Review

Alternatives to Pharmacological and Psychotherapeutic Treatments in Psychiatric Disorders

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Abstract: Nowadays, most of the patients affected by psychiatric disorders are successfully treated with psychotherapy and pharmacotherapy. Nevertheless, according to the disease, a variable percentage of patients results resistant to such modalities, and alternative methods can then be considered. The purpose of this review is to summarize the techniques and results of invasive modalities for several treatment-resistant psychiatric diseases. A literature search was performed to provide an up-to-date review of advantages, disadvantages, efficacy, and complications of Deep-Brain Stimulation, Magnetic Resonance-guided Focused-Ultrasound, radiofrequency, and radiotherapy lesioning for depression, obsessive-compulsive disorder, schizophrenia, addiction, anorexia nervosa, and Tourette’s syndrome. The literature search did not strictly follow the criteria for a systematic review: due to the large differences in methodologies and patients’ cohort, we tried to identify the highest quality of available evidence for each technique. We present the data as a comprehensive, narrative review about the role, indication, safety, and results of the contemporary instrumental techniques that opened new therapeutic fields for selected patients unresponsive to psychotherapy and pharmacotherapy.

Keywords: addiction; deep-brain stimulation; DBS; eating disorders; depression; MRgFUS; obsessive-compulsive disorder; psychosurgery; schizophrenia; Tourette’s syndrome

1. Introduction

Psychosurgery was developed from the need to manage patients affected by untreatable mental pathologies. The history of neurosurgical treatment for psychiatric disorders started in 1935, when Antonio Moniz, a Portuguese neurologist, proposed the prefrontal leucotomy to section the white matter connections between the prefrontal cortex and the thalamus. For such research, he received the Nobel Prize in 1949 [1]. Then, Freeman and Watts modified the Moniz’s procedure, developing a faster surgical technique called “trans-orbital leucotomy” [2]. Since then, the number of procedures performed to treat psychiatric disorders has rapidly grown, reaching its apex in the 50s [3]. Nonetheless, the primary surgical treatment of psychiatric diseases was represented by “disconnection” procedures to separate white matter tracts from the prefrontal lobes. However, the need for reducing the serious adverse effects, cognitive alterations, and personality changes associated with such treatments led to a progressive reduction of such procedures. Finally, the advent of pharmacotherapy appeared to determine an irreversible stop to psychosurgery. However, over the last years, a better understanding of overall cerebral functions, along with the enormous technological advances in neurosurgery, has led to reconsidering the role of neurosurgical procedures in treating some psychiatric disorders, in a multidisciplinary approach that makes these procedures more effective, suitable, and more consistent in terms of results.

Functional surgery based on deep-brain stimulation (DBS) was first tried, in patients with psychiatric disorders, more than sixty years ago [4]. As it happened for movement...
disorders, DBS has almost totally replaced ablative neurosurgical procedures in psychiatric neurosurgery. More recently, the adjunct of radiotherapy procedures as cyber-knife or gamma-knife (GK), and the introduction of Magnetic Resonance–guided Focus Ultrasound procedures (MRgFUS), opened new therapeutic fields for selected psychiatric patients who are unresponsive to psychotherapy and pharmacotherapy. To evaluate the role of such treatments and their impact on patients with psychiatric disorders, and also to better define which patients could benefit from such treatments and what could be the best targets, we will first summarize the indication, mechanisms of action, and clinical outcomes of instrumental techniques used for the treatment of psychiatric disorders (Table 1); then, we will discuss these results in the context of current and future psychiatric applications.

**Table 1. Overview of the different techniques currently used.**

| Technique | Step 1 | Step 2 | Step 3 | Treatment |
|-----------|--------|--------|--------|-----------|
| GK        | Positioning of a stereotactic frame to the patient’s head (for the target’s coordinates) | Acquisition of stereotactic MRI images for localizing the target; setup of the target’s coordinates | The patient and the stereotactic frame are fixed into a hemispherical helmet connected to the Main unit of the GK apparatus | The radiation sources are up to 201 γ radiation-emitting Cobalt units connected to 4 or 8 mm collimators; the target is drawn on MRI images, and the total radiation dosage and radiation duration are decided for appropriate target lesioning (usually, single 4-mm isocenter with a maximum dose of 140–160 Gy) |
| RF        | Positioning of a stereotactic frame to the patient’s head (for the target’s coordinates) | Acquisition of stereotactic MRI images for localizing the target; setup of the target’s coordinates | The patient is led to the operating room; target’s coordinates are brought into the sterile stereotactic apparatus | Two burr holes are made 3 cm in front of the coronal suture and 2.5 cm lateral to the midline; the thermoelectrode is inserted to the target and a thermic lesion is made |
| DBS       | Positioning of a stereotactic frame to the patient’s head (for the target’s coordinates) | Acquisition of stereotactic MRI images for localizing the target; setup of the target’s coordinates | The patient is led to the operating room; target’s coordinates are brought into the sterile stereotactic apparatus | Two burr holes are made 3 cm in front of the coronal suture and 2.5 cm lateral to the midline; the stimulating electrode is brought to the target structure and then fixed to the skull and connected to a subcutaneous internal pulse generator |
| MRgFUS    | Positioning of a stereotactic frame to the patient’s head (for the target’s coordinates) | Acquisition of stereotactic MRI images for localizing the target; setup of the target’s coordinates | The patient and the frame are fixed to the MRI FUS suite, which contains up to 1096 Ultrasound beams’ sources | The target is drawn on stereotactic MRI images; multiple and gradual sessions of US administration are performed, to reach lesional temperatures (at least 53 °C) with a variable amount of energy requirement (20,000–40,000 J) |

**2. Literature Review**

The present review will focus on DBS, MRgFUS, and other instrumental therapeutics to treat neuropsychiatric syndromes, mainly major depressive disorder (MDD) and obsessive-compulsive disorders (OCDs). Following a brief overview of the rationale, indications, brain targets, mechanism of action, and results of such treatments, we will discuss the main results according to the available literature. With this aim, we performed a search on MEDLINE and Scopus databases for the indication terms: surg* OR neurosurg* OR psychosurg* OR radiosurg* OR capsuloto* OR tractoto* OR leucoto* OR leuko* OR radio-surg* OR radiosurg* OR stereota* OR stereo-ta* OR gamma kni* OR gamma-ra* OR deep brain stimulation OR DBS OR neurosurgical procedures/AND depression OR schizophrenia OR obsessive compuls* OR obsessive-compuls* OR eating disorders* OR addiction. The reference lists of relevant papers were inspected for further studies that could fit the inclusion criteria. The search was conducted on the literature before October 2020, comprising only articles with English full text, without historical limitations. The literature search did not strictly follow the criteria for a systematic review: due to the large differences in methodologies and patients’ cohort, we tried to identify the highest quality of available evidence for each technique. Considering the extreme heterogeneity and the limited number of published trials, we present the data as a comprehensive (narrative) review. In this context, we have also included our subjective experience and future per-
spectives: all the reported techniques are available and used at our Institution, a tertiary national referral center.

3. Major Depressive Disorder (MDD)

The physiopathology of MDD includes the dysfunction of several relevant networks within the limbic system, secondary to a network anomaly rather than from the alteration of a single structure or circuit. Functional neuroimaging in depressed patients tended to show hypoactivity in the dorsolateral prefrontal cortex and hyperactivity in the orbitofrontal cortex and the amygdala [5]. The medial prefrontal cortex and related structures are involved in the genesis of MDD: amygdala, hypothalamus, periaqueductal gray (PAG), locus coerelus, raphe, and brainstem autonomic nuclei, which play significant roles in organizing visceral and behavioral responses to stressors and emotional stimuli. For example, dysfunction of the medial prefrontal cortex could lead to disinhibition of the central amygdaloid nucleus and Bed Nucleus of Stria Terminalis (BNST), which in turn would activate cortisol secretion from the hypothalamus. Dysfunction in the reward-learning system involving ventral tegmental area (VTA) and its projections to anterior cingulate cortex (ACC), nucleus accumbens (NAc), and medial prefrontal cortex could contribute to anhedonia; an excessive functional dominance of Default Mode Network (comprising medial prefrontal cortex and posterior cingulate cortex) over Task-Positive-Network (that includes associative frontal and parietal cortices) could facilitate a depressive state trough negative self-referential information [6].

About 30% of depressed patients do not respond to conventional treatments (two different monotherapy trials and psychotherapy) [7,8]. Moreover, about 10–20% of patients are unresponsive to a combination of at least three different-acting molecules (as serotonin and noradrenaline reuptake inhibitors or tricyclic antidepressant), administrated at adequate dosages for at least six weeks. MDD inclusion criteria for invasive procedures comprise an age \( \geq 30 \) years, a score \( \geq 20 \) at Hamilton Depression Rating Scale (HDRS), a score \( \geq 17 \) at Beck Depression Inventory scale (BDI), a duration of disease of at least two years, resistance to three different mechanisms of antidepressant pharmacological action, resistance to at least six months of psychotherapy, resistance to electroconvulsive therapy and transcranial magnetic stimulation.

3.1. MDD and Lesional Procedures

Lesional procedures determine long-lasting damage to a specific brain structure involved in the genesis of symptoms. Different lesional targets have been used for MDD: anterior limb of internal capsule (ALIC), anterior cingulate gyrus (ACG), subcaudate tract (ST), or a combination of the latter two (the so-called limbic leukotomy). Lesional procedures, developed from the 40–50s, are rarely used nowadays.

3.1.1. Anterior Capsulotomy

Leksell and Talairach in the 40s targeted the ALIC just superior to the ventral striatum [9,10], to interrupt fibers connecting the orbital frontal cortex, ventral striatum, and thalamic nuclei [11]. The only report of long-term outcome of surgical anterior capsulotomy for MDD has been reported by Christmas [12]: 20 patients between 1992 to 1999 were submitted to the procedure, which was bilateral and targeted the anterior third of ALIC. At seven years follow-up, 50% and 40% of patients were defined as “responsive” or “remitted”, respectively.

3.1.2. Subcaudate Tractotomy

This procedure was initially performed by Knight in 1964 [13], to treat hypochondrias, chronic pain, hysteria, anxiety, depression. The target was the “substantia innominata”, which lies “below the caudate nucleus level and contains few afferent fibers from the ascending thalamofrontal radiation” [13]. The lesions were performed by stereotactically depositing radioactive Yttrium Y90, to obtain a localized effect. In his initial paper Knight
stated that, of 23 depressive patients treated with ST, 17 had “no symptoms”, 3 had “slight symptoms and no treatment required”, and 3 “improved, with some symptoms requiring treatment”. In 1995 the team of the Brook General Hospital in London reported a series of MDD patients treated from 1979 to 1991 [14]; after one year, 63 had no depressive symptoms, 53 had improved, and 57 were unchanged. The most frequent complications were marked fatigue, weight gain, and seizures, with a mortality rate of 3%.

3.1.3. Anterior Cingulotomy

Among lesional procedures for MDD, anterior cingulotomy was the most used. The ACG has multiple and reciprocal connections with the hippocampus, amygdala, hypothalamus, orbitofrontal cortex, PAG, and assigns emotional value to stimuli and in conditioned emotional learning [15]. The target is generally a point located 20 mm posterior to the frontal horn’s anterior tip, 7 mm lateral to the midline, and 5 mm superior to the corpus callosum. Ballantine in 1967 described the first stereotactic anterior cingulotomy for several psychiatric disorders, including MDD. He reported an overall improvement in 77% of patients with fear and MDD [16]. In 1998, Spangler et al. reported a series of 15 MDD patients treated with anterior cingulotomy, and 60% of these had a decrease of BDI score of >50%, 12% of them were partial responders [17]. The same group in 2008 reported that, among 33 MDD patients, 30% were considered responders, and 43% were partial responders, based on a decrease of at least 35% in the BDI score and on a final Clinical Global Improvement (CGI) score of 2 or less [18]. The transient complications included temporary impaired memory, urinary incontinence, one seizure, one abscess successfully treated with surgical drainage and antibiotic therapy.

3.1.4. Limbic Leucotomy

Limbic Leucotomy (LL) is a combination of anterior cingulotomy and subcaudate tractotomy initially described by Kelly and Richardson in 1973. Five of their initial 40 patients were affected by MDD, and 4/5 of them showed acceptable to considerable improvement of depressive symptoms. Subsequent studies of the same authors reported a percentage of improvement from 30 to 78% [19,20]. In 2008 Cho et al. performed limbic leucotomy via radiofrequency (RF) thermocoagulation on 18 bipolar patients. At seven years, significant improvements according to the HDRS and Hamilton Anxiety Rating Scale (HARS) was described [21]. Montoya et al. reported that three out of six MDD patients treated with this technique were responders according to physician-rated assessments of global functioning [22]. Adverse events in the whole series of 21 subjects were urinary incontinence (14%), impaired short-term memory (9%), and seizures (5%).

3.2. MDD and MRgFUS

MRgFUS is a recently introduced invasive and non-surgical procedure consisting of delivering a certain number of ultrasound beams to an intended intracranial target through a stereotactic and phased-array system, facilitating therapeutical levels of energy at the desired target (Table 1). The resulting lesional effect can be evaluated in an Magnetic Resonance imaging (MRI)-implemented operating room suite. MRgFUS has already been used for essential tremor, Parkinson’s disease, OCD, and untractable dyskinesias in ON-Med states of Parkinson’s disease [23]. So far, only one case of MDD treated with MRgFUS has been reported [24]; the target was the ALIC. HDRS decreased from 26 (preoperative) to 7 (at one-year follow-up); BDI decreased from 26 to 12 during the same time. This 56-year-old patient subjectively stated an ameliorated quality of life and started to re-attend social activities.

3.3. MDD and Radiosurgical Lesions

Only one case report described, so far, the results of a radiosurgical procedure specifically for MDD; rather, MDD appears as comorbidity of other psychiatric disorders, primarily OCD, treated with this modality; in these cases, results are scattered and confused.
when searching for clear outcomes [25]. In the above-mentioned report, GK subcaudate tractotomy was used in one patient affected by MDD who had attempted suicide multiple times; target (substantia innominata) was located anteroinferiorly to NAc. Maximum dose was 130 Gy for both left and right targets and target sizes were measured at the 50% isodose line; an initial response was noticed after 1.5 months from the procedure, with maximal effect appreciated at 4-months’ follow-up, and stability of the effect at four years follow-up [26].

3.4. MDD and DBS

The advantages of DBS for MDD are reversibility and modularity; moreover, they don’t create permanent lesions on the target.

Following pioneering Benabid and Pollack’s studies of DBS in movement disorder [27] and taking into account the beneficial therapeutic effects, neuromodulation has also been considered for psychiatric disorders, mainly MDD and obsessive disorders. For MDD, several brain targets have been used for neuromodulation, including subcallosal cingulate gyrus (SCG), NAc, ventral capsule/ventral striatum (VC/VS), ALIC, medial forebrain bundle (MFB), lateral habenular complex (lHB), and inferior thalamic peduncle (ITP). Comparing results among manuscripts is difficult because of the different used scales.

The subgenual cortex (SGC) was considered for DBS in MDD because its regional blood flow inversely correlated with mood level [28,29], and because of its inclusion in large-scale networks involved in depression [30]. The initial report was due to Mayberg et al. [31]; the authors reported that four out of six patients resulted in being responders at six months’ follow-up. Later, Lozano et al. reported a 55% response rate at 12 months follow-up in 20 patients [32]. Excellent reviews exist about overall outcomes, with a response rate up to 45% [33–35]. However, no standard anatomical coordinates or stimulation parameters exist. Recently, Riva-Posse et al. demonstrated the utility of an individualized tractography map based on a connectomic “hotspot” individuated by diffusion tensor imaging (DTI) and connectivity of SGC with bilateral forceps minor, cingulum bundle and medial branch of uncinate fasciculus, with 72.7% of response rate at six months and of 81.8% at 12 months [36].

NAc is a critical structure in the behavioral response to reward-seeking, and it can be considered an interface between the limbic and the motor system. Schlaepfer showed that NAc DBS led to an increase of metabolic activity in the dorsolateral prefrontal cortex and decreased metabolic activity in the ventromedial prefrontal cortex, thus reverting the metabolic picture typical of MDD [37]. Subsequently, Bewernick reported a one-year 50% remission rate in 10 patients treated with NAc DBS, and confirmed these metabolic changes [38]. The same authors reported a 45% response rate at 48 months in 11 patients [39].

The so-called VC/VS complex is a marchland between the ventral portion of these two structures, i.e., ALIC and NAc. The denomination relies on the fact that such structures can be targeted together with the same stereotactic trajectory; this region has been stimulated for OCD in one study that also pointed out the anti-anxiety and antidepressant effect of VC/VS DBS [40]; then, Malone and co-workers reported a 53% response rate at 12 months in 17 MDD patients after VC/VS DBS [41]. Disappointing results were reported in a randomized, sham-controlled study by Dougherty and co-workers: after 16-weeks’ follow-up of thirty patients, there was no significant difference in response rate between active and sham groups; furthermore, the response rate was low in the open-label continuation phase (up to 26.7%) [42].

The MFB has recently been addressed as an essential structure as a target for DBS to treat MDD. It can be considered “a structural correlate of the system for appetitive motivation (reward-seeking) and euphoric feelings—a state of positive affective excitement, rather than sensory pleasure” [43]. This bundle is connected to crucial structures implicated in MDD, such as SCG, NAc, and ALIC, and its stimulation activates the VTA, a significant source of dopamine innervation in the mesolimbic system [44]. MFB is constituted by a
main trunk that splits into two parts: an inferomedial branch (imMFB) running through the lateral third ventricular wall to the lateral hypothalamus and ending in the olfactory tubercle; and a superolateral branch (slMFB) that courses within the ALIC, thus connecting the NAc and the prefrontal cortex to VTA. The anterior thalamic radiation connects the anterior nucleus of the thalamus and the dorsomedial thalamus to the prefrontal cortex. Anterior thalamic radiation also courses within the ALIC, near the slMFB, and medial to it, so it is likely that MFB DBS also involves this fiber bundle [43].

In this context, slMFB is the target for DBS, determining a rapid antidepressant action. Schlaepfer and coauthors performed bilateral slMFB-DBS in 7 patients: the average Montgomery–Åsberg Depression Rating Scale (MADRS) of the whole sample was reduced by more than 50% at day seven after onset of stimulation [45]. At last observation (12–33 weeks), six patients were responders; four were classified as remitters. Another interesting paper by Fenoy and co-workers shows a rapid and significant antidepressant effect after bilateral slMFB DBS: three out of four patients resulted in being responders after one week of stimulation, and after 26 months of stimulation, two out of four patients had a decrease of more than 80% in MADRS score [46]. An extension of the cited study [45], written by Bewernick and co-workers, reported that six of eight patients (75%) were responders at 12 months follow-up and four years follow-up [47]. lHB seems to harbor hyperactive neurons in MDD [48]; this could restrain activity in the noradrenergic, dopaminergic, and serotoninergic circuits connected to it [49]. Sartorius and co-workers reported results of lHB DBS in one patient, who reached remission after one month; sudden malfunction of the pulse generator led to transient symptoms’ recurrence, that disappeared after repair of the neurostimulator [50].

Finally, ITP connects the thalamus’s intralaminar nuclei to the orbitofrontal cortex, which is hyperactive in MDD [51]. These fibers would increase the inhibitory effect of the orbitofrontal cortex to the ventral striatum and other deep brain structures involved in the reward system. To date, only one patient received ITB DBS, with a reduction of HDRS from 42 (preoperative period) to 3 points (post-operative period) for 8 months; switching off stimulation led to symptoms’ recurrence, which promptly withdraw after turning on the neurostimulator [52].

Table 2 summarizes all findings obtained from the literature analysis of instrumental therapeutics for MDD.
Table 2. Most representative works for major depressive disorder (MDD).

| Technique | Author (Year) | Target | Patients | Study | Results |
|-----------|--------------|--------|----------|-------|---------|
| GK        | Park (2016)  | SI     | 1        | OLS   | HAMD17 decreased from 23 to 4 at 4 years FU |
| RF        | Christmas (2011) | ALIC   | 20       | OLS   | 50% response and 40% remission after 7 years’ FU |
| RF        | Hodgkis (1995) | SI     | 183      | OLS   | After one year-FU: 63 pts remitted, 53 had improved, 57 not changed or deteriorated |
| RF        | Ballantine (1967) | ACC   | 26       | OLS   | FU from 3 months to 4 years 20 pts: significantly improved; of these, 8 considered “well”; 6 pts: unsatisfactory results |
| RF        | Spangler (1996) | ACC   | 15       | OLS   | 60% of pts had a decrease in BDI of >50%; 12% of pts were “partial responders” |
| RF        | Shields (2008) | ACC   | 33       | OLS   | Mean FU of 30 months: 30% responders (>50% decrease in BDI); 40% partial responders (>35% decrease in BDI) or a CGI score ≤ 2 |
| RF        | Cho (2008)    | ACC/SI | 16       | OLS   | 68.8% of pts had a marked response (CGPSS ≥ 3); 18.9% had a possible response (CGPSS 2), 12.6% did not improve or worsened (CGPSS 0 or 1) |
| RF        | Montoya (2002) | ACC/SI | 6        | OLS   | 3 out of six pts were responders according to physician-rated-assessment |
| MRgFUS    | Kim (2018)    | ALIC   | 1        | OLS   | At one year, HDRS decreased from 26 to 7 and BDI from 26 to 12 |
| DBS       | Lozano (2012) | SCG    | 21       | OLS   | 50% reduction in HRSD: 57% of pts at 1 month, 48% at 6 months, 29% at 12 months |
| DBS       | Holtzheiner (2017) | SCG | 90       | RCT   | No significant difference in response during the double-blind, sham-controlled phase |
| DBS       | Riva-Posse (2018) | SCG | 11       | OLS   | 9 pts (81.8%) responders (HDRS decrease ≥ 50%) and 6 pts remitters (HDRS ≤ 7) at 12 months |
| DBS       | Schlaepfer (2008) | NAc  | 3        | OLS   | Mean HDRS dropped from 33.7 to 19.7 and mean MADRS mean 35.7 to 24.7 after one week FU |
| DBS       | Bewernick (2010) | NAc   | 10       | OLS   | 5 pts (50%) were responders (HDRS decrease ≥ 50%) at one-year FU |
| DBS       | Bewernick (2012) | NAc   | 11       | OLS   | 5 pts (45%) were responders at 2-4 years’ FU |
| DBS       | Malone (2009)  | VC/VS  | 15       | OLS   | MADRS response rate was 53% and remission rate was 40% at one-year FU |
| DBS       | Dougherty (2015) | VC/VS | 30       | RCT   | No significant difference in response rates between the active (20%) and the control (14.3%) groups; response rate at 2 years’ FU in Open-label phase was 23.3% |
| DBS       | Schlaepfer (2013) | MFB  | 7        | OLS   | 6 out of 7 pts responders (MADRS reduction ≥ 50%) and 4 out of 7 pts remitters (MADRS < 10) (FU 12–33 weeks) |
| DBS       | Fenoy (2016)   | MFB    | 4        | OLS   | 3 out of 4 patients responders (MADRS score reduction ≥ 50%) at the last follow-up |
| DBS       | Bewernick (2017) | MFB | 8        | OLS   | 6 out of 8 pts (75%) responders (MADRS score reduction ≥ 50%) and 4 pts (50%) remitters (MADRS < 10) at 12 months |
| DBS       | Sartorius (2010) | IHB   | 1        | OLS   | HDRS decreased from 35 to 0 after 12 weeks of high voltage DBS (10.5 V) and after relapse due to malfunction from bicycle accident |
| DBS       | Jimenez (2013) | ITP    | 1        | OLS   | HDRS decreased from 42 to 6 after 9-year FU |

4. Obsessive-Compulsive Disorder (OCD)

The neuropsychological impairments of OCD could be explained by the different brain regions possibly involved, as the orbitofrontal cortex, the ACG, and striatum. The corticostriatal-thalamic-cortical (CSTC) circuitry mediates the cognitive-affective impairments seen in OCD, with activation or inhibition of different components of this circuitry driving the compulsive and impulsive features. The serotonergic, dopaminergic, glutamatergic, and GABAergic systems contribute to OCD.

First-line treatments include cognitive behavioral therapy with fear exposure and response prevention [53], as well as pharmacotherapy, based on Serotonin reuptake inhibitors. Not-responder patients may also benefit from clomipramine [54]. During the last twenty years, a resurgent interest in stereotactic psychosurgery started after DBS for movement disorders. This attention led to the first DBS applications for OCD in 1999, by
Nuttin and coauthors, who targeted with DBS the same “old” lesional target for OCD, represented by the ALIC [55]. Since then, after the paucity of new publications from the 1980s, and an evident renaissance of such field from 2000 until the present was reported in the literature.

4.1. OCD and DBS

The US Food and Drug Administration (FDA) approved the DBS of the ALIC in 2009; however, other effective targets for OCD include NAc, VC/VS, subthalamic nucleus (STN), internal capsule (IC), ITP, and BNST [56–60]. Sturm in 2003 firstly performed DBS of the NAc [61], based on anatomo-clinical considerations in patients treated by anterior capsulotomy, subcaudate tractotomy, and DBS of ALIC. The neurobiological substructures of OCD include abnormalities in the basal ganglia and frontal regions [62]; patients with OCD present abnormal metabolic activity in the orbitofrontal cortex, the anterior cingulate/caudal medial prefrontal cortex, and the caudate nucleus [63–65]. However, during the last years, DBS has experienced a conceptual paradigm-shift from focal stimulation of specific nuclei toward modulating brain networks [66]: the effectiveness of modulation of the different brain targets proposed so far could be explained by the involvement of these targets in the same brain network.

A careful screening of patients with OCD candidates to DBS is mandatory, and not all patients could receive such treatment. The potential candidates must satisfy the following conditions: chronicity (duration of illness, usually over five years), severity according to the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) with a score of 28 or greater [67], and treatment resistance defined as a failure to respond to three first-line medications (selective serotonin reuptake inhibitors or clomipramine), two second-line medications (augmentation strategies), and at least six months of cognitive-behavioral therapy [59].

Different targets have been used during the years following DBS, with about 60% response rate. OCD is a complex and heterogeneous disease, with many different symptoms that reflect the complexity of the different brain structures involved, as the ALIC, the VC/VS, the NAc, the anteromedial STN, or the ITP. Sturm in 2003 firstly performed DBS of the NAc [61], based on anatomo-clinical considerations in patients treated by anterior capsulotomy, subcaudate tractotomy, and DBS of ALIC. The neurobiological substructures of OCD include abnormalities in the basal ganglia and frontal regions [62]; patients with OCD present abnormal metabolic activity in the orbitofrontal cortex, the anterior cingulate/caudal medial prefrontal cortex, and the caudate nucleus [63–65]. However, during the last years, DBS has experienced a conceptual paradigm-shift from focal stimulation of specific nuclei toward modulating brain networks [66]: the effectiveness of modulation of the different brain targets proposed so far could be explained by the involvement of these targets in the same brain network.

Alonso and coauthors analyzed 31 studies (published between 1999 and 2014) for a total of 116 patients that received DBS for OCD [69]. The most frequent target nuclei were the striatal areas (ALIC, VC/VS, NAc), then the STN and the ITP. The ventral ALIC’s fiber tract via the ventral striatum borders the BNST and connects the medial prefrontal cortex to the thalamus. The VC/VS complex is involved in a pathway comprising the medial orbitofrontal cortex, the dorsomedial thalamus, the amygdala, and the habenula (HB). DBS targeting the NAc reduces OCD symptoms by decreasing excessive fronto-striatal connectivity between NAc and the lateral and medial prefrontal cortex. DBS of the anteromedial STN is useful when targeting the STN’s inferior medial border, primarily connected to the lateral orbitofrontal cortex, dorsal anterior cingulate, and dorsolateral prefrontal cortex. Finally, ITP-DBS recruits a bidirectional fiber pathway between the orbitofrontal cortex and the thalamus. Globally, these functional connectivity studies show that the various DBS targets lie within the same diseased neural network [68]. All these targets improve mood and behavioral adaptability.

Alonso and coauthors analyzed 31 studies (published between 1999 and 2014) for a total of 116 patients that received DBS for OCD [69]. The most frequent target nuclei were the striatal areas (ALIC, VC/VS, NAc), then the STN and the ITP. The percentage of Y-BOCS reduction was around 45%. However, a better response was present in older patients with sexual/religious obsessions and compulsions. Interestingly, no significant differences were detected in efficacy between the different targets. This meta-analysis also showed that severe adverse effects were less frequent after DBS for OCD than after lesional techniques. Islam et al. reported a better outcome for patients who underwent DBS of the BNST compared with the NAc [59]. The BNST is considered as a part of a striatal circuitry comprising descending glutamatergic input from the prefrontal and insular cortex and the basolateral amygdala, with ascending modulatory inputs [70]. Therefore, it is part of the “extended amygdala,” involved in stress and reward responses [71].

Globally, the average percentage of responders to DBS was 60%, and the response is commonly defined as an OCD symptom reduction of at least 30–35% measured on the
Y-BOCS [34]. There were no differences in the outcome, considering the different targets [68].

Despite the results on obsessions and compulsions, DBS’s effects on anxiety and depression are unclear: a randomized controlled trial by Mallet et al. excluded improvement about these manifestations [72]. Moreover, some studies reported a temporary increase of panic symptoms and anxiety after DBS of striatal areas, whereas these symptoms were resolved by changing parameter settings [73,74].

One recent review by Pepper et al. reported, in 2019, the outcome of anterior capsulotomy for OCD, comprising not only DBS but also lesional procedures [75], for a total of 512 patients between 1961 and 2018. Using the Y-BOCS scores as an outcome measure (whereas not always available), 73% of patients had a clinical response, and 24% of patients went into remission (Y-BOCS score < 8). Globally, the rate of major complications was 2%, whereas the most part was asymptomatic or resulted in transient symptoms; nine (1.8%) of 512 patients had intracerebral hemorrhage. The most common side effect was weight gain, reported in 13% of all patients (69 of 512). In October 2020, Chabardes and coauthors presented the results of a prospective, observational, monocentric study about DBS of the non-motor STN in 19 patients with treatment-resistant OCD [76]. At a 24-month follow-up, the mean Y-BOCS score was reduced from 33.3 to 15.8. Fourteen patients among 19 were considered responders, 5 out of 19 being improved over 75%, and 10 out of 19 over 50%. The most frequent adverse events consisted of transient DBS-induced hypomania and anxiety. Therefore, the authors concluded that this procedure is an effective and relatively safe procedure for OCD.

4.2. Gamma-Knife and Radiofrequency Ablation for OCD

Ablative surgery for OCD is most commonly performed with RF ablation, with an electrode stereotactically inserted through a burr hole into the target. From 2002 to 2018, 158 patients underwent RF of the bilateral ALIC: 79% of them (125 of 158) had a clinically significant response [75]. Also, GK is used to perform capsulotomy, with 60 patients on 90 reported as clinically significant responders in a recent review [75]. Radiation necrosis after GK capsulotomy (using a dose of 200 Gy) has been described [77,78]. A dose of 140–180 Gy (maximum dose) is typically used to perform a GK capsulotomy, considering the ventral aspect of the ALIC as the target.

4.3. OCD and MRgFUS

MRgFUS technology currently does not allow for lesioning of the anterior cingulate or other targets remote from the brain’s geometric center. For OCD, the primary strategy is always the anterior capsulotomy. Kim et al. presented for the first time, in 2018, a series of 11 patients with a bilateral thermal lesioning of the ALIC through FUS (51–56 °C >3 s, 10-mm ellipse) [79]. All the patients presented a Y-BOCS score > 28 and had failed conventional medical therapies. After treatment, six patients were responders according to the degree of improvement in their OCD severity and Y-BOCS scores reduction; moreover, FUS was considered adequate for depressive and anxiety symptoms, without severe adverse events (some patients experienced only transient headaches and nausea during the procedure). Interestingly, mean OCD, depression, and anxiety scores improved early, significantly by one week, and they continued to improve at 24-month follow-up. In 2020, Davidson reported 16 patients with major psychiatric disorders, comprising seven OCD patients, that received bilateral capsulotomy using FUS [80].

There were no serious adverse events; on the other hand, non-serious adverse events as transient headaches and pin-site swelling were quite common. Six OCD patients completed a six-month follow-up; the authors presented the detailed results of this series in another paper [81], with a response rate for OCD in four patients out of six. The mean pretreatment Y-BOCS of 33 decreased to 22 in responders patients, which also presented substantial improvements in mood, anxiety, and quality of life. Despite the small number of patients so far reported, MRgFUS capsulotomy shows a favorable side-effect profile compared to other lesional methods.
In Table 3 are reported the most representative studies for treatment of OCD.

### Table 3. Obsessive-compulsive disorder (OCD) and instrumental therapeutics.

| Technique | Author (year) | Target | Study | Patients | Results |
|-----------|---------------|--------|-------|----------|---------|
| DBS       | Nuttin (1999) | ALIC   | OLS   | 4        | 3 patients improvement and one of these had a 90% reduction in compulsive and ritual behaviours |
| DBS       | Jiménez (2007) | ITP    | OLS   | 1        | Decrease in Y-BOCS score from 40 to 15 at 15-month follow-up (37.5%) |
| DBS       | Huff (2010)   | NAc    | Double-blind controlled | 10 | Mean Y-BOCS scores decreased significantly from 32.2 to 25.4 at 1 year follow-up |
| DBS       | Franzini (2010) | NAc  | OLS   | 2        | Y-BOCS score improvement in both (Patient 1 from 38 to 22, Patient 2 from 30 to 20) |
| DBS       | Franzini (2015) | BNST (4); NAc (4) | OLS | 8 | 6/8 showed significant improvement at Y-BOCS |
| DBS       | Anderson (2003) | ALIC | OLS   | 1        | 3-month postoperative Y-BOCS score was 7 (preoperatively 34) |
| DBS       | Sturm (2003)  | NAc    | OLS   | 4        | Nearly total recovery in 3/4 |
| DBS       | Mallet (2008) | STN    | Double-blind crossover | 16 | Y-BOCS score significantly lower than the score after sham stimulation (19.8 vs. 26) |
| DBS       | Abelson (2005) | ALIC | Pilot double-blind | 4 | Y-BOCS declined more with stimulators ON (19.8%) than with them OFF (10.5%) |
| DBS       | Greenberg (2010) | VC/VS | OLS   | 26       | Mean Y-BOCS score decreased with stimulation, reaching 20.9 at 36 months (from 34 at baseline) |
| DBS       | Chabardes (2020) | STN | OLS   | 19       | At 24-month follow-up, the mean Y-BOCS score improved by 53.4% (from 33.3 to 15.8) |
| GK        | Sheehan (2013) | ALIC | OLS   | 5        | The mean Y-BOCS score improved from 32 to 13 |
| GK (9), RF (16) | Rück (2008) | ALIC | OLS   | 25       | The mean Y-BOCS score was 34 preoperatively and 18 at long-term follow-up |
| GK        | Rasmussen (2018) | ALIC | OLS   | 55       | 31/55 (56%) improvement of ≥35% over the 3-year follow-up period at Y-BOCS |
| MRgFUS    | Kim (2018)    | ALIC   | OLS   | 11       | The mean Y-BOCS score improved from 34.4 to 21.3 at 24-month follow-up |
| MRgFUS    | Davidson (2020) | ALIC | OLS   | 7        | Response rate was 66.6% (>35% improvement in Y-BOCS score) |

### 5. Schizophrenia

Schizophrenia is a heterogeneous clinical syndrome that involves behavioral, emotional, and cognitive domains without pathognomonic symptoms [82].

The original dopaminergic hypothesis, resulting from the evidence of the efficacy of antipsychotic drugs, assumes that the positive symptoms of schizophrenia derive from dopaminergic hyperactivity, mainly through the mesolimbic pathway. From the VTA to the VS, including the NAc through the MFB, this neural pathway is involved in reward and reinforcement [83]. More recently, it has been postulated that this dopaminergic transmission pathway involves a tonic-phasic signaling system to filter out reward stimuli’ importance [84]. Dysregulation of this process in schizophrenic patients would reverberate at the cortical level resulting in psychotic symptoms due to an improper attribution of salience to stimuli that would usually be ignored [85].

A new glutamatergic hypothesis is recently emerging, sustaining that a GABAergic dysregulation in hippocampal circuits, decreasing inhibitory regulation, leads to early glutamatergic hyperactivity of the hippocampus efferences, thus resulting in a hyper-dopaminergic activity [86]. This constant stimulation would hesitate in a hippocampal atrophy [87]. Conversely, the negative and cognitive symptoms of schizophrenia have been attributed to a hypodopaminergic state along the mesocortical pathway, from VTA to the prefrontal cortex [88]. Neuroimaging findings corroborate these scenarios by reporting progressive atrophy of the frontal and temporal lobes and the hippocampus with reduced frontal activation in this disorder [89]. Moreover, HB, presumably about adverse stimuli,
through its connections with VTA inhibits dopaminergic transmission; its dysfunction could play a role in the pathogenesis of schizophrenia [90].

Antipsychotic medications are the most widely used therapy. Unfortunately, up to one-half of patients suffer from treatment-resistant schizophrenia (TRS), a subtype of the disease with worse outcome and functional disability, associated with earlier age of onset and more severe and often familial forms of the condition [91].

Schizophrenia and Instrumental Therapeutics

Invasive therapies were traditionally the first treatment available for schizophrenic patients. In 1935, Moniz performed the first prefrontal leucotomy. Afterward, Freeman developed his transorbital approach. Nevertheless, with the emergence of antipsychotic therapy in the 50s and the severe sequelae resulting from these procedures, psychosurgery fell into disuse [88].

The introduction of minimally invasive stereotaxic surgery, which allowed targeted lesioning with fewer complications, brought psychosurgery back into use for schizophrenia too (Table 4).

Table 4. Contemporary instrumental therapeutics for schizophrenia.

| Procedure | Author (Year) | Study Design | Targets | Sample Size | Outcomes | Comments |
|-----------|---------------|--------------|---------|-------------|----------|----------|
| DBS       | Plewnia (2008)| OLS          | Right NAc | 1           | Reduction in symptoms (25% at Y-BOCS) and improvement in psychosocial functioning (58% at Global Assessment of Functioning) | Woman with intractable OCD and residual symptoms of schizophrenia |
| DBS       | Corripio (2020)| Randomized trial | NAc (n = 3); ACC (n = 4) | 7           | 2/3 of NAc and 2/4 of ACC reached a significant improvement in symptoms (≥25% increase at the PANSS total score) | 3/4 of responsive cases worsened after the pulse generator was switched; NAc exhibited a more marked and rapid improvement |
| DBS       | Wang (2020)   | OLS          | HB       | 2           | Efficacy during the first 6 months, although only one patient maintained the result after one year | Positive symptoms were particularly improved |

Leiphart and Valone reported a significant improvement in schizophrenic patients treated with stereotactic surgery in the following order: cingulotomy, frontal leukotomy with cingulotomy, anterior callosotomy, frontal leukotomy, and subcaudate tractotomy [92]. In the late 1990s, DBS, a significantly less invasive and reversible surgical treatment, was adopted [88]. In 2008, Plewnia et al. documented, in a case of intractable OCD with residual symptoms of schizophrenia treated with unilateral DBS of right NAc, a reduction in symptoms, and an improvement in psychosocial functioning (58% measured by the Global Assessment of Functioning) [93].

The first small randomized trial, in which patients with TRS received DBS in the NAc or in subgenual ACC, was completed just in 2020 [94]. A total of 7 cases have been treated: 2/3 of patients with NAc as the target, and 2/4 in case of ACC, reached a significant improvement in symptoms, defined as a ≥25% increase at the Positive and Negative Symptoms Scale (PANSS) total score. Three of the four cases showing a significant response worsened after the pulse generator was switched off in a double-blind condition. Furthermore, patients with electrodes implanted in the NAc exhibited a more marked and rapid improvement. Lastly, in 2020, Wang et al. performed DBS of HB in two cases of TRS, achieving efficacy during the first six months, although only one patient maintained the result after one year with a PANSS total score improvement of 31.7% [90].

6. Tourette's Syndrome

Gilles de la Tourette Syndrome (TS) manifestations are secondary to a developmental dysfunction of the CSTC loop [95]. This closed-loop network of parallel circuits (motor,
 associative, limbic) between cortex and basal ganglia is involved in motor, cognitive, and emotional processes. In particular, the motor loop circuit includes the frontal motor cortex and the somatosensory cortex, the dorsal striatum (putamen), the posteroverentral part of the internal globus pallidus (pGPI), the substantia nigra (SN) pars reticulata, the motor nuclei of the thalamus in its direct pathway and, besides, the external globus pallidus (GPe) and the dorsolateral STN in its indirect pathway. The dopaminergic affinences on the striatum determine the direct pathway’s activation, causing positive modulation of the motor cortex. Accordingly, dopaminergic hyperactivity in TS would be implicated in the generation of motor and verbal tics. Treatment of TS requires a combination of psychoeducation support and pharmacological therapy, mainly with antipsychotics and alpha-adrenergic agonists, with a satisfactory response rate [96]. Unfortunately, in some cases, the symptomatology persists in adulthood and appears resistant to conventional treatments, or patients experience medication side effects, resulting in severe social and professional disability.

The first case of surgical treatment of TS dates to 1960, when Baker in Toronto performed a bimedial leucotomy in a 22-year-old man: after surgery, he showed a marked reduction in tics and panic attacks [97]. Ten years later, Hassler and Dieckmann reported the first stereotactic thalamotomies on intralaminar, medial, and the ventro-oralis internus (Voi) nuclei of the thalamus in 3 patients with a significant tics’ reduction or resolution [98]. Globally, a total of 65 cases of intractable TS were presented undergoing ablative surgery through prefrontal lobotomy, bimedial frontal leucotomy, limbic leucotomy, anterior cingulotomy, medial, intralaminar, and ventrolateral thalamotomies, campotomy and dentatotomy [99].

**DBS in Tourette’s Syndrome**

The introduction of DBS for TS in 1999 by Vanderwalle et al., using the thalamic nuclei previously targeted by Hassler, definitively supplanted lesional surgery [100]. Since that point, several targets along the CSTC loop have been explored with DBS, presumably due to the complexity and variety of phenotypical manifestations of this condition ranging from a movement disorder to a psychiatric disease. Following the 2015 guidelines, to indicate DBS for TS should be attested the refractoriness to pharmacological therapy with at least three classes of drugs including alpha-adrenergic agonists and antipsychotics, the presence of severe tics [Yale Global Tic Severity Scale (YGTSS) score > 35/50] with functional impairment, and adequate social support [101]. Nowadays, the most promising target for stimulation appears to be the Voi centromedian-parafascicular thalamic complex (Vo-CM-Pf), the intersection zone between centromedian nucleus, substantia periventricularis, and Voi.

A double-blind, randomized trial in 2011, including six patients, showed a 49% improvement at a one-year follow-up at the YGTSS [102]. The stimulation of centromedian nucleus and substantia periventricularis leads to a benefit on tics and behavioural dysfunctions by suppressing excitatory feedback projections to the limbic and motor parts of the striatum, whereas the stimulation of the Voi influences the orofacial tics by working on the respective projections of the premotor cortex. Servello et al., in 2016, presented a large cohort of 48 patients treated with DBS, 40 of whom were targeted in the Vo-CM-Pf, reporting a reduction in tics at the YGTSS of over 50% (78.4% in 29/37 cases examined) [103]. Interestingly, they placed the target 2 mm more anteriorly, reached the associative-limbic connections, and influenced the behavioral components of TS. About other promising targets, Gpi was investigated by Kefalopoulou et al. in 2015 in a double-blind, randomized trial, achieving a total score at YGTSS significantly lower than in the off-stimulation phase (mean improvement of 12.4 points, 15.3%) [104]. They selected in 13 patients the anteromedial Gpi (aGpi) and, in 2 cases, the pGpi based on dystonic components. Indeed, it is retained that pGpi is part of the CSTC motor loop, while aGpi is part of the associative-limbic CSTC loop.

Other alternative targets have been selected in associated comorbidities, whereas only in limited reports: NAc, ALIC, STN, and GPe (Table 5).
Table 5. Instrumental therapeutics for Tourette Syndrome (TS).

| Procedure          | Author (Year)       | Study Design | Targets                                                                 | Sample Size | Outcomes                                                                 | Comments                                                                 |
|--------------------|---------------------|--------------|-------------------------------------------------------------------------|-------------|--------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Lesional surgery   | Baker (1962)        | OLS          | Bimedial frontal leucotomy                                              | 1           | Marked reduction in tics and panic attacks at one-year follow-up         | Postoperative complication of frontal abscess, successfully treated with evacuation and antibiotics |
| Stereotactic lesioning | Hassler (1970)     | OLS          | Intralaminar, medial, and Voi nuclei of the thalamus                  | 3           | Significant tics' reduction or resolution (100% in Patient 1, 90% in Patient 2, and 70% in Patient 3) | No details about the tic-rating method                                      |
| DBS                | Vanderwalle (1999)  | OLS          | Intralaminar, medial, and Voi nuclei of the thalamus                  | 1           | At 1-year follow-up, tics resolved with stimulation                     | They decided to stimulate the thalamic nuclei targeted by Hassler          |
| DBS                | Ackermans. (2011)   | Double-blind randomized | Vo-CM-Pf                                                                 | 6           | 49% improvement at a one-year follow-up at the YGTSS                  | Tic severity during ON stimulation was significantly lower than during OFF stimulation |
| DBS                | Servello (2016)     | Cohort study | Vo-CM-Pf (n = 40); pGpi; aGpi; NAc-ALIC                              | 48          | Reduction in tics at the YGTSS of over 50% (78.4% in 29/37 cases examined) | Target 2 mm more anteriorly, reaching the associative-limbic connections |
| DBS                | Kefalopoulou (2015) | Double-blind randomized cross-over trial | aGpi (n = 13); pGpi (n = 2)                                             | 15          | Total score at YGTSS significantly lower than in the off-stimulation phase (mean improvement of 12.4 points, 15.3%) | pGpi is part of the CSTC motor loop, while aGpi is part of the associative-limbic CSTC loop |
| DBS                | Kuhn (2007)         | OLS          | NAc/ALIC                                                               | 1           | Improvement in tics frequency and severity over two and half year follow-up (41% at YGTSS) | Also improvement of comorbid OCD                                           |
| DBS                | Martinez-Torres et al. (2009) | OLS          | STN                                                                    | 1           | Tics frequency diminished by 97% at 1 year. In OFF stimulation immediate increase in tic frequency. | Comorbid PD: 57% improvement in the motor part of the Unified Parkinson’s Disease Rating Scale at 1 year |
| DBS                | Piedimonte (2013)   | OLS          | GPe                                                                    | 1           | 70.5% improvement at YGTSS at six months                               | Loss of therapeutic effect with the battery exhausted                     |
| GK                 | Richieri (2018)     | OLS          | ALIC                                                                  | 1           | Clinical remission at 1 year                                           | A case of intractable TS and OCD, non-responsive to DBS of pGpi and thalamus |

Kuhn et al. performed DBS of NAc/ALIC on a patient with TS and comorbid OCD, determining an improvement in obsessive-compulsive symptoms and tics frequency and severity [105]. A case of bilateral STN DBS was described in a 38-year-old male patient with Parkinson's disease and concomitant TS; after surgery, the patient experienced an improvement in both conditions [106]. More recently, due to its connection with STN's sensory-motor area, the central part of the GPe has been used for the stimulation [107]. Finally, it has been recently reported a case of intractable TS and OCD, non-responsive to DBS of pGpi and thalamus, which underwent anterior capsulotomy by GK, with remission of both conditions [108]; this report suggests, therefore, also the possible use of radiosurgery for the treatment of these challenging patients.
7. Eating Disorders

Eating disorders (ED) are chronic, potentially deadly illnesses that comprise anorexia nervosa (AN), bulimia nervosa, food craving, and binge eating disorder. All these conditions comprise pathological eating behaviors and body image disturbance. Whereas obesity is not strictly classified as an ED, it is a potential risk factor and a consequence of ED [109]. Existing treatments for ED have limited proven efficacy, especially in adults with AN. Psychological interventions are the treatment of choice for most eating disorders, but a significant proportion of patients have no benefits from these approaches. Non-invasive brain stimulation and neurofeedback are emerging treatments in such cases [110]. However, recognizing the alterations in circuits involved in reward processing, appetite regulation, and self-regulatory, coupled with the advances in understanding the neurobiology of eating disorders [111], led to surgical treatment as DBS. Despite non-invasive neuromodulation as repetitive transcranial magnetic or direct current stimulations are employed for eating disorders, it seems that the results of these techniques are modest and generally more mixed, if compared to stereotactic ablation and DBS [111].

7.1. Anorexia Nervosa and DBS

Refractoriness to AN therapies is defined as the lack of response to repeated interventions over an extended time (5–10 years) [112]. In such cases, neuromodulation has been anecdotal proposed. For example, in four adolescents with AN, DBS of NAc determined an average weight increase of 65% [113]. Lipsman et al. in 2013 presented a phase one pilot trial, including six patients who underwent DBS of the SCG: nine months after surgery, three patients increased their body mass index (BMI) greater than their historical baseline [114]; however, also AN-related obsessions and anxiety improved in four patients. The most extensive series so far presented about DBS for AN comprises 16 patients, in which the target was the SCG [115]; this series is the extension of the above-mentioned earlier series of six patients [114]. In the newest series, the average BMI at surgery was 13.83; after 12 months of stimulation, the mean BMI increased to 17.34.

DBS was also associated with significant improvements in depression, anxiety, and affect regulation [115]. The most frequent adverse event was transient pain, but 44% of patients presented severe adverse events, as electrolyte disturbances, related to the underlying illness. Metabolic imaging depicted relevant changes in glucose metabolism in brain structures implicated in AN at follow-up, confirming that invasive neuromodulation directly affects the brain networks related to AN. In June 2020, Villalba Martinez and coauthors presented the six-months follow-up results of a phase II trial involving a series of eight adults (mean age of 40.75 years) with treatment-resistant AN, present for more than 10 years, which received SCG or NAc DBS [116]; the exact target was selected according to the comorbidities (affective or anxiety disorders, respectively). In fact, seven patients were affected by MDD, OCD, or panic disorders. The complications regarded skin infection or wound dehiscence in three patients. The six-months analysis showed that DBS did not produce a statistically significant increase in BMI: 5/8 patients achieved an increase of ≥10% in BMI, and three among eight presented changes in AN behavior, as reduced physical activity and use of laxatives and diuretics. Globally, the patient-reported measure of quality of life improved in the majority of patients. However, long-term follow-up is necessary to elucidate the effects and outcomes of DBS for AN.

7.2. General Consideration about Eating Disorders

The treatment of bulimia nervosa currently is demanded to non-invasive transcranial stimulation, and it seems that invasive approaches have not yet been presented [117]. It can be postulated that, regarding morbid obesity, the pathophysiologic mