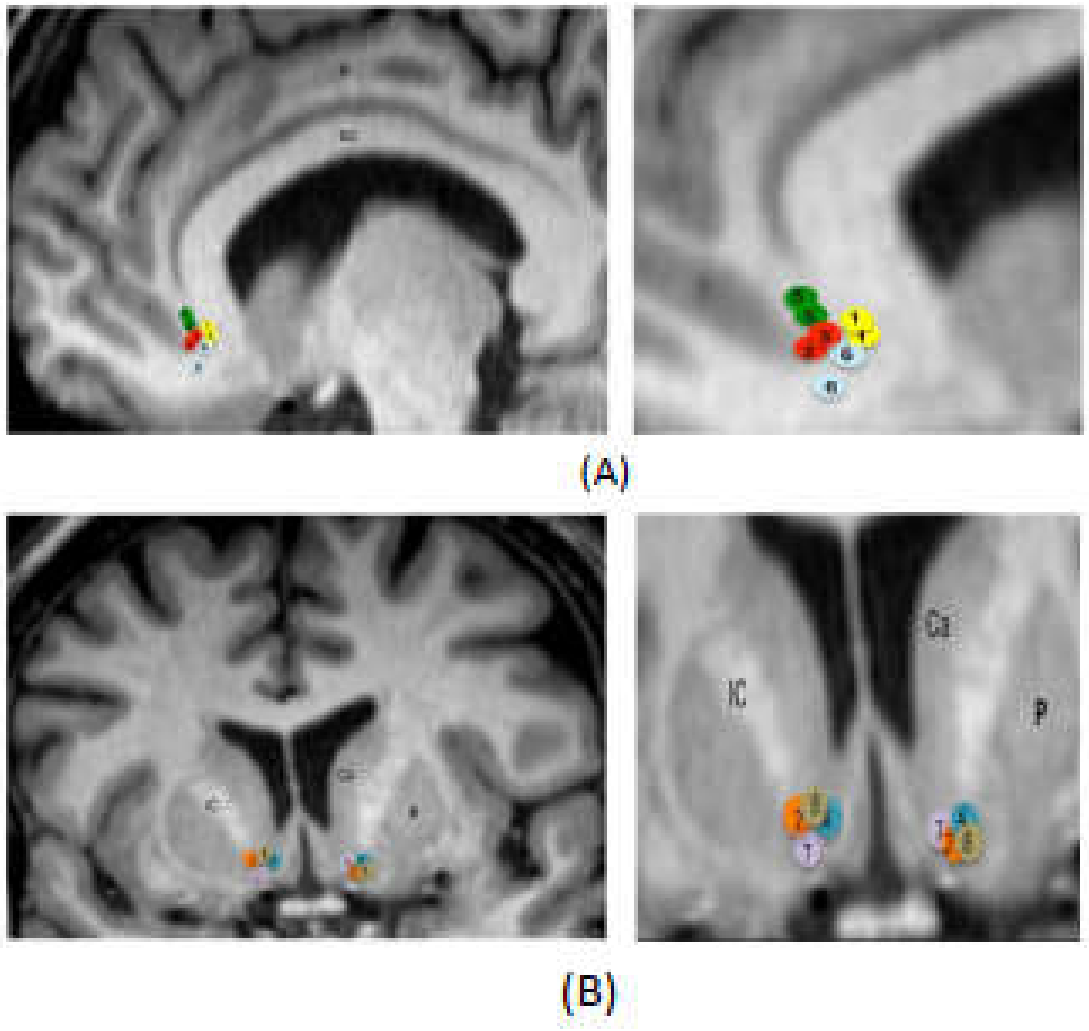

Figure 8. *Reproduced from the trial by Villalba Martínez and colleagues [13], with Location of electrode implantation in the DBS SCC group (A) and the DBS NAc group (B) the figure on the right side of both groups is a close up CA=caudate nucleus, CI=internal capsule. P= putamen.*

3.1.3 Other DBS targets from case-reports

A 56-year-old woman with a 40-year history of intermittent episodes of anorexia nervosa comorbid with major depressive disorder was treated with DBS in the subgenual cingulate, which forms part of the anterior cingulate cortex. The anterior cingulate cortex has been shown to be overactive in response to images of food using fMRI [12], [26]. Furthermore, studies have implicated the anterior cingulate cortex in body perception, the hedonism of food, as well as depression and OCD pathophysiology which are commonly comorbid in Anorexic patients [26]. Israel et al., [26] applied the DBS in this patient to treat her recurrent treatment-resistant depression, but these researchers subsequently noticed the improvement in her anorexia as well. The stimulation parameters in this patient varied considerably from those already mentioned in anorexia treatment opting for intermittent stimulation of 2 minutes on at 130 Hz, 5mA followed by 1 minute off. The women's BMI increased from

14.1 kg/m2 at baseline to 19.1 kg/m2 at 36-month follow-up. Furthermore, the researchers used an eating disorder examination questionnaire, the eating attitudes test-26 (EAT-26), to evaluate her response to the DBS showing improvement from a baseline of 40.56 which indicates a complete eating disorder, to a score of 1 at the 36-month follow up indicating no eating disorder. Importantly this questionnaire contains questions regarding body image perception which the women had altered in the baseline questionnaire and completely normal at the 36-month follow up indicating the reversal of pathological overactivation of the anterior cingulate cortex can revert this clinical component of anorexia.

Another case report by McLaughlin et al.,[27] of a 48-year-old woman who underwent DBS treatment for Intractable obsessive-compulsive disorder. The DBS was in the ventral capsule/ventral striatum, with stimulation being bilateral at 120 Hz, 7.5 V. The study reported an improvement in the women's comorbid Anorexia, when stimulating this zone. The ventral caudate has been shown to play a role in food response in addition to connecting to the prefrontal cortex, specifically the ventral and orbital regions, which is an important area for the hedonic response to food. Furthermore, these zones have been shown to present hypermetabolism in response to food images in Anorexic patients analyzed using fMRI [14], [27]. The woman, in this case, showed a BMI increase of 18.5 kg/m2 at baseline to 19.6 kg/m2 but more importantly reported that she had less fear of weight gain. Fear of weight gain in anorexia has been hypothesized by Castro and colleagues [15] to be controlled by the frontal cortex. Thus, the impact of the DBS in the ventral caudate with its subsequent efferent connection to the orbital region could explain this reduction. Therefore, we can consider the ventral capsule/ventral striatum as a promising, although not the most, target for DBS treatment of anorexia.

Blomstedt et al [28] reported a case of a 58-year-old female who had a childhood onset of remitting and relapsing anxiety and anorexia nervosa and later presented with major depressive disorder. This patient's indication for DBS in the medial forebrain bundle (MFB) and bed nucleus of the stria terminalis (BNST) was her major depressive disorder. Despite this, the researchers' hoped improvements in her anxiety and anorexia would also be seen due to the afferents and efferent of the targeted regions being implicated in these diseases. The patient first received DBS in the MFB, but due to progressive blurred vision the stimulation was permanently halted. The positive initial response, in regard to symptom reduction, led to surgeons implanting a second set of DBS electrodes this time in the BNST. The patient responded well to the Bilateral BNST 130 Hz, 2.8-3 V stimulation. She improved in terms of the primary outcome of the surgery shown by her scores in depression, HAM-D 22 at baseline to 6 at 36-month follow up, and anxiety, HAM-A 34 at baseline to 15 at 36-month follow up. In respect to anorexic improvement, the patient had a worsening BMI of 16.2 kg/m2 at baseline to 14.5 kg/m2 at 36-month follow-up. This result coupled with the fact that neither the MFB nor the BNST has been directly implicated as primary drivers of pathological circuitry in anorexia nervosa manifestation renders this nucleus a less promising target than all previously mentioned for this disease.

Contrasting Blomstedt and colleague's findings, a group led by Manuelli [29] reported positive outcomes for DBS in the BNST in 37-year-old woman who had suffered from refractory Anorexia Nervosa since childhood. The BNST was stimulated with 130 Hz, 60 us, and varying voltages from 1 mA to a maximum of 5 mA. This patient was

reported to have a BMI of 16.31 kg/m2 prior to surgery, which improved to a normal BMI (>18.5kg/m2) of 18.98 kg/m2 at the latest reported follow up. This study, similar to the approach taken by Israeli et al, also used the EAT-26 questionnaire to assess the patient's body image perception, finding improvements in this assessment as well with scores decreasing from 68 at baseline to 39 at 6-month follow up. Furthermore, this study also showed the patient's improvement in obsessive-compulsive behaviors, with an improved YBCOS from 29 at baseline to 14 at follow up. Despite the positive effects reported in this case, it should be noted that this patient was also receiving extensive nutritional counseling and cognitive behavioral therapy throughout the treatment process. These cofounders could help explain the drastic difference in results compared to the BNST DBS completed by Blomstedt et al., [28]

3.1.4 Summary of qualitative analysis

Table 2 below provides a summary of the 11 studies included in the qualitative analysis.

Table 2. *Summary of qualitative analysis of DBS studies in anorexia nervosa.*

Author	*n*	Patients	Procedure	Stimulation Parameters	*Body Mass Index*	*Psychological Parameters*	Adverse Events
Israël et al., 2010	1	A 56-year-old female with a 40-year history of intermittent episodes of Anorexia Nervosa comorbid with major depressive disorder.	Bilateral DBS in the subcallosal cingulate (part of the anterior cingulate cortex)	Intermittent stimulation of 2 minutes on at 130 Hz, 5mA followed by 1 minute off	BMI increased from 14.1 kg/m2 at baseline to a healthy (>18.5 kg/m2) BMI of 19.1 kg/m2 at 36-month follow-up	Eating Attitudes Test-26 (EAT-26) from a baseline of 40.56 (eating disorder) to 1 (no eating disorder) at the 36-month follow up	None
Zhang et al., 2013	4	Adolescent female patients (13-17) with the restrictive subtype of Anorexia	Bilateral DBS in the nucleus accumbens (NAc).	Not reported	BMI increased from 12.13 kg/m2 at baseline to 15.65 kg/m2 at 1-month follow-up	Not reported	None
Wu et al., 2013	4	Adolescent female patients (14-16) with anorexia nervosa. Comorbid OCD in 3 of the patients and one with generalized anxiety disorder	Bilateral DBS in the nucleus accumbens (NAc).	Bilateral at 180 Hz, 6 V.	The surgeries were staggered so follow-up times were heterogenous for this group. The mean follow-up was 38 months and Patient BMI increased from 11.86 kg/m2 at baseline to 19.6 at the latest follow-up.	Anxiety improved from a mean HAM-A 19 at baseline to 2 at the latest follow-up (mean of 38 months). Obsessive-compulsion symptoms also decreased from a mean YBOCS of 20 at baseline to 1.7 at the latest follow up (mean 38 months)	None
Wang et al., 2013	2	A 28-year-old and 18-year-old woman with refractory anorexia nervosa	Bilateral DBS in the nucleus accumbens (NAc).	Bilateral at 135-180 Hz and 2.5-3.8 V	improvement of mean BMI from 13.1 kg/m2 at baseline to 19.4 kg/m2 at a 1-year-follow-up.	Anxiety improved from a mean HAM-A 29.5 at baseline to 17.5 at a 6-month follow-up. Obsessive-compulsion symptoms also decreased from a mean YBOCS of 22 at baseline to 13.5 at 6-month follow-up. Depression symptoms improved from 22 at baseline to 10.5 at 6-month follow-up.	Both patients reported postoperative cephalgia of 3-4 days. No serious effects were reported.

