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Deep brain stimulation in obsessive-compulsive disorder: Results from meta-analysis

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ABSTRACT

The aim of this work is to investigate the effectiveness of Deep Brain Stimulation (DBS) in patients with severe Obsessive Compulsive Disorder (OCD) who are resistant to pharmacological treatments, focusing on obsessive compulsive, depressive and anxiety symptoms as well as global function. A systematic review and meta-analysis including 25 studies (without language restrictions) from between 2003 and 2020 was performed. A total of 303 patients were evaluated twice (before and after DBS). After DBS treatment OCD patients with resistance to pharmacological treatments showed a significant improvement of obsessive-compulsive symptoms (25 studies; SMD=2.39; 95% CI, 1.91 to 2.87; $P<0.0001$), depression (9 studies; SMD= 1.19; 95%CI, 0.84 to 1.54; $P<0.0001$), anxiety (5 studies; SMD=1.00; 95%CI, 0.32 to 1.69; $P=0.004$) and functionality (7 studies; SMD=-3.51; 95%CI, -5.00 to -2.02; $P=0.005$) measured by the standardized scales: Yale Brown Obsessive Compulsive Scale (YBOCS), Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HAM-A) and Global Assessment of Function (GAF). Publication bias were discarded by using funnel plot. The main conclusions of this meta-analysis highlight the statistically significant effectiveness of DBS in patients with severe OCD who are resistant to conventional pharmacological treatments, underlying its role in global functioning apart from obsessive-compulsive symptoms.

1. Introduction

Obsessive-compulsive disorder (OCD) has been recognized by The World Health Organization as one of the ten biggest causes of global health problems (Baxter et al., 2014). The prevalence rate of OCD is 1.8% in children-youths and 1.2% in adults (2.3 lifetime prevalence) (Canals et al., 2012; Ruscio et al., 2010). The onset of symptoms appears during childhood and adolescence in about 50% of patients with OCD (Fenske and Petersen, 2015) and the average age of onset is 19.5 (Goodman et al., 2014) with variable course (Visser et al., 2014; Bjornsson et al., 2011). It has been associated with low quality of life, high disability levels and a heavy burden on caregivers and family (Jahangard et al. 2018; Fineberg et al., 2013), comparable to other disabling mental illnesses such as schizophrenia (Bobes et al., 2001).

OCD is characterized by the presence of persistent thoughts, images or impulses, which are experienced as intrusive and senseless (obsessions) and/or excessive repetitive behaviors or mental acts (compulsions) intended to neutralize the anxiety induced by the obsessions (American Psychiatric Association, 2000).

The first-line of treatment in OCD is selective serotonin re-uptake inhibitor (SSRIs) in combination with cognitive behavioral therapy, and the daily dose of SSRI or clomipramine is usually higher in the treatment of OCD than in the treatment of depression (Denys, 2006). Response rates vary between studies but approximately 60-80% respond to first-line treatment with SSRI or psychotherapy and about 90% of treatment including antipsychotics, leaving about 10% of patients with an unsatisfactory response and a high level of suffering (Denys, 2006). These patients are referred to as treatment-resistant or treatment-refractory.

Physical procedures that include brain surgery and deep brain

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stimulation (DBS) are reserved for these cases. In comparison with brain surgery, which causes of an irreversible injury to by radiofrequency or gamma rays focusing on one of the brain targets (cingulotomy and capsulotomy). DBS is a technique that affects cortico-striated-thalamus-cortical (CSTC) circuit fiber by implanting an electrical device in a brain target such as the anterior limb of the internal capsule/accumbens nucleus or thalamus/subthalamic nucleus (Vázquez-Bourgon et al., 2019; Alonso et al., 2015). These devices modify the targets operation with electricity sent from a pacemaker placed below the clavicle or under the abdominal skin. One of the many advantages is that the psychiatrist can modify the voltage used during the stimulation to modify the response (Perez et al., 2018).

The principal DBS targets used in resistant OCD patients are shown in Fig. 1: nucleus accumbens (NAc), subtalamic nucleus (STN), the bed nucleus of stria terminalis (BNST), anterior limb of internal capsule (ALIC), inferior thalamic peduncle (ITP) and medial forebrain bundle (MFB) (Vázquez-Bourgon et al., 2019). Regarding which target is the most effective, the results to date are contradictory. It has been hypothesized that the different response among patients may be related to different symptom profiles and partially distinct neural substrates (van den Heuvel et al., 2009). This fact allows us to think of individualized treatments by selecting therapeutic targets according to the symptomatic dimension presented by the patients (Mar-Barrutia et al., 2021).

This meta-analytical work focuses on the assessment of the efficacy of DBS in resistant and severe patients with OCD emerging from doubled-blind, sham-controlled trials, and observational studies. We focus on changes in obsessive compulsive behavior, depression, anxiety symptoms and functionality after the neuromodulator treatment.

2. Methods

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) (Moher et al., 2015) were followed to perform this meta-analysisband was prospectively registered on PROSPERO (CRD42021276362).

2.1. Search strategy

An electronic literature search was performed without language restrictions using MEDLINE/Pubmed, COCHRANE library, Fisterra, Scielo and Medes from the inception of the database until December 31, 2020. It was supplemented by a manual search of reference lists of included articles and relevant review on the topic. Search terms were (1) Obsessive Compulsive Disorder and (2) Deep Brain Stimulation and (3) Electric Stimulation. Authors of identified studies were contacted by email to obtain missing data required for meta-analysis.

2.2. Study selection/inclusion criteria

We included studies with the following characteristics: (1) human patients diagnosed with OCD; (2) where DBS technique was used; (3) quantitative data (mean +/- SD) of YBOCS, HAM-D, HAM-A and GAF (case reports or studies with at least 3 patients) (4) baseline and follow-up data available (brief clinical trials interventions and on-off results are not included).

All studies required patients whose symptoms of OCD were severe (with a score of between 24 and 31 on YBOCS) and resistant to pharmacological treatment (at least twelve weeks with high-dose SSRIs and

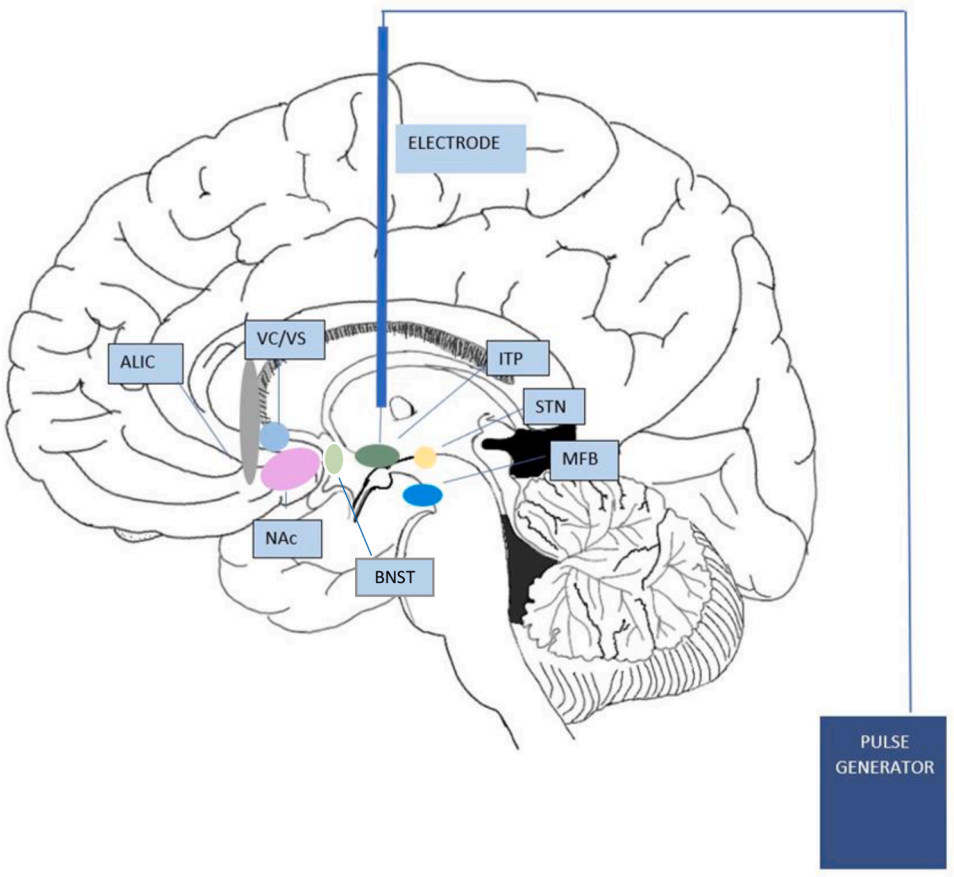

Fig. 1. Principal targets of Deep Brain Stimulation
ALIC: Anterior limb of the internal capsule; BNST: bed nucleus of the stria terminalis; ITP: Inferior thalamic peduncle; MFB: Medial forebrain bundle; NAc: Nucleus accumbens; STN: Subthalamic nucleus; VC/VS: Ventral capsule/ventral striatum.

augmentation strategies).

YBOCS (Goodman, 1989) constitutes the main way of objectively measuring the degree of OCD severity and its scale ranges from 0 to 40, with mild OCD being 16 or below and moderate/severe/extreme OCD from 24 to 40. HAM-D (Hamilton, 1967) ranges from 0 to 52, with mild depression from 8 to 13, moderate depression from 14 to 18 points, and severe depression above 22. HAM-A (Hamilton, 1959) ranges from 0 to 56. A score of 17 or less indicates mild levels of anxiety, a score of between 18 and 24 indicates moderate severity and finally a score of 24 to 30 indicates severe anxiety. HAM-D and HAM-A are the most frequently used scales to score depressive and anxiety symptoms in OCD patients.

GAF is a global assessment of function that considers three areas (psychological, social and occupational), as a hypothetical continuum of mental health. It determines the affectation of symptomatology of patients´ daily lives on a scale of 0 to 100, from low to superior functioning (Endicott, 1976).

2.3. Data extraction and outcomes

The selected data were extracted and entered by S.C and S.J-F, and the information was verified by each of them. All inconsistencies found were resolved by consensus.

2.4. Data analysis

Psychopathological data determined by standardized tests were meta-analyzed separately if the data was provided in ≥3 studies. We performed four different meta-analyses with clinical results from YBOCS, HAM-D, HAM-A and function assessment from GAF in patients with OCD before and after DBS.

Standardized mean differences (SMD) were estimated according to weight of sample size [±95% confidence intervals (CI)]. The heterogeneity among studies was explored by means of a X^2 test of homogeneity together with the I^2 statistic (a $P<0.05$ and an I^2 ≥50% indicating significant heterogeneity). We used funnel graphs (trial effect against trial size) to investigate the likelihood of publication bias. All data were analyzed with Review Manager 5.2 (http://community.cochrane.org/); analyses were two-sided, with alpha=0.05 and without correction for multiplicity.

3. Results

3.1. Search results

Of the 6.209 citations found, 352 articles were excluded based on title and abstract review and among the 35 potentially eligible our meta-

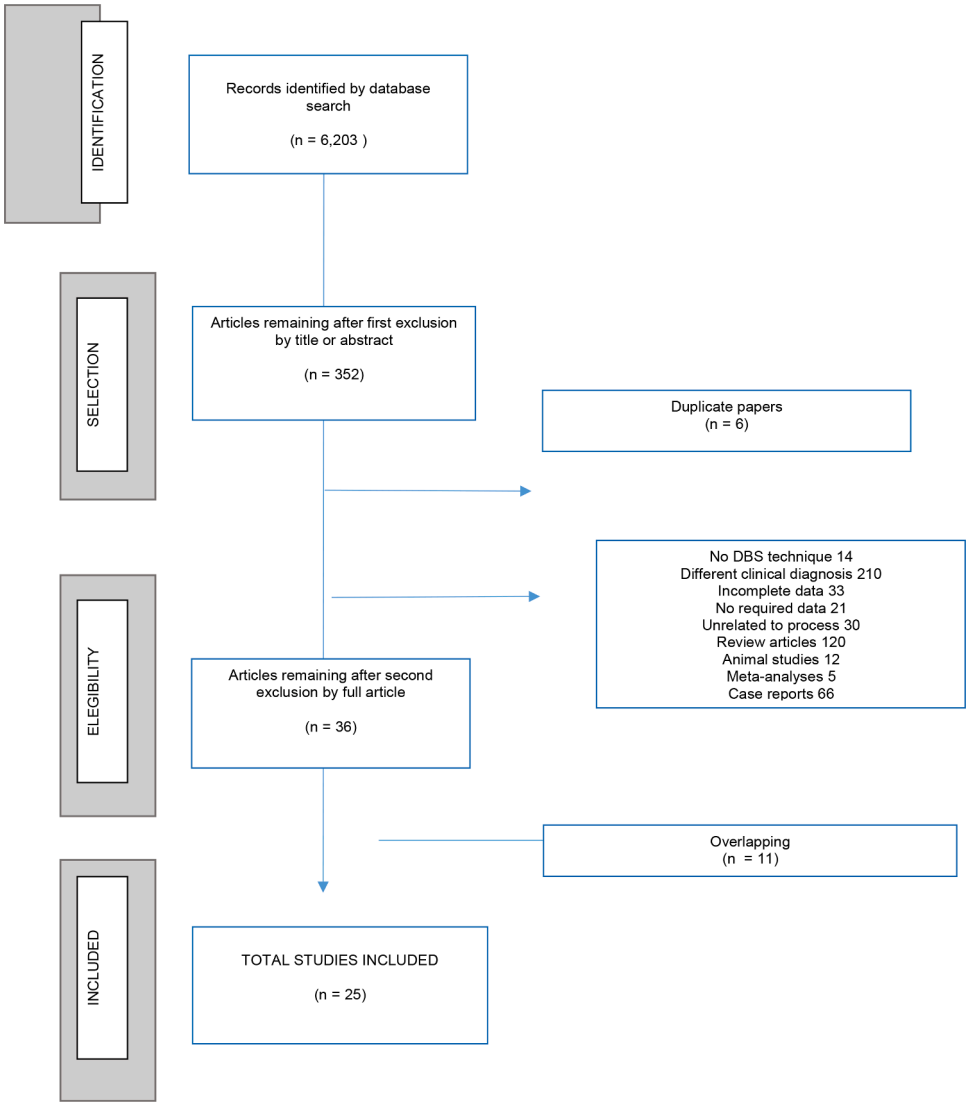

Fig. 2. Flow chart of article selection process

analysis included 25. After the first exclusion, 352 were excluded after full-text review for the following reasons (Fig. 2): (1) DBS was not applied (14 articles); (2) duplicated articles (6 articles); (3) no selected data were included (54 articles); (4) unrelated to process (30 articles); (5) Review articles (125); (6) Animal studies (12 articles); (7) Case reports (66 articles). This selection yielded 25 eligible studies (Fig. 2).

According to quality requirements considered by the CONSORT and STROBE statements for clinical trials and observational studies (Eldridge et al., 2016; Von Elm et al., 2007), the global quality of the studies included in the analysis was medium (13/25), as only 12 studies fulfilled quality criteria. Therefore, 10 studies were series of cases, 6 studies were observational and 8 were double-blinded clinical trial (supplemental Table S1).

3.2. Participant's characteristics

Characteristics of the 303 patients with OCD are presented in Table 1. Mean age of patients was 38.78 ± 8.72 and 44.85% were female. The mean illness duration of the disease was 21.31 ± 8.76. The mean age of the onset of the disease was 16 ± 7.21. During the DBS most of the patients were under pharmacological treatment: 74.4% were taking antidepressants, 55.82% were taking antipsychotics; 10.34% were taking mood stabilizers and 22.95% were taking anxiolytics. YBOCS, HAM-D, HAM-A and GAF score at baseline were 32.26 ± 3.50; 20.89 ± 5.86; 25.22 ± 5.75 and 34.00 ± 4.23 respectively.

3.3. OCD patients before and after deep brain stimulation

Yale–Brown Obsessive Compulsive Scale, YBOCS: Patients with OCD had a significant improvement after DBS (25 studies; SMD=2.39; 95% CI, 1.91 to 2.87; $P<0.0001$; $I^2=72\%$) (Fig. 3a). Publication bias was discarded by funnel plot. Sensitivity analysis which consisted of replicating the meta-analysis by excluding one of the studies at each step, did not significantly change the results.

Subgroup analysis found that YBOCS results improved after DBS using different targets: VC/VS (5 studies; SMD=3.72; 95%CI, 1.25 to 6.18; $P<0.0001$; $I^2=64\%$); NAc (3 studies; SMD=2.14; 95% CI, 1.46 to 2.81; $P=0.003$; $I^2=89\%$).

Considering only randomized double-blinded, on-off clinical trials, YBOCS changes continued to be significant, but heterogeneity did not change (8 studies; SMD=2.51; 95% CI, 1.80 to 3.22; $P<0.0001$; $I^2=66\%$).

Hamilton Depression Rating Scale, HAM-D: Scoring significantly decreased after DBS (9 studies; SMD= 1.19; 95%CI, 0.84 to 1.54; $P<0.0001$; $I^2=17\%$) (Fig. 3b). Funnel plot graphic seemed to discard the publication bias. Sensitivity analysis, with the replication of the analysis by excluding one of the studies at each step, did not change the results although we found an improvement in heterogeneity after the exclusion of one study reported in two different articles (Haq et al., 2011; Okun et al., 2007) (SMD=1.32; 95% CI, 1.02 to 1.62; $P<0.0001$; $I^2=0\%$).

Considering only randomized double-blinded, on-off clinical trials, HAM-D changes continue to be significant, but we found an improvement in heterogeneity (4 studies; SMD= 1.12; 95% CI, 0.67 to 1.56; $P<0.0001$; $I^2=0\%$).

Hamilton Anxiety Rating Scale, HAM-A: Scoring in anxiety significantly change after treatment with DBS (5 studies; SMD=1.00; 95%CI, 0.32 to 1.69; $P=0.004$; $I^2=59\%$) (Fig. 3c). Sensitivity analysis did not change the results although we found an improvement in heterogeneity after the exclusion of one study (Roh et al., 2012) (4 studies; SMD=1.11; 95% CI, 0.77 to 1.46; $P<0.0001$; $I^2=0\%$).

Global Assessment of Functioning, GAF: After DBS results improved significantly (7 studies; SMD=-3.51; 95%CI, -5.00 to -2.02; $P=0.005$; $I^2=90\%$) (Fig. 3d). Funnel plot graphic seemed to discard publication bias.

Table 1
Characteristics of patients included.

	OCD (n = 303)	
Age, mean (SD); n=274	38.78± 8.72	
Female sex, %; n=303	44.85%	
Illness duration, years, mean (SD); n=186	21.31 (8.76)	
Age at onset, years, mean (SD); n=136	16 (7.21)	
Treatment		
Antidepressant (%) 15 studies; n=195	74.4%	
Antipsychotics (%) 15 studies; n=195	55.82%	
Anxiolytics (%) 5 studies; n=195	22.95%	
Mood stabilizers (%) 15 studies; n=195	10.34%	
Psychometric studies	Baseline	Follow-up (mean 36.98 months)
YBOCS, mean (SD) 25 studies; n = 303	32.26 (3.5)	19.49 (7.01)
HAM-D 9 studies; n = 110	20.89 (5.86)	12.08 (7.02)
HAM-A 5 studies; n = 79	25.22 (5.75)	11.88 (8.75)
GAF 7 studies; n = 130	34 (4.23)	60.12 (9.78)

GAF: Global Assessment of Functioning scale; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale; Y-BOCS: Yale-Brown Obsessive-Compulsive Scale.

4. Discussion

This comprehensive meta-analysis includes patients with severe and resistant OCD treated with DBS. We found that after treatment the patients experienced a significant improvement in obsessive-compulsive, affective symptoms (depressive and anxiety) and functionality measured with YBOCS, HAM-D, HAM-A and GAF respectively. In the case of YBOCS, we found a significant improvement in subgroups analysis after stimulation of VC/VS and NAc nucleous. Changes with other target could not performed due to the lack of studies which evaluate different targets independently.

4.1. Obsessive-compulsive symptomatology

We found that in patients after treatment, the random effect model estimated a standardized mean difference of 2.39 in YBOOCS-score (confidence interval from 1.91 to 2.87) and a further small reduction considering only randomized double-blinded, on-off clinical trials, 2.51 (from 1.80 to 3.22). This result agrees with findings of a previous meta-analytic work, in which the authors found a 41.5% reduction of YBOCS-score in severe and resistant OCD after treatment with DBS with a global percentage of respondents of 60.0% (Alonso et al., 2015). However, there are some doubts about which of the DBS targets (ALIC, VC/VS, NAc, limbic STN, or ITP) are the most efficacious. Traditionally NAc has been the most stimulated area and it seems to be effective in controlling obsessive-compulsive symptomatology during bilateral stimulation (Alonso et al., 2015) although there are some doubts about its efficacy in unilateral treatment (Huff et al., 2010).

Tyagi et al. (2019) find that during VC/VS and amSTN (anteromedial subthalamic nucleus) stimulation, the magnitude of Y-BOCS reduction at either site does not differ, but the patient also exhibits other different effects during stimulation of both brain areas. While stimulation of the amSTN could be beneficial in cognitive functioning such as flexibility, stimulation of the VC/VS could result in an improvement of mood (Tyagi et al., 2019). In the present work, as the previous author hypothesized, we found that patients with severe and resistant OCD experienced significant improvement of obsessive-compulsive

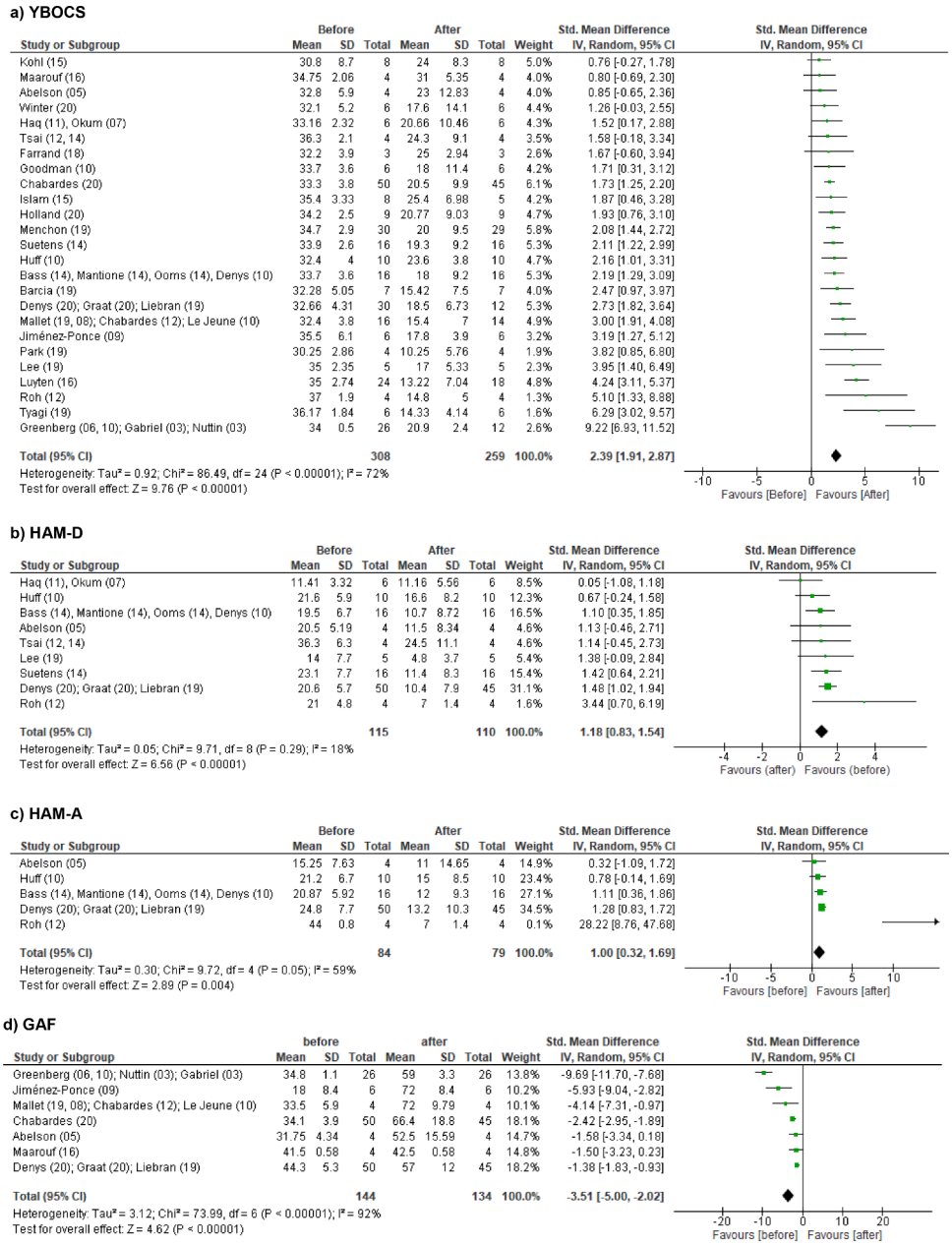

Fig. 3. Results: before and after DBS in patients with OCD

symptoms after stimulation of the different targets without differences between VC/VS and NAc. The reason for this result could be that there are not specific differences in obsessive-compulsive symptoms between them. DBS could have distant effects on abnormal neural connectivity in the CSTC circuit and might explain why stimulation of different brain regions finally achieves similar percentages of improvement (Alonso et al., 2015).

Regarding the long-term efficacy of the treatment, many studies have reported satisfactory results (measured with YBOCS), for example after the stimulation of the VC/VS the improvement could continue for more than 36 months (Fayad et al., 2016) and up to 5 years after the stimulation of the NAc (Islam et al., 2015; Kohl et al., 2015; Mantione et al., 2014; Ooms et al., 2014; Denys et al., 2010). After reviewing several studies, it was found that accumulative effect could explain why sometimes DBS response does not always occur at the beginning (Borders et al., 2018). Moreover, results are better on average in those patients who receive the implants more recently in the progression of the disease (Greenberg et al., 2010) and the interruption of the treatment could produce physical and psychological deterioration by way of OCD relapse and anxiety and depression rebound (Ooms et al., 2014).

According to our results, severe patients could have a significant reduction of obsessive-compulsive symptoms, however, a persistence of symptomatology has been described in almost 40% of patients (Greenberg et al., 2010). Any improvement needs to be considered in a positive way because even small improvements can make a big difference to a patient's day-to-day functioning. Consequently, the effectiveness of the treatments must take functionality and QoL into account as well as symptomatology (Katschnig, 2006).

4.2. *Affective symptomatology*

Most of the studies published focus their attention on obsessive-compulsive symptoms after DBS and there is little literature for changes in mood in patients with severe and resistant OCD. In our work,

we found significant changes of HAM-D and HAM-A score after treatment with DBS with low heterogeneity (18% and 59% respectively).

Some authors have found that DBS could modify affective symptoms itself (Goodman et al., 2010; Greenberg et al., 2010). This statement was made after observing patients with resistant depression after treatment with DBS in the VC/VS who showed significant improvement across multiples scales of depression, anxiety, and global function (Malone, 2010). Patients with OCD may present impairments in associative learning processes due to negative, threatening or fearful stimuli which impacts on emotional appraisal and processing of emotional stimuli (Berlin et al., 2017). Polosan et al., (2019) find that stimulation of the limbic associative STN enhances the positive appraisal of low-intensity stimuli, resulting in an improvement in negative cognitive bias.

Although the effect on affective symptoms has been shown, the duration of this treatment could be only temporary. Denys et al., (2010) indicate that treatment with DBS would decrease symptoms in a sequential order (depressive symptoms first, anxiety symptoms second, obsessions third and compulsions fourth) and in a fixed sequence (mood improvement in seconds, anxiety within minutes and obsessions within days, while compulsion took weeks or even months). Focusing on anxiety symptoms, BNST clearly improves anxiety in OCD patients (Denys et al., 2010). DBS on the NAc has shown a profound effect on anxiety and depression with lower effect on OCD characteristic symptomatology (Mantione et al., 2014), as in the case with patients with MDD who show an immediate result in anhedonic, antidepressive and anxiolytic (Bewernick et al., 2010).

4.3. Functionality

Regarding functionality, we have found moderate but significant modifications with a standardized mean difference on GAF-score of 3.51 (from 2.01 to 5.00). The magnitude of our results could determine on some occasions a jump from one functional category to another, i.e. there are a total of 10 categories from 0 to 100, where the highest is "superior functioning" and the lowest "persistent danger of severely hurting, persistent inability to maintain personal hygiene or serious suicidal act with expectation of death". A study of the Dutch population with psychiatric diseases finds the GAF score is positively correlated to all QoL aspects and patients with social functioning problems have lower QoL scores than those without such problems (Trompenaars et al., 2007). This idea indicates that small changes in the GAF score could be important regarding QoL.

Patients could experience an improvement in QoL years after the initiation of DBS, even when no further reduction of OCD severity was evident. This suggests that factors other than obsessive-compulsive symptoms, can influence QoL such as motivation and reward-processing. Patients would therefore need time to adapt to and benefit from their new situation (Alonso et al., 2015).

Moving along, some of the previously mentioned authors emphasize the need to find good and bad response predictors and biomarkers (Tyagi et al., 2019; Tastevin et al., 2019; Rappel et al., 2018; Maarouf et al., 2016; Alonso et al., 2015; Tsai et al., 2014; Chabardès et al., 2013; Denys et al., 2010; Greenberg et al., 2010). We already have biomarkers, for example, the biomarker of the non-motor STN which can be obtained during intra-operative MRI scans (Chabardès et al., 2013), the theta activity at the ventro-medial STN (Rappel et al., 2018) and post-operative stimulation-induced smile/laughter which may predict long-term OCD response to DBS (Tsai et al., 2014). There is also the possibility that neuroimaging could predict the probability of the clinical benefit of DBS because metabolism in the subgenual cingulate cortex, measured before surgery, was directly correlated to the extent of OCD improvement during DBS (Greenberg et al., 2010).

4.4. Strengths and limitations

This study has several important strengths: (1) we independently analyzed 4 parameters of scales -YBOCS, HAM-D, HAM-A and GAF (which has not been studied before in a meta-analysis)-; (2) we have included randomized double-blinded, on-off clinical trials in our work; (3) we performed subgroup analyses according to the DBS target applied to OCD patients and the characteristics of the study; and (4) we performed sensitivity analyses to check, if the results obtained were similar in both direction and magnitude of effect and statistical significance, this indicates that the analysis was robust.

Compared to the prior meta-analyses, we decided to exclude several studies that had been included in Alonso et al., (2015), Kisely et al., (2014) and Schruers et al., (2019) meta-analyses for the following reasons: (1) Case reports or studies with less than 3 patients (necessary to calculate mean and standard deviation); (2) Follow-up data was not shown; (3) studies included the same sample of patients; and (4) Studies based on animal results.

Our meta-analysis is the only one that uses mean and standard deviation instead of percentage of response. The reason for this was to try to distance ourselves from results measured in percentage response, because this classification could not define the individual patient's subjective experience. For example, a patient with A YBOCS baseline of 20 it would only have to decrease 7 points while in a patient with A YBOCS baseline of 38 the reduction should be 13 points (almost double). This indicates that the greater the severity of the disease, the greater reduction in YBOCS is necessary, a fact that can distort the real effectiveness of DBS. In addition, we considered other clinical target such as GAF or affective symptoms to determine the effectivity of DBS in patients with OCD.

However, our results need to be interpreted within in their limitations. These include a relatively small number of which most were observational studies and series of cases, as well as the clinical heterogeneity (different follow-up period, electrode design, unique path of orbit thalamic fibers in each patient, stimulation parameters and design of electrical device), which made it difficult to establish the best application procedure. In addition, we were unable to analyze the cognitive effect on each objective or to consider the different dimensional categories or the effects of previous pharmacological treatments. Finally, another point that was not taken into account in this work was the individual duration of each of the studies included, which could modify the results. These were a potential risk which limited the quality of this work and were addressed by the comprehensive and systematic review of the literature and by the use of stringent inclusion criteria.

4.5. Conclusions and further directions

In OCDs resistant to pharmacological treatment, DBS seems to be an effective treatment as shown by the significant improvement in YBOCS, HAM-A, HAM-D and GAF, with major changes in YBOCS scores.

Therefore, further research is needed to carry out personalized DBS studies in OCDs according to the affected dimensions, which could determine the existence of OCD phenotypes and their possible correlation with specific targets.

The generalization of dimensional YBOCS use could be useful in the study of DBS directed at specific targets. In the same way, further research should focus on finding predictors of good and bad responses, relevant biomarkers and analytical measurements that correlate with the severity of the disease. This could constitute a breakthrough in DBS techniques.

In addition, studies need to be large, and any confounding variables need to be measured and controlled. It is hoped that increased research and knowledge will aid in using DBS in a more personalized way based on clinical benefits experienced.

The main conclusions of these meta-analyses highlight the statistically significant effectiveness of DBS in severe and treatment resistant OCDs, emphasizing its role in obsessive–compulsive symptoms and the improvement observed in patients' global functioning. This benefit of global functioning could constitute a possible new outcome indication of

efficacy.

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Contributors

S. C., S.J-F., L.G-R. participated in the design of the study, the literature review, interpretation of the data and the drafting of the article. P.G-D., F.D-A. and J.M-O. participated in the literature review, the interpretation of the data and the drafting of the article. All authors approved the final version of the manuscript.

Declaration of Competing Interest

The researchers report no biomedical financial interests or potential conflicts of interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2022.114869.

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