Lipsman et al. 2013	6	Adult women (mean age of 38 years old) with refractory Anorexia nervosa with 5 of the 6 presenting at least 1 comorbid psychiatric illness (Major depressive disorder, obsessive-compulsive disorder, or generalized anxiety disorder)	Bilateral DBS in the subcallosal cingulate (SCC).	Bilateral at 130 Hz and 5–7 V	Mean BMI increase of 13.7 kg/m2 at baseline to 16.6 kg/m2 at 9-month follow up	The mean Yale-Brown–Cornell eating disorder scale (YBC-EDS=) decreased from 26.5 to 18.35 at 6-month follow-up. Depression symptoms (HAMD) improved from 17.8 at baseline to 10.7 at 6-month follow-up. Anxiety improved from a mean Beck anxiety inventory (BAI) of 31.2 at baseline to 21.7 at a 6-month follow-up. Obsessive-compulsion symptoms also decreased from a mean YBOCS of 25 at baseline to 13.2 at 6-month follow-up.	4 of 6 patients reported including a seizure, air embolus, Pancreatitis, hypokalemia, Pain, nauseas intraoperative panic Attack, Refeeding delirium, hypophosphatemia Increased lead impedance, Worsening mood, QT prolongation, seizure
McLaughlin et al., 2013	1	A 48-year-old female with treatment-refractory OCD and Anorexia Nervosa since Childhood.	Bilateral ventral capsule/ventral striatum electrode placement	Bilateral at 120 Hz, 7.5 V	BMI increase of 18.5 kg/m2 at baseline to 19.6 kg/m2 at follow up	Not evaluated using a validated scale, but the patient reported to the physicians a reduction in her previous fear of weight gain	None
Lipsman et al., 2017	16	Adult women (mean age of 34 years old) with refractory Anorexia nervosa	Bilateral DBS in the subcallosal cingulate (SCC).	Bilateral at 130 Hz and 5–7 V	Mean patient BMI improved from a baseline of 13.8 kg/m2 to a mean BMI of 17.4 kg/m2 at 1-year follow-up.	The mean Yale-Brown–Cornell eating disorder scale (YBC-EDS=) decreased from 26.5 to 18.35 at 6-month follow-up. Depression symptoms (HAMD) improved from 19.4 at baseline to 8.79 at 1-year follow-up. Anxiety improved from a mean Beck anxiety inventory (BAI) of 38.00 at baseline to 27.17 at a 1-year follow-up. Obsessive-compulsion symptoms also decreased from a mean YBOCS of 27.88 at baseline to 19.79 at 1-year follow-up.	11 of 16 patients reported including 2 seizures, an air embolus, Pancreatitis, hypokalemia, Pain, nauseas intraoperative panic Attack, Refeeding delirium, hypophosphatemia Increased lead impedance, Worsening mood, QT prolongation, a fracture, a surgical site infection, and a Seroquel overdose

Blomstedt et al., 2017	1	A 58-year-old female with childhood-onset of remitting and relapsing anxiety and anorexia nervosa. A comorbid major depressive disorder presented with onset later in life.	Bilateral DBS to the bed nucleus of the stria terminalis (BNST) following termination of DBS of the medial forebrain bundle due to adverse effects.	Bilateral at 130 Hz, 2.8-3 V	BMI of 16.2 kg/m2 at baseline decreased to 14.5 kg/m2 at 36-month follow-up.	HAM-D 22 at baseline to 6 at 36-month follow up, and anxiety, HAM-A 34 at baseline to 15 at 36-month follow up	None (although this patient received DBS in the medial forebrain bundle (MFB) in a prior surgery which produced blurred vision leading to the permanent halt of stimulation of the MFB).
Manuelli et al., 2019	1	A 37-year-old female with childhood-onset refractory Anorexia Nervosa.	Bilateral DBS to the bed nucleus of the stria terminalis (BNST)	Not reported	BMI increased from 16.31 kg/m2 at baseline to a healthy (>18.5 kg/m2) BMI of 18.98 kg/m2 at 6-month follow-up	Eating Attitudes Test-26 (EAT-26) improvement from a baseline of 69 (eating disorder) to 39 (eating disorder) at the 6-month follow-up, despite remaining in the range of an eating disorder (>20). YBOCS improvement from 29 (Severe symptoms) at baseline to 14(mild symptoms) at 6-month follow-up.	None
Liu et al., 2020	28	Adult women (mean age of 23 years old) with refractory Anorexia nervosa. 12 of them presented comorbid Major depressive disorder, 9 obsessive-compulsive disorder, and 7 generalized anxiety disorder	Bilateral DBS in the nucleus accumbens (NAc).	Bilateral at 130 Hz, 2.8-3 V	BMI increased from a mean of 13.01 kg/m2 at baseline to 17.73 kg/m2 at 2-year follow-up	Depression symptoms (HAMD) improved from 26.93 at baseline to 15.93 at 2-year follow-up. Anxiety improved from a HAMA of 21.39 at baseline to 12.63 at a 2-year follow-up. Obsessive-compulsion symptoms also decreased from a mean YBOCS of 20.46 at baseline to 13.04 at 2-year follow-up.	Cephalgia, sweating, flushing, and pain until 3-4 days post-operative. No serious side effects.

Villalba et al., 2020	8	7 Adult women and 1 man (mean age 40.75) with long-term (mean disease duration 25.5 years) Anorexia Nervosa. 7 of them presented comorbid Major depressive disorder, 3 obsessive-compulsive disorder, and 3 panic disorder.	Bilateral DBS in the nucleus accumbens (NAc). For the patients with binge-eating/purgative Anorexia nervosa. Bilateral DBS in the subcallosal cingulate (SCC) for the Restrictive Anorexia nervosa.	Bilateral at 130 Hz, 5 Ma independent of the target selected	For the 4 patients receiving DBS in the SCC, the BMI increased slightly from a mean of 12.95 kg/m2 at baseline to 14.96 kg/m2 at 6-month follow-up For the 4 patients receiving DBS in the NAc, the BMI remained essentially the same with a mean of 12.39 kg/m2 at baseline to 12.82 kg/m2 at 6-month follow-up Overall, neither group showed a statistically significant increase in BMI.	The group did not show a significant increase in the mean Yale-Brown–Cornell eating disorder scale (YBC-EDS=). The 8 patients decreased from a mean of 111.38 to 87.62 at 6-month follow-up. For the 4 patients receiving DBS in the SCC, the YBCOS improved from a mean of 14.5 at baseline to 8.75 at 6-month follow-up. Depression also significantly improved from a mean HAMD of 13.5 at baseline to 4.75 at 6-month follow-up. For the 4 patients receiving DBS in the NAc, the YBCOS improved less than the SCC group with changes from a mean of 18.5 at baseline to 16.5 at 6-month follow-up. Depression also improved less with a mean HAMD of 17.25 at baseline to 16.25 at 6-month follow-up.	3 patients required dermatological surgical interventions for; a necrotic eschar, skin dehiscence, and a surgical site infection.

3.2 Results of quantitative synthesis

3.2.1 Assessment of BMI, the primary outcome

As is shown in **Table 3**, 24 patients were included for the analysis of body mass index. Patients who received NAc-DBS (n=14) slightly outnumbered patients who underwent SCC-DBS (n=10). There were no differences in the sex composition between the two groups. Some important differences existed between the groups, and their statistical difference was determined using two-way t-tests. Compared with patients in the SCC group, patients in the NAc group were younger at the time of surgery (NAc = 23.71 ± 14.56 vs SCC = 38.10 ± 8.56, p-value = .010714), but despite this they did not have a statistically significant difference in their duration of symptoms (NAc = 9.76 ± 13.88 vs SCC = 19.5 ± 8.73, p-value = .059628). Regarding the body mass index (BMI) prior to DBS surgery, the two groups showed a significant difference with the NAc group presenting a lower BMI (NAc = 12.27 ± 0.95 vs SCC = 14.82 ± 2.40, P-value = .001511). Finally, the latest reported follow up time did not have a significant difference between the groups (SCC = 14.64 ± 18.45 vs NAc = 7.80 ± 1.55, P-value = .257603)

Table 3. *Individual patient data from the studies included in the assessment of BMI*

Target (source)	***Age***	***Duration (Yrs)***	***BMI PRE***	***BMI POST***	***Months reported***
Subcallosal cingulate [21]	24	13	16	21	9
Subcallosal cingulate [21]	39	23	16.3	16	9
Subcallosal cingulate [21]	35	18	14.6	14.3	9
Subcallosal cingulate [21]	40	4	18.4	14	9
Subcallosal cingulate [21]	35	15	16.9	20	9
Subcallosal cingulate [21]	57	37	14.2	14.1	9
Subcallosal cingulate [13]	37	26	16.22	18.43	6
Subcallosal cingulate [13]	45	16	10.94	12.37	6
Subcallosal cingulate [13]	36	22	13.07	15.18	6
Subcallosal cingulate [13]	33	21	11.57	13.86	6
MEAN SCC:	**38.1**	**19.5**	**14.82**	**15.924**	**7.8**
STANDARD DEVIATION SCC:	**8.56**	**8.73**	**2.40**	**2.90**	**1.55**
Nucleus Accumbens [16]	14	2.33	12.2	22.1	48
Nucleus Accumbens [16]	15	1.5	13.3	18.4	48
Nucleus Accumbens [16]	16	1.25	12	19.2	9
Nucleus Accumbens [16]	15	1.08	10	18.6	48
Nucleus Accumbens [24]	28	2	13.3	18	12
Nucleus Accumbens [24]	18	3	12.9	20.8	12
Nucleus Accumbens [25]	16	1.08	11.8	17.9	1
Nucleus Accumbens [25]	12	2.33	11.2	13.1	1
Nucleus Accumbens [25]	13	1.5	13.3	14.5	1
Nucleus Accumbens [25]	10	3.5	12.2	17.1	1
Nucleus Accumbens [13]	45	32	13.44	12.51	6
Nucleus Accumbens [13]	39	25	11.83	12.42	6
Nucleus Accumbens [13]	57	41	12.33	13.94	6

Nucleus Accumbens [13]	34	19	11.98	12.44	6
MEAN NAc:	**23.71**	**9.76**	**12.27**	**16.50**	**14.64**
STANDARD DEVIATION NAc:	**14.56**	**13.88**	**0.95**	**3.29**	**18.45**

The data from the SCC group and NAc group was assessed using an Analysis of covariance (ANCOVA) approach to assess whether the post-test means for BMI, when adjusted for pre-test BMI, differed between these two groups. The full calculation and tables are available in the Supplemental Data 1, and the results in **Error! Reference source not found.** are presented below.

Table 4. *Results from the ANCOVA of BMI*

Source of Variation	***SS***	***df***	***MS***	***F***	***P-value***
DBS Target Zone (SCC vs NAC)	2.136140096	1	2.13614	0.45678	0.50251
Pre-Treatment BMI	5.285243827	1	5.285244	1.130178	0.293287
Within	215.1176251	46	4.67647		

The result of the ANCOVA for BMI, with a p-value = .50251, shows that there is no significant difference in postoperative BMI between the Group receiving DBS in the SCC and the other in the NAc. This result is when accounting for the covariant of pretreatment BMI. It should be noted that the samples varied significantly in age as well which was not accounted for using this ANCOVA approach.

3.2.2 Assessment of the secondary outcome YBCOS

Individual patient data regarding the psychological parameters were not included in 2 of the studies (sources [16] and [25]) that were used in the primary outcome assessment. Thus, the data from the 4 studies included of the analysis of the obsessive-Compulsive symptomatology, scored using the YBCOS, are shown in **Table 4** below. 16 patients were included for the analysis of YBCOS. Differing from the primary outcome, in this analysis patients who received NAc-DBS (n=6) were outnumbered by patients who underwent SCC-DBS (n=10). Again, there were no differences in the sex composition between the two groups.

Unlike the group of patients comprising the primary outcome, no significant differences existed between the NAc and SCC groups for this outcome, which was determined using two-way t-tests. There was no difference in the age at the time of surgery between the SCC and NAc groups for this outcome (SCC = 38.10 ± 8.56 vs NAc = 36.83 ± 13.56, p-value = .820611). Furthermore, they did not have a statistically significant difference in their duration of symptoms (SCC = 19 ± 8.73 vs NAc = 20.33 ± 15.64, p-value = .892077). Neither did the groups differ significantly in their preoperative YBOCS Score (SCC = 20.80 ± 11.13 vs NAc = 19.83 ± 6.74, P-value = .85114). Finally, the latest reported follow up time was the same for all 16 patients at 6 months and thus evidently there was no statistical difference (SCC = 6 ± 0 vs NAc = 6 ± 0, P-value = 1).

Table 4. *Individual patient data from the studies included in the assessment of YBOCS*

Target (source)	***Age***	***Duration (yrs)***	***YBOCS Pre***	***YBOCS Pos***	***Months reported***
Subcallosal cingulate [21]	24	13	32	24	6
Subcallosal cingulate [21]	39	23	28	9	6
Subcallosal cingulate [21]	35	18	26	17	6
Subcallosal cingulate [21]	40	4	4	5	6
Subcallosal cingulate [21]	35	15	35	9	6
Subcallosal cingulate [21]	57	37	25	15	6
Subcallosal cingulate [13]	37	26	10	10	6
Subcallosal cingulate [13]	45	16	4	0	6
Subcallosal cingulate [13]	36	22	20	25	6
Subcallosal cingulate [13]	33	21	24	0	6
MEAN SCC:	**38.1**	**19.5**	**20.8**	**11.4**	**6**
STANDARD DEVIATION SCC:	**8.56**	**8.73**	**11.13**	**8.83**	**0**
Nucleus Accumbens [24]	28	2	29	17	6
Nucleus Accumbens [24]	18	3	15	10	6
Nucleus Accumbens [13]	45	32	24	26	6
Nucleus Accumbens [13]	39	25	12	0	6
Nucleus Accumbens [13]	57	41	15	17	6
Nucleus Accumbens [13]	34	19	24	21	6
MEAN NAc:	**36.83**	**20.33**	**19.83**	**15.17**	**6**
STANDARD DEVIATION NAc:	**13.56**	**15.64**	**6.74**	**9.11**	**0**

The data from the SCC group and NAc group was assessed using an Analysis of covariance (ANCOVA) approach to assess whether the post-test means for YBOCS, when adjusted for pre-test YBOCS, differed between these two groups. The full calculation and tables are available in the Supplemental Data 1 and the results table is presented in **Table 5** below.

Table 5. *Results from the ANCOVA of YBOCS*

Source of Variation	***SS***	***df***	***MS***	***F***	***P-value***
DBS Target Zone (SCC vs NAC)	105.6832	1	105.6832	4.521597	0.041811
Pre-Treatment YBOCS	346.2504	1	346.2504	14.81413	0.000577
Within	701.1894	30	23.37298		

The result of the ANCOVA for YBOCS, with a p-value = .041811, shows that a significant difference exists in postoperative BMI between the Group receiving DBS in the SCC and the other in the NAc. The SCC group with a postoperative mean YBOCS of 11.40 at follow up was significantly lower than the NAc group's mean of 15.17.

3.2.3 Assessment of the secondary outcome HAMD

The studies that comprised the individual patient data assessed for YBOCS also reported the HAMD and this is reflected in the **Table 6** below. As the patients remained the same, the age, duration and follow up time again did not differ between the SCC and NAc groups. Furthermore, the severity of the patient's depression symptoms, as assessed by the HAMD score, prior to undergoing DBS showed no difference between the groups (SCC = 16.30 ± 6.73 vs NAc = 19.00 ± 6.03, P-value = .434088).

Table 6. *Individual patient data from the studies included in the assessment of HAMD*

Target (source)	***Age***	***Duration (yrs)***	***HAMD Pre***	***HAMD Pos***	***Months reported***
Subcallosal cingulate [21]	24	13	26	9	6
Subcallosal cingulate [21]	39	23	21	9	6
Subcallosal cingulate [21]	35	18	12	2	6
Subcallosal cingulate [21]	40	4	22	25	6
Subcallosal cingulate [21]	35	15	22	4	6
Subcallosal cingulate [21]	57	37	4	15	6
Subcallosal cingulate [13]	37	26	17	2	6
Subcallosal cingulate [13]	45	16	9	8	6
Subcallosal cingulate [13]	36	22	15	6	6
Subcallosal cingulate [13]	33	21	15	1	6
MEAN SCC:	**38.1**	**19.5**	**16.3**	**8.1**	**6**
STANDARD DEVIATION SCC:	**8.56**	**8.73**	**6.73**	**7.31**	**0**
Nucleus Accumbens (18)	28	2	20	13	6
Nucleus Accumbens (18)	18	3	24	8	6
Nucleus Accumbens [13]	45	32	9	13	6
Nucleus Accumbens [13]	39	25	15	2	6
Nucleus Accumbens [13]	57	41	25	22	6
Nucleus Accumbens [13]	34	19	21	26	6
MEAN NAc:	**36.83**	**20.33**	**19**	**14**	**6**
STANDARD DEVIATION NAc:	**13.56**	**15.64**	**6.03**	**8.83**	**0**

The data from the SCC group and NAc group was assessed using an Analysis of covariance (ANCOVA) approach to assess whether the post-test means for HAMD, when adjusted for pre-test HMD, differed between these two groups. The full calculation and tables are available in the Supplemental Data 1, and the results table is presented in **Table 7** below.

Table 7. *Results from the ANCOVA of HAMD*

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*
DBS Target Zone (SCC vs NAC)	121.3781	1	121.3781	4.250014	0.048007
Pre-Treatment HAMD	20.83372	1	20.83372	0.729486	0.399819
Within	856.7836	30	28.55945		

The result of the ANCOVA for HAMD, with a p-value = .048007, shows that a significant difference exists in postoperative HAMD between the Group receiving DBS in the SCC and the other in the NAc. The SCC group's postoperative mean HAMD of 8.10 at follow up was significantly lower than the NAc group's mean of 14.00.

4. Discussion

This study provided a comprehensive summary of the publications on DBS treatment of anorexia nervosa based on a qualitative analysis and an individual patient-level data meta-analysis. It is well understood that traditional treatment strategies, such as psychotherapy are incapable of producing remission in about one half of patients with AN. Thus, new treatment strategies, such as DBS, should be explored in this refractory group of patients. This individual patient data meta-analysis provided evidence that in DBS targeting the SCC is superior to DBS targeting the NAc for producing improvements in comorbid depression (HAMD) and obsessive compulsive (YBOCS) symptoms. This may seem trivial at first glance as the diagnosis criteria for AN does not explicitly include obsessive-compulsive symptoms, nor depressive symptoms. Despite this, there are very important ties between these comorbid conditions and thus lowering them may also have an indirect effect on AN remission.

Levinson and colleague's [30] work highlighted that about 40% of patients suffering from anorexia nervosa also suffer from obsessive-compulsive disorder. This can be explained due to the strong positive genetic correlation between AN and OCD. Anorexia nervosa has a higher genetic correlation, at about 50%, with OCD than any other disease as shown in Figure 9 [31]. Anorexia Nervosa has also been conceptualized as a form of OCD by some authors who believe the fear of weight gain and body dysmorphic thoughts in Anorexia are obsessions fulfilled with subsequent compulsive eating restriction behavior [32]. This viewpoint would provide further importance to the DBS targeting the SCC's larger impact on YBOCS scores, as the fear of weight gain and body dysmorphic thoughts are direct diagnosis criteria of AN using the DSM-V.

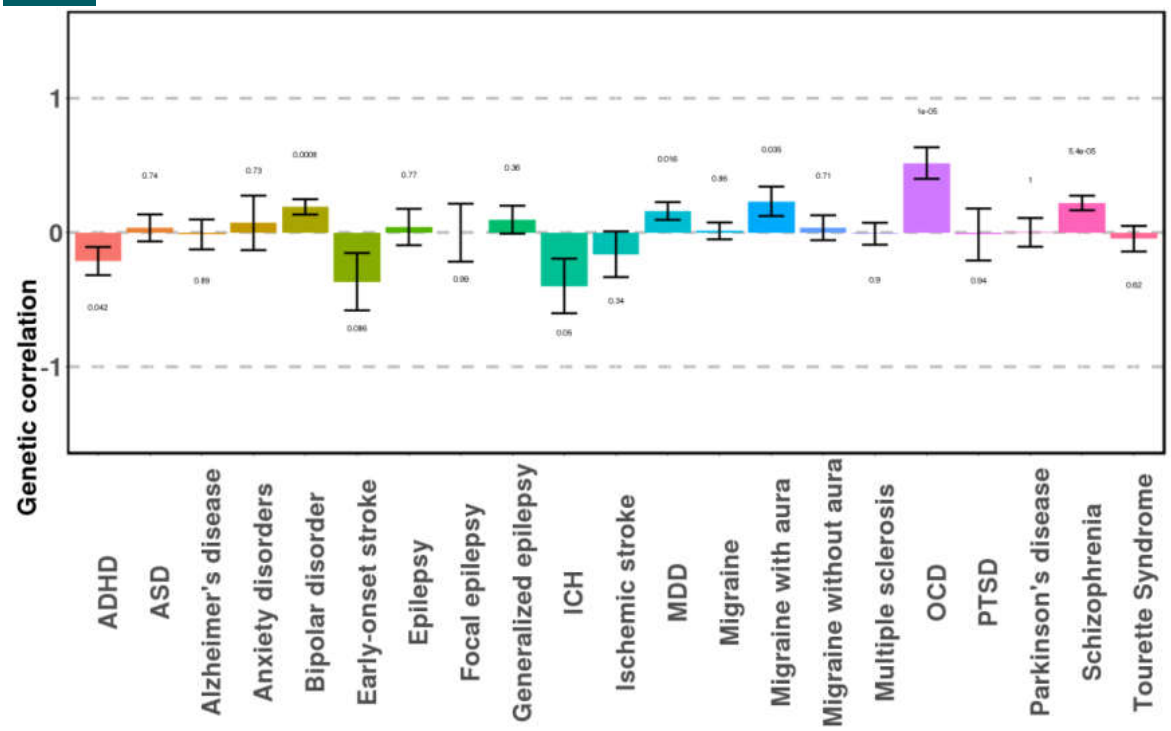

Figure 9: Genetic correlations for anorexia nervosa, reproduced from [31].

Depression also has a positive correlation with AN, but to a much lesser extent according to Anita and colleagues [31]. Also, comorbid major depressive disorder is important in the prognosis of anorexia nervosa, as a work by Carretier and colleagues [33] showed an increased risk of suicidality, aphagia, and pervasive refusal syndrome. Thus, taken together, the HAMD and YBOCS are implicated in the genetic predisposition, etiology, and prognosis of AN and their improvement. Therefore, improvements in YBOCS and HAMD can be seen as indirectly representative of patient improvement in anorexia.

The body mass index, on the other hand, did not show a significant difference between the SCC and NAc groups. This result may be due to the heterogenicity between the two groups. The mean age of the patients receiving DBS of the SCC, 38.10 years old, was significantly older than the mean age of 23.71 years old in the NAc group. Furthermore, although the T-test did not show a statistically significant difference, there was nearly one in the difference in the duration of the disease between the groups (p=059628). The one-way ANCOVA approach used in this study did not account for these cofounders and thus this result may not accurately reflect the true difference. Although no difference was found between the SCC and NAc it should be noted that both produced improvements in BMI in. These findings of improvement in BMI regardless of the zone targeted are in line with a traditional meta-analysis conducted by Karaszewska et al., [34] and a systematic review by Potes et al., [35] which found DBS capable of weight restoration, improving the quality of life, and reducing psychiatric symptoms severity in AN patients.

5. Strengths and Limitations

This analysis conducted the first comprehensive comparison of SCC and NAc as the stimulation targets in AN. Furthermore, as the study considered the heterogeneity of preoperative values of BMI, YBOCS, and HAMD between the groups, it was able to statistically assess the postoperative values removing the influence the baseline values had. This study has the potential to help future investigators identify the most appropriate target for DBS in AN. This ultimately will help improve results in future sham-controlled trials, accelerating the implication of DBS to improve the lives of patients suffering from AN.

This systemic analysis and individual patient data meta-analysis had several limitations. First, this study included 72 patients of which only 1 was male. This ratio is not representative of AN, which typically affects about 3 women for each man, and thus the ability to apply these results to men suffering from AN is evidently limited. Another limitation lies in the fact that all the publications used in the analysis were either experimental studies without random allocation, “Quasi-Experimental Studies”, or case reports. This limits the quality of evidence in which this analysis is based upon. The study design using the ANCOVA analysis attempted to mitigate some of the confounding this non randomization produced, but admittingly, it is not possible to remove it completely through statistical analysis alone. Finally, in the quantitative analysis some studies were not included due to a lack of individual patient data which may have incremented reporting bias in the quantitative analysis.

6. Conclusion

Anorexia Nervosa is an illness with a high mortality and high relapse rates and thus DBS could potentially play a role in treatment-refractory patients. As of date, DBS is investigational in nature and not a standard treatment option with mixed results due to a large heterogenicity in; target zones, stimulation parameters, and patient demographics (Table 2 from the qualitative analysis). The targeted zones have included the SCC, NAc, subgenual cingulate, ventral capsule/ventral striatum, and MFB/BNST. Furthermore, anecdotical data from patients with movement disorders with DBS of the GPi and STN have also reported some small changes in eating habits when these areas are stimulated. The most promising DBS targets for anorexia nervosa to date are unsurprisingly the two targets with trials involving the greatest number of patients, the NAc and SCC. Amongst the 8 studies of the SCC and NAc that fit inclusion criteria, both targets have produced heterogeneous results in terms of effectivity. Both of these aforementioned brain regions have scientific rationale for being selected as DBS target for Anorexia, but neither has been tested, as of date, in sham-controlled trials. Thus, moving forward, investigators of these controlled trials will need to choose which zone to implant the DBS electrodes. Based on the outcomes of this investigation, which showed statistically significant improvements in YBOCS and HAMD scores, the subcallosal cingulate has shown to be a better target for improving psychological outcomes. Furthermore, although the BMI was not shown to differ in this study, it is important to note that the groups of patients assessed for BMI, receiving SCC vs NAc, were significantly different in age. Finally, both targets have shown to be generally safe, with very few serious adverse effects reported in either. Thus, as the primary goal of Anorexia Nervosa treatment is to return the patient to a physiological bodyweight, both the SCC and NAc warrant future investigation.

Furthermore, if the sample population is composed of patients with comorbid depression or obsessive-compulsion, DBS of the SCC should be prioritized over the NAc. Finally, independent of the target zone chosen, further investigation should be done in the form of randomized, controlled trials with larger sample sizes to determine the efficacy, optimal stimulation parameters, inclusion criteria, and potential for standard clinical use.

7. Funding and ethical considerations

This study received no outside funding, nor has affiliation with any entity performing the studies included in this investigation.

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9. Annexes:

1. Joanna Briggs Institute Critical Appraisal 1 - Israel et al., 2010
2. Joanna Briggs Institute Critical Appraisal 2 - Wu et al., 2013
3. Joanna Briggs Institute Critical Appraisal 3 - McLaughlin et al., 2013
4. Joanna Briggs Institute Critical Appraisal 4 - Lipsman et al., 2013
5. Joanna Briggs Institute Critical Appraisal 5 - Zhang et al., 2013
6. Joanna Briggs Institute Critical Appraisal 6 - Wang et al., 2013
7. Joanna Briggs Institute Critical Appraisal 7 - Lipsman et al., 2017
8. Joanna Briggs Institute Critical Appraisal 8 - Blomstetdt et al., 2017
9. Joanna Briggs Institute Critical Appraisal 9 - Manuelli et al., 2019
10. Joanna Briggs Institute Critical Appraisal 10 - Liu et al., 2020
11. Joanna Briggs Institute Critical Appraisal 11 - Villalba et al., 2020
12. Statistical Analysis Excel Workbook

JBI CRITICAL APPRAISAL CHECKLIST FOR CASE REPORTS

Reviewer_Matthew James Weinrauch_____ Date____29/01/2022___

Author_____Israel et al._____Year__2010_____ Record Number____01M_____

	Yes	No	Unclear	Not applicable
1. Were patient's demographic characteristics clearly described?	■	☐	☐	☐
2. Was the patient's history clearly described and presented as a timeline?	☐	■	☐	☐
3. Was the current clinical condition of the patient on presentation clearly described?	■	☐	☐	☐
4. Were diagnostic tests or assessment methods and the results clearly described?	■	☐	☐	☐
5. Was the intervention(s) or treatment procedure(s) clearly described?	■	☐	☐	☐
6. Was the post-intervention clinical condition clearly described?	■	☐	☐	☐
7. Were adverse events (harms) or unanticipated events identified and described?	☐	■	☐	☐
8. Does the case report provide takeaway lessons?	■	☐	☐	☐

Overall appraisal: Include ■ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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JBI CRITICAL APPRAISAL CHECKLIST FOR QUASI-EXPERIMENTAL STUDIES

Reviewer_Matthew James Weinrauch_____ Date____29/01/2022___

Author_____Wu et al. _____Year_____2013_____ Record Number____02M_____

	Yes	No	Unclear	Not applicable
1. Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	■	☐	☐	☐
2. Were the participants included in any comparisons similar?	■	☐	☐	☐
3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	☐	☐	☐	■
4. Was there a control group?	☐	■	☐	☐
5. Were there multiple measurements of the outcome both pre and post the intervention/exposure?	☐	■	☐	☐
6. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	■	☐	☐	☐
7. Were the outcomes of participants included in any comparisons measured in the same way?	■	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	■	☐
9. Was appropriate statistical analysis used?	☐	■	☐	☐

Overall appraisal: Include ■ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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JBI CRITICAL APPRAISAL CHECKLIST FOR CASE REPORTS

Reviewer_Matthew James Weinrauch_____ Date____29/01/2022___

Author_____ McLaughlin et al._____ Year____2013_____ Record Number____03M_____

	Yes	No	Unclear	Not applicable
1. Were patient's demographic characteristics clearly described?	■	☐	☐	☐
2. Was the patient's history clearly described and presented as a timeline?	☐	■	☐	☐
3. Was the current clinical condition of the patient on presentation clearly described?	■	☐	☐	☐
4. Were diagnostic tests or assessment methods and the results clearly described?	■	☐	☐	☐
5. Was the intervention(s) or treatment procedure(s) clearly described?	■	☐	☐	☐
6. Was the post-intervention clinical condition clearly described?	■	☐	☐	☐
7. Were adverse events (harms) or unanticipated events identified and described?	☐	■	☐	☐
8. Does the case report provide takeaway lessons?	■	☐	☐	☐

Overall appraisal: Include ■ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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JBI CRITICAL APPRAISAL CHECKLIST FOR QUASI-EXPERIMENTAL STUDIES

Reviewer_Matthew James Weinrauch_____ Date____29/01/2022___

Author_____ Lipsman et al. _____ Year_____2013____ Record Number____04M_____

	Yes	No	Unclear	Not applicable
1. Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	■	☐	☐	☐
2. Were the participants included in any comparisons similar?	■	☐	☐	☐
3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	☐	☐	☐	■
4. Was there a control group?	☐	■	☐	☐
5. Were there multiple measurements of the outcome both pre and post the intervention/exposure?	■	☐	☐	☐
6. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	■	☐	☐	☐
7. Were the outcomes of participants included in any comparisons measured in the same way?	■	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	■	☐
9. Was appropriate statistical analysis used?	☐	■	☐	☐

Overall appraisal: Include ■ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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JBI CRITICAL APPRAISAL CHECKLIST FOR QUASI-EXPERIMENTAL STUDIES

Reviewer_Matthew James Weinrauch_____ Date____29/01/2022___

Author_____Zhang et al. _____Year_____2013_____ Record Number____05M_____

	Yes	No	Unclear	Not applicable
1. Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	☒	☐	☐	☐
2. Were the participants included in any comparisons similar?	☐	☒	☐	☐
3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	☐	☐	☒	☐
4. Was there a control group?	☒	☐	☐	☐
5. Were there multiple measurements of the outcome both pre and post the intervention/exposure?	☐	☒	☐	☐
6. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	☐	☒	☐	☐
7. Were the outcomes of participants included in any comparisons measured in the same way?	☒	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☒	☐
9. Was appropriate statistical analysis used?	☒	☐	☐	☐

Overall appraisal: Include ☒ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

JBI CRITICAL APPRAISAL CHECKLIST FOR QUASI-EXPERIMENTAL STUDIES

Reviewer_Matthew James Weinrauch_____ Date____29/01/2022___

Author_____Wang et al. _____Year_____2013_____ Record Number____06M_____

	Yes	No	Unclear	Not applicable
1. Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	■	☐	☐	☐
2. Were the participants included in any comparisons similar?	■	☐	☐	☐
3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	☐	☐	☐	■
4. Was there a control group?	☐	■	☐	☐
5. Were there multiple measurements of the outcome both pre and post the intervention/exposure?	☐	■	☐	☐
6. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	■	☐	☐	☐
7. Were the outcomes of participants included in any comparisons measured in the same way?	■	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	■	☐
9. Was appropriate statistical analysis used?	■	☐	☐	☐

Overall appraisal: Include ■ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

JBI CRITICAL APPRAISAL CHECKLIST FOR QUASI-EXPERIMENTAL STUDIES

Reviewer_Matthew James Weinrauch_____ Date____29/01/2022___

Author____Lipsman et al. _____Year_____2017____ Record Number____07M_____

	Yes	No	Unclear	Not applicable
1. Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	☒	☐	☐	☐
2. Were the participants included in any comparisons similar?	☒	☐	☐	☐
3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	☐	☐	☐	☒
4. Was there a control group?	☐	☒	☐	☐
5. Were there multiple measurements of the outcome both pre and post the intervention/exposure?	☐	☒	☐	☐
6. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	☒	☐	☐	☐
7. Were the outcomes of participants included in any comparisons measured in the same way?	☒	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☒	☐
9. Was appropriate statistical analysis used?	☒	☐	☐	☐

Overall appraisal: Include ☒ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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JBI CRITICAL APPRAISAL CHECKLIST FOR CASE REPORTS

Reviewer_Matthew James Weinrauch_____ Date____29/01/2022___

Author_____Blomstedt et al._____ Year____2013_____ Record Number____08M_____

	Yes	No	Unclear	Not applicable
1. Were patient's demographic characteristics clearly described?	■	☐	☐	☐
2. Was the patient's history clearly described and presented as a timeline?	☐	■	☐	☐
3. Was the current clinical condition of the patient on presentation clearly described?	■	☐	☐	☐
4. Were diagnostic tests or assessment methods and the results clearly described?	■	☐	☐	☐
5. Was the intervention(s) or treatment procedure(s) clearly described?	■	☐	☐	☐
6. Was the post-intervention clinical condition clearly described?	■	☐	☐	☐
7. Were adverse events (harms) or unanticipated events identified and described?	☐	■	☐	☐
8. Does the case report provide takeaway lessons?	■	☐	☐	☐

Overall appraisal: Include ■ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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JBI CRITICAL APPRAISAL CHECKLIST FOR CASE REPORTS

Reviewer_Matthew James Weinrauch_____ Date____29/01/2022___

Author_____Manuelli et al._____Year____2019____ Record Number____09M_____

	Yes	No	Unclear	Not applicable
1. Were patient's demographic characteristics clearly described?	■	☐	☐	☐
2. Was the patient's history clearly described and presented as a timeline?	■	☐	☐	☐
3. Was the current clinical condition of the patient on presentation clearly described?	■	☐	☐	☐
4. Were diagnostic tests or assessment methods and the results clearly described?	■	☐	☐	☐
5. Was the intervention(s) or treatment procedure(s) clearly described?	■	☐	☐	☐
6. Was the post-intervention clinical condition clearly described?	■	☐	☐	☐
7. Were adverse events (harms) or unanticipated events identified and described?	☐	■	☐	☐
8. Does the case report provide takeaway lessons?	■	☐	☐	☐

Overall appraisal: Include ■ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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JBI CRITICAL APPRAISAL CHECKLIST FOR QUASI-EXPERIMENTAL STUDIES

Reviewer_Matthew James Weinrauch_____ Date____29/01/2022___

Author____Liu et al._____ Year_____2020____ Record Number____10M_____

	Yes	No	Unclear	Not applicable
1. Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	■	☐	☐	☐
2. Were the participants included in any comparisons similar?	■	☐	☐	☐
3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	☐	☐	☐	■
4. Was there a control group?	☐	■	☐	☐
5. Were there multiple measurements of the outcome both pre and post the intervention/exposure?	■	☐	☐	☐
6. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	■	☐	☐	☐
7. Were the outcomes of participants included in any comparisons measured in the same way?	■	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	■	☐
9. Was appropriate statistical analysis used?	■	☐	☐	☐

Overall appraisal: Include ■ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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JBI CRITICAL APPRAISAL CHECKLIST FOR QUASI-EXPERIMENTAL STUDIES

Reviewer_Matthew James Weinrauch_____ Date____29/01/2022___

Author_____Villalba et al. _____Year_____2020____ Record Number____11M_____

	Yes	No	Unclear	Not applicable
1. Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	■	☐	☐	☐
2. Were the participants included in any comparisons similar?	■	☐	☐	☐
3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	☐	☐	☐	■
4. Was there a control group?	☐	■	☐	☐
5. Were there multiple measurements of the outcome both pre and post the intervention/exposure?	■	☐	☐	☐
6. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	■	☐	☐	☐
7. Were the outcomes of participants included in any comparisons measured in the same way?	■	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	■	☐
9. Was appropriate statistical analysis used?	■	☐	☐	☐

Overall appraisal: Include ■ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

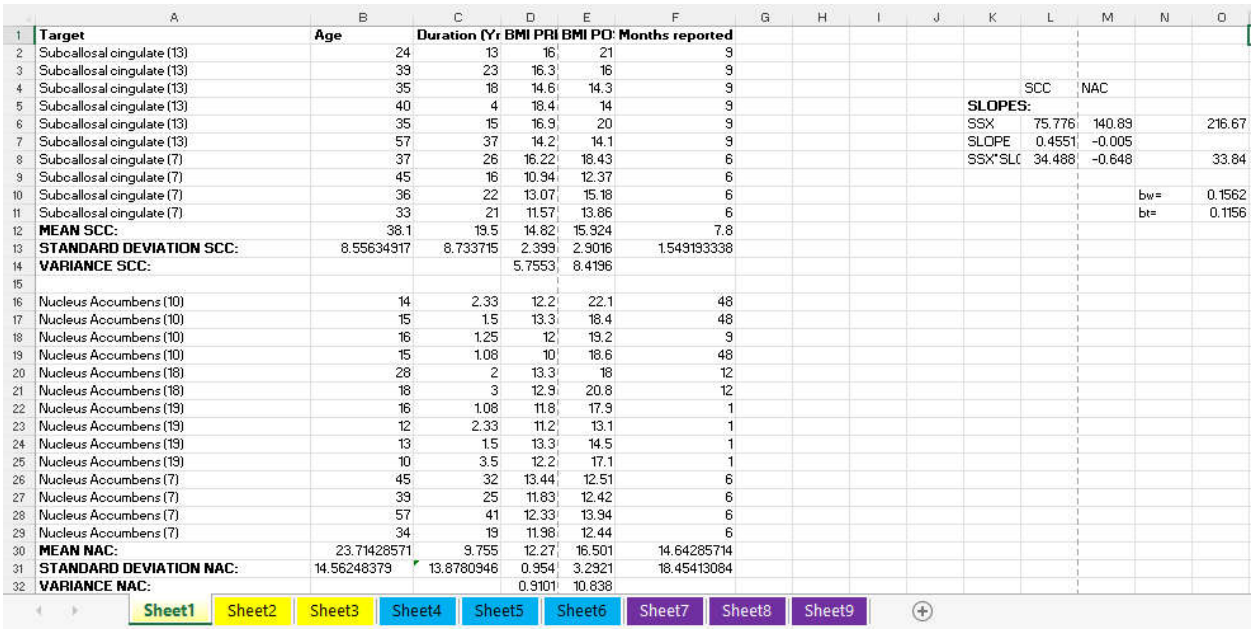
_____

_____

_____

Annex 12: Statistical Analysis Excel Workbook

Sheets 1-3 BMI Analysis:



	A	B	C	D	E	F	K	L	M	N	O
1	**Target**	**Age**	**Duration (Yr**	**BMI PRI**	**BMI PO:**	**Months reported**					
2	Subcallosal cingulate (13)	24	13	16	21	9					
3	Subcallosal cingulate (13)	39	23	16.3	16	9					
4	Subcallosal cingulate (13)	35	18	14.6	14.3	9		SCC	NAC		
5	Subcallosal cingulate (13)	40	4	18.4	14	9	**SLOPES:**				
6	Subcallosal cingulate (13)	35	15	16.9	20	9	SSX	75.776	140.89		216.67
7	Subcallosal cingulate (13)	57	37	14.2	14.1	9	SLOPE	0.4551	-0.005		
8	Subcallosal cingulate (7)	37	26	16.22	18.43	6	SSX*SLO	34.488	-0.648		33.84
9	Subcallosal cingulate (7)	45	16	10.94	12.37	6					
10	Subcallosal cingulate (7)	36	22	13.07	15.18	6				bw=	0.1562
11	Subcallosal cingulate (7)	33	21	11.57	13.86	6				bt=	0.1156
12	**MEAN SCC:**	38.1	19.5	14.82	15.924	7.8					
13	**STANDARD DEVIATION SCC:**	8.55634917	8.733715	2.399	2.9016	1.549193338					
14	**VARIANCE SCC:**			5.7553	8.4196						
15											
16	Nucleus Accumbens (10)	14	2.33	12.2	22.1	48					
17	Nucleus Accumbens (10)	15	1.5	13.3	18.4	48					
18	Nucleus Accumbens (10)	16	1.25	12	19.2	9					
19	Nucleus Accumbens (10)	15	1.08	10	18.6	48					
20	Nucleus Accumbens (18)	28	2	13.3	18	12					
21	Nucleus Accumbens (18)	18	3	12.9	20.8	12					
22	Nucleus Accumbens (19)	16	1.08	11.8	17.9	1					
23	Nucleus Accumbens (19)	12	2.33	11.2	13.1	1					
24	Nucleus Accumbens (19)	13	1.5	13.3	14.5	1					
25	Nucleus Accumbens (19)	10	3.5	12.2	17.1	1					
26	Nucleus Accumbens (7)	45	32	13.44	12.51	6					
27	Nucleus Accumbens (7)	39	25	11.83	12.42	6					
28	Nucleus Accumbens (7)	57	41	12.33	13.94	6					
29	Nucleus Accumbens (7)	34	19	11.98	12.44	6					
30	**MEAN NAC:**	23.71428571	9.755	12.27	16.501	14.64285714					
31	**STANDARD DEVIATION NAC:**	14.56248379	13.8780946	0.954	3.2921	18.45413084					
32	**VARIANCE NAC:**			0.9101	10.838						

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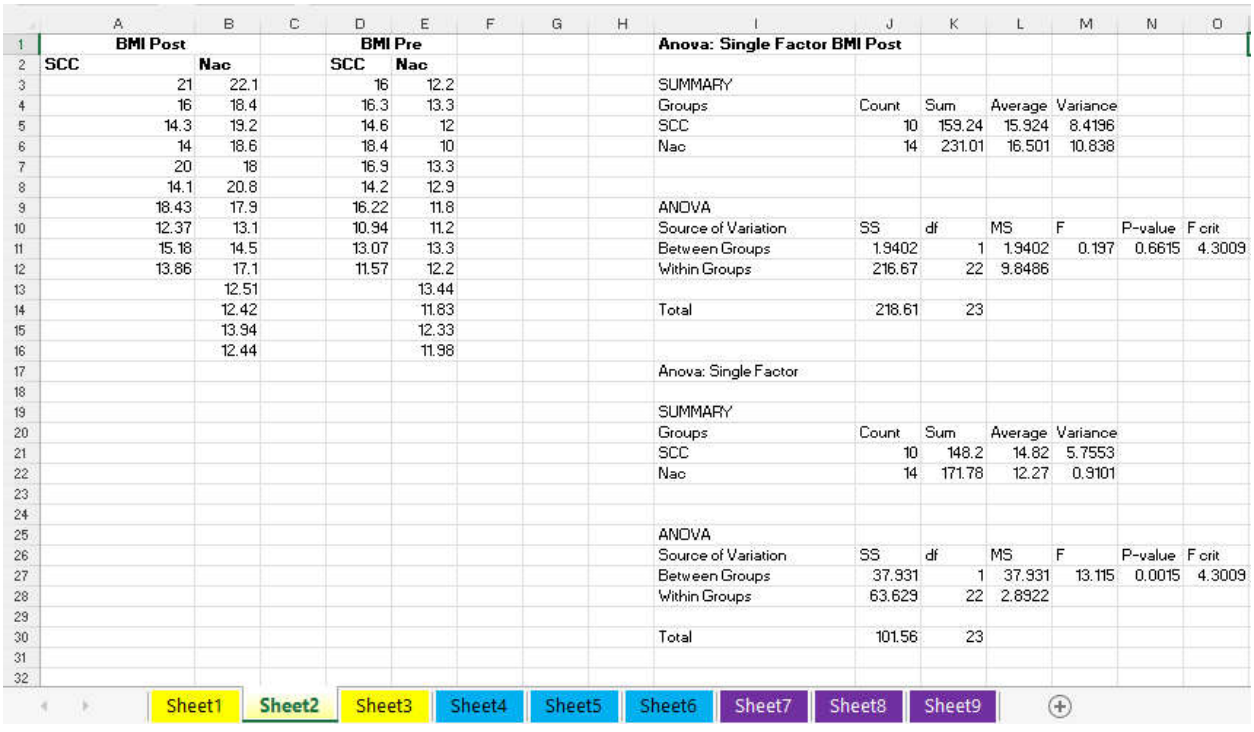
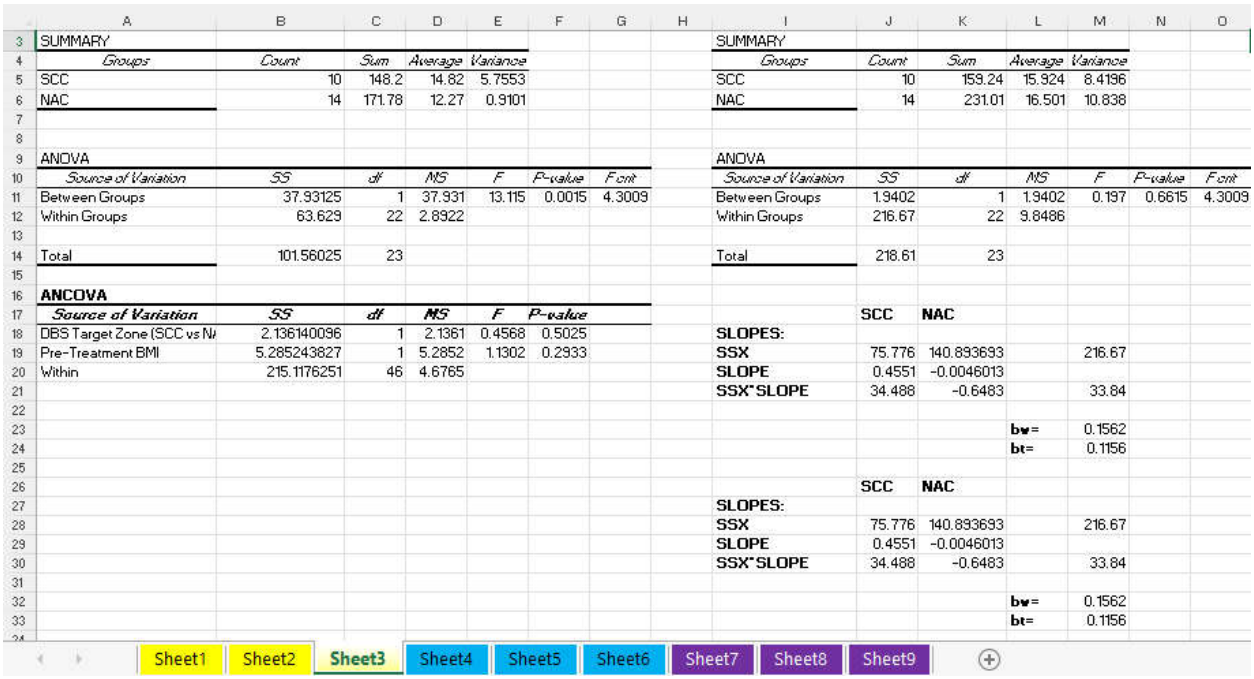


	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
1	**BMI Post**			**BMI Pre**					**Anova: Single Factor BMI Post**						
2	**SCC**	**Nac**		**SCC**	**Nac**										
3	21	22.1		16	12.2				SUMMARY						
4	16	18.4		16.3	13.3				Groups	Count	Sum	Average	Variance		
5	14.3	19.2		14.6	12				SCC	10	159.24	15.924	8.4196		
6	14	18.6		18.4	10				Nac	14	231.01	16.501	10.838		
7	20	18		16.9	13.3										
8	14.1	20.8		14.2	12.9										
9	18.43	17.9		16.22	11.8				ANOVA						
10	12.37	13.1		10.94	11.2				Source of Variation	SS	df	MS	F	P-value	F crit
11	15.18	14.5		13.07	13.3				Between Groups	1.9402	1	1.9402	0.197	0.6615	4.3009
12	13.86	17.1		11.57	12.2				Within Groups	216.67	22	9.8486			
13		12.51			13.44										
14		12.42			11.83				Total	218.61	23				
15		13.94			12.33										
16		12.44			11.98										
17									Anova: Single Factor						
18															
19									SUMMARY						
20									Groups	Count	Sum	Average	Variance		
21									SCC	10	148.2	14.82	5.7553		
22									Nac	14	171.78	12.27	0.9101		
23															
24															
25									ANOVA						
26									Source of Variation	SS	df	MS	F	P-value	F crit
27									Between Groups	37.931	1	37.931	13.115	0.0015	4.3009
28									Within Groups	63.629	22	2.8922			
29															
30									Total	101.56	23				
31															
32															

Sheet1 | Sheet2 | Sheet3 | Sheet4 | Sheet5 | Sheet6 | Sheet7 | Sheet8 | Sheet9



SUMMARY						
Groups	*Count*	*Sum*	*Average*	*Variance*		
SCC	10	148.2	14.82	5.7553		
NAC	14	171.78	12.27	0.9101		

ANOVA						
Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	37.93125	1	37.931	13.115	0.0015	4.3009
Within Groups	63.629	22	2.8922			
Total	101.56025	23				

ANCOVA					
Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*
DBS Target Zone (SCC vs N	2.136140096	1	2.1361	0.4568	0.5025
Pre-Treatment BMI	5.285243827	1	5.2852	1.1302	0.2933
Within	215.1176251	46	4.6765		

SUMMARY				
Groups	*Count*	*Sum*	*Average*	*Variance*
SCC	10	159.24	15.924	8.4196
NAC	14	231.01	16.501	10.838

ANOVA						
Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	1.9402	1	1.9402	0.197	0.6615	4.3009
Within Groups	216.67	22	9.8486			
Total	218.61	23				

	SCC	**NAC**		
SLOPES:				
SSX	75.776	140.893693		216.67
SLOPE	0.4551	-0.0046013		
SSX*SLOPE	34.488	-0.6483		33.84
			bw=	0.1562
			bt=	0.1156

	SCC	**NAC**		
SLOPES:				
SSX	75.776	140.893693		216.67
SLOPE	0.4551	-0.0046013		
SSX*SLOPE	34.488	-0.6483		33.84
			bw=	0.1562
			bt=	0.1156

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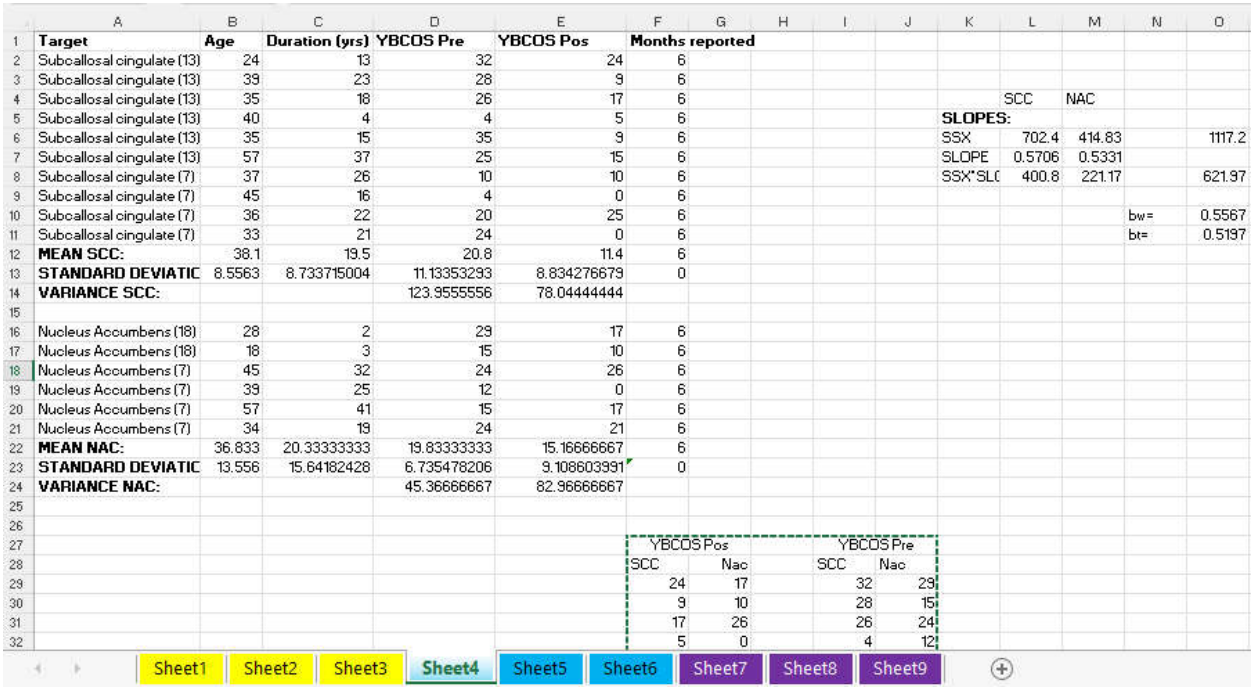
Sheets 4-6 YBCOS Analysis



Target	Age	Duration (yrs)	YBCOS Pre	YBCOS Pos	Months reported
Subcallosal cingulate (13)	24	13	32	24	6
Subcallosal cingulate (13)	39	23	28	9	6
Subcallosal cingulate (13)	35	18	26	17	6
Subcallosal cingulate (13)	40	4	4	5	6
Subcallosal cingulate (13)	35	15	35	9	6
Subcallosal cingulate (13)	57	37	25	15	6
Subcallosal cingulate (7)	37	26	10	10	6
Subcallosal cingulate (7)	45	16	4	0	6
Subcallosal cingulate (7)	36	22	20	25	6
Subcallosal cingulate (7)	33	21	24	0	6
MEAN SCC:	38.1	19.5	20.8	11.4	6
STANDARD DEVIATIC	8.5563	8.733715004	11.13353293	8.834276679	0
VARIANCE SCC:			123.9555556	78.04444444	
Nucleus Accumbens (18)	28	2	29	17	6
Nucleus Accumbens (18)	18	3	15	10	6
Nucleus Accumbens (7)	45	32	24	26	6
Nucleus Accumbens (7)	39	25	12	0	6
Nucleus Accumbens (7)	57	41	15	17	6
Nucleus Accumbens (7)	34	19	24	21	6
MEAN NAC:	36.833	20.33333333	19.83333333	15.16666667	6
STANDARD DEVIATIC	13.556	15.64182428	6.735478206	9.108603991	0
VARIANCE NAC:			45.36666667	82.96666667	

			SCC	NAC
SLOPES:				
SSX	702.4	414.83		1117.2
SLOPE	0.5706	0.5331		
SSX*SL(	400.8	221.17		621.97
			bw=	0.5567
			bt=	0.5197

YBCOS Pos		YBCOS Pre	
SCC	Nac	SCC	Nac
24	17	32	29
9	10	28	15
17	26	26	24
5	0	4	12

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YBOCS Post			YBOCS Pre	
SCC	Nac		SCC	Nac
24	17		32	29
9	10		28	15
17	26		26	24
5	0		4	12
9	17		35	15
15	21		25	24
10			10	
0			4	
25			20	
0			24	

Anova: Single Factor YBOCS Post

SUMMARY

Groups	Count	Sum	Average	Variance
SCC	10	114	11.4	78.044
Nac	6	91	15.167	82.967

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	53.204	1	53.204	0.6667	0.4279	4.6001
Within Groups	1117.2	14	79.802			
Total	1170.4	15				

Anova: Single Factor YBOCS Pre

SUMMARY

Groups	Count	Sum	Average	Variance
SCC	10	208	20.8	123.96
Nac	6	119	19.833	45.367

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	3.5042	1	3.5042	0.0365	0.8511	4.6001
Within Groups	1342.4	14	95.888			
Total	1345.9	15				

Sheet1 Sheet2 Sheet3 Sheet4 **Sheet5** Sheet6 Sheet7 Sheet8 Sheet9

Anova: Single Factor **PRETREATMENT YBOCS**

SUMMARY

Groups	*Count*	*Sum*	*Average*	*Variance*
SCC	10	208	20.8	123.96
NAC	6	119	19.833	45.367

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	3.5042	1	3.5042	0.0365	0.8511	4.6001
Within Groups	1342.4	14	95.888			
Total	1345.9	15				

ANCOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*
DBS Target Zone (SCC vs NAC)	105.68	1	105.68	4.5216	0.0418
Pre-Treatment YBCOS	346.25	1	346.25	14.814	0.0006
Within	701.19	30	23.373		

Anova: Single Factor **POSTTREATMENT YBOCS**

SUMMARY

Groups	*Count*	*Sum*	*Average*	*Variance*
SCC	10	114	11.4	78.044
NAC	6	91	15.167	82.967

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	53.204	1	53.204	0.6667	0.4279	4.6001
Within Groups	1117.2	14	79.802			
Total	1170.4	15				

	SCC	**NAC**		
SLOPES:				
SSX	702.4	414.83		1117.2
SLOPE	0.5706	0.5331		
SSX*SLOPE	400.8	221.17		621.97
			bw=	0.5567
			bt=	0.5197

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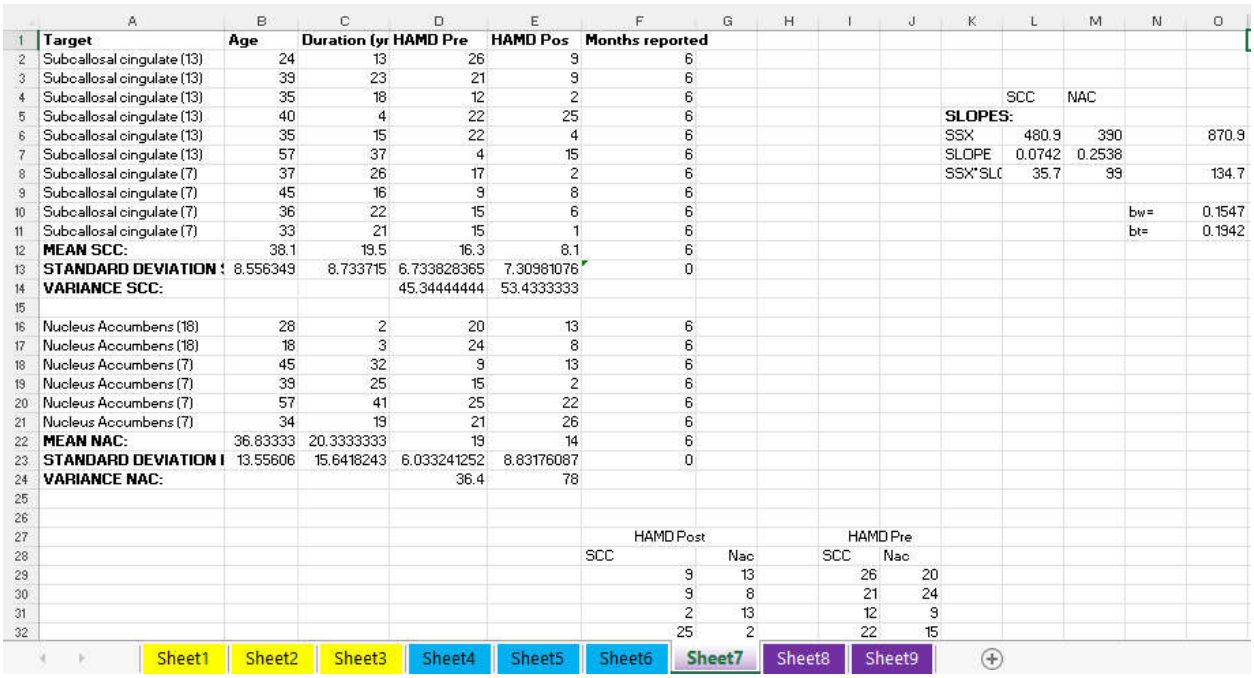
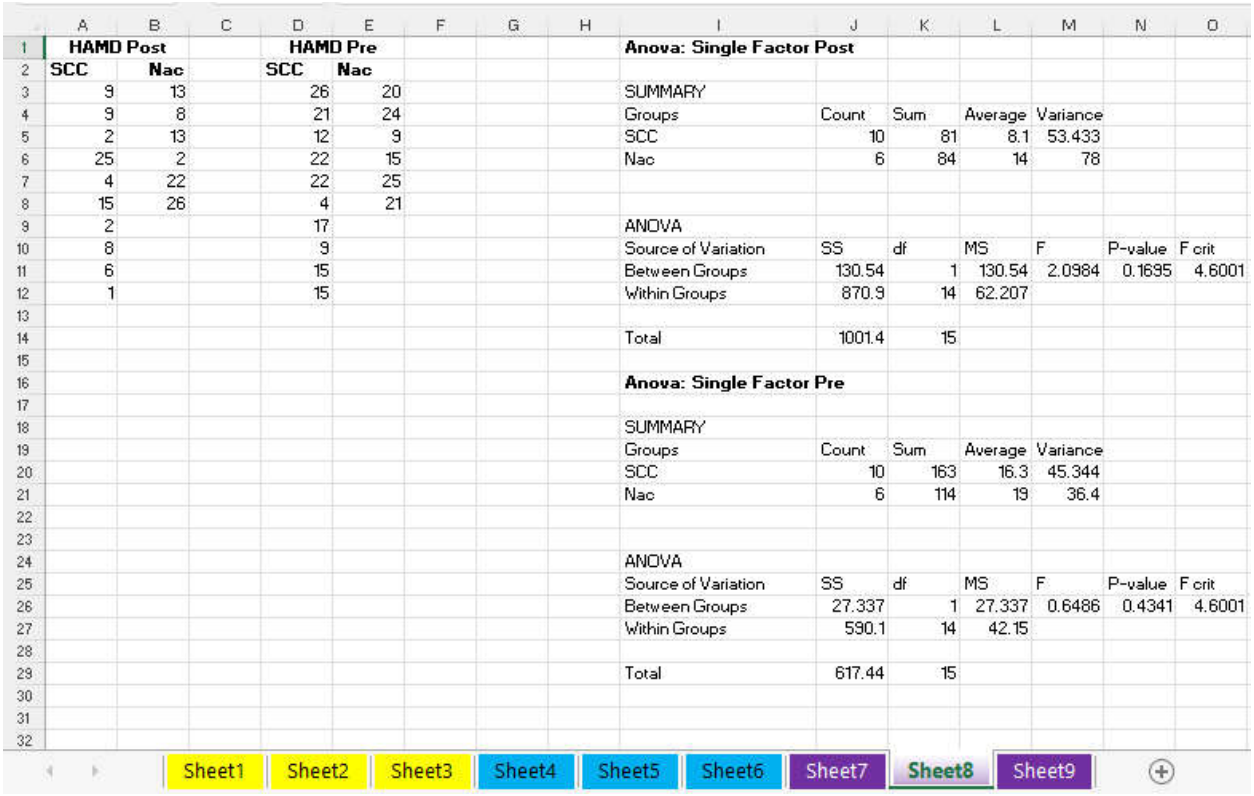
Sheets 7-9 HAMD Analysis



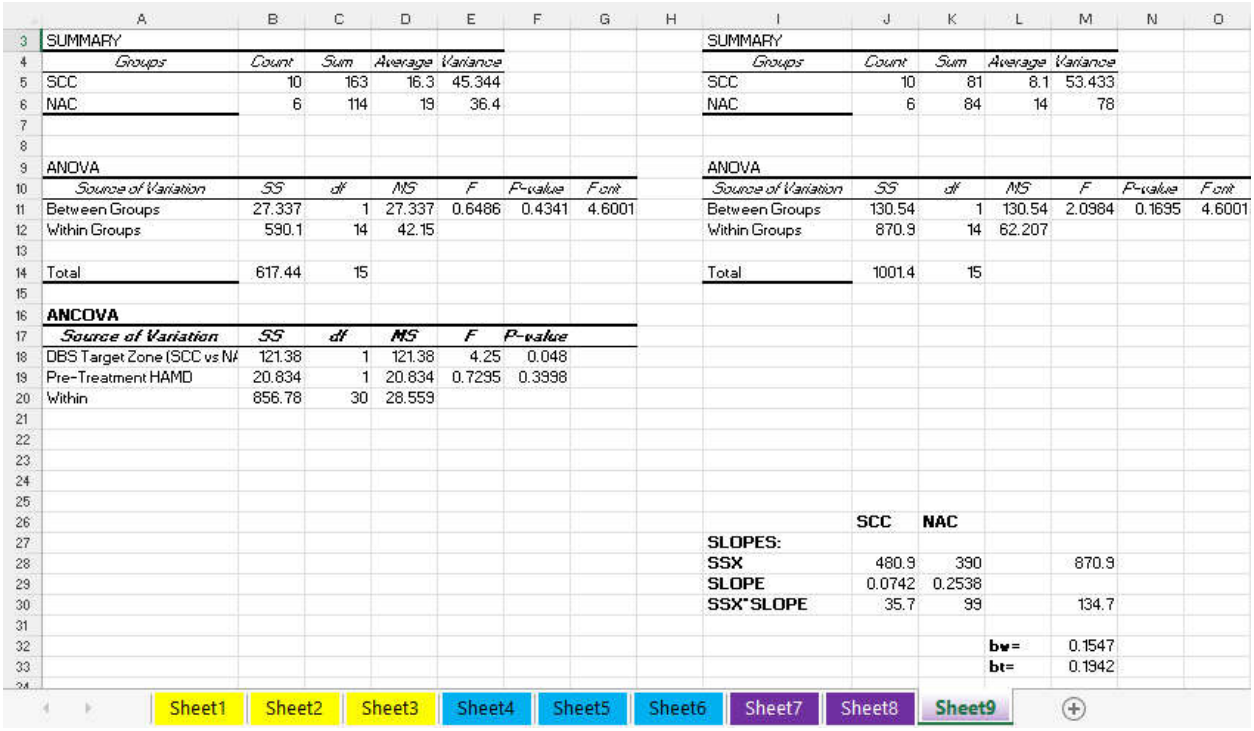
	A	B	C	D	E	F	K	L	M	N	O
1	**Target**	**Age**	**Duration (yr**	**HAMD Pre**	**HAMD Pos**	**Months reported**					
2	Subcallosal cingulate (13)	24	13	26	9	6					
3	Subcallosal cingulate (13)	39	23	21	9	6					
4	Subcallosal cingulate (13)	35	18	12	2	6		SCC	NAC		
5	Subcallosal cingulate (13)	40	4	22	25	6	**SLOPES:**				
6	Subcallosal cingulate (13)	35	15	22	4	6	SSX	480.9	390		870.9
7	Subcallosal cingulate (13)	57	37	4	15	6	SLOPE	0.0742	0.2538		
8	Subcallosal cingulate (7)	37	26	17	2	6	SSX*SLO	35.7	99		134.7
9	Subcallosal cingulate (7)	45	16	9	8	6					
10	Subcallosal cingulate (7)	36	22	15	6	6				bw=	0.1547
11	Subcallosal cingulate (7)	33	21	15	1	6				bt=	0.1942
12	**MEAN SCC:**	38.1	19.5	16.3	8.1	6					
13	**STANDARD DEVIATION S**	8.556349	8.733715	6.733828365	7.30981076	0					
14	**VARIANCE SCC:**			45.34444444	53.4333333						
15											
16	Nucleus Accumbens (18)	28	2	20	13	6					
17	Nucleus Accumbens (18)	18	3	24	8	6					
18	Nucleus Accumbens (7)	45	32	9	13	6					
19	Nucleus Accumbens (7)	39	25	15	2	6					
20	Nucleus Accumbens (7)	57	41	25	22	6					
21	Nucleus Accumbens (7)	34	19	21	26	6					
22	**MEAN NAC:**	36.83333	20.3333333	19	14	6					
23	**STANDARD DEVIATION I**	13.55606	15.6418243	6.033241252	8.83176087	0					
24	**VARIANCE NAC:**			36.4	78						
25											
26											
27						HAMD Post		HAMD Pre			
28						SCC	Nac	SCC	Nac		
29						9	13	26	20		
30						9	8	21	24		
31						2	13	12	9		
32						25	2	22	15		

Sheet1 | Sheet2 | Sheet3 | Sheet4 | Sheet5 | Sheet6 | **Sheet7** | Sheet8 | Sheet9



	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
1	**HAMD Post**			**HAMD Pre**					**Anova: Single Factor Post**						
2	**SCC**	**Nac**		**SCC**	**Nac**										
3	9	13		26	20				SUMMARY						
4	9	8		21	24				Groups	Count	Sum	Average	Variance		
5	2	13		12	9				SCC	10	81	8.1	53.433		
6	25	2		22	15				Nac	6	84	14	78		
7	4	22		22	25										
8	15	26		4	21										
9	2			17					ANOVA						
10	8			9					Source of Variation	SS	df	MS	F	P-value	F crit
11	6			15					Between Groups	130.54	1	130.54	2.0984	0.1695	4.6001
12	1			15					Within Groups	870.9	14	62.207			
13															
14									Total	1001.4	15				
15															
16									**Anova: Single Factor Pre**						
17															
18									SUMMARY						
19									Groups	Count	Sum	Average	Variance		
20									SCC	10	163	16.3	45.344		
21									Nac	6	114	19	36.4		
22															
23															
24									ANOVA						
25									Source of Variation	SS	df	MS	F	P-value	F crit
26									Between Groups	27.337	1	27.337	0.6486	0.4341	4.6001
27									Within Groups	590.1	14	42.15			
28															
29									Total	617.44	15				
30															
31															
32															

Sheet1 | Sheet2 | Sheet3 | Sheet4 | Sheet5 | Sheet6 | Sheet7 | **Sheet8** | Sheet9



	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
3	SUMMARY								SUMMARY						
4	*Groups*	*Count*	*Sum*	*Average*	*Variance*				*Groups*	*Count*	*Sum*	*Average*	*Variance*		
5	SCC	10	163	16.3	45.344				SCC	10	81	8.1	53.433		
6	NAC	6	114	19	36.4				NAC	6	84	14	78		
7															
8															
9	ANOVA								ANOVA						
10	*Source of Variation*	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*		*Source of Variation*	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
11	Between Groups	27.337	1	27.337	0.6486	0.4341	4.6001		Between Groups	130.54	1	130.54	2.0984	0.1695	4.6001
12	Within Groups	590.1	14	42.15					Within Groups	870.9	14	62.207			
13															
14	Total	617.44	15						Total	1001.4	15				
15															
16	**ANCOVA**														
17	***Source of Variation***	***SS***	***df***	***MS***	***F***	***P-value***									
18	DBS Target Zone (SCC vs NA	121.38	1	121.38	4.25	0.048									
19	Pre-Treatment HAMD	20.834	1	20.834	0.7295	0.3998									
20	Within	856.78	30	28.559											
21															
22															
23															
24															
25															
26										**SCC**	**NAC**				
27									**SLOPES:**						
28									**SSX**	480.9	390		870.9		
29									**SLOPE**	0.0742	0.2538				
30									**SSX*SLOPE**	35.7	99		134.7		
31															
32												**bw=**	0.1547		
33												**bt=**	0.1942		

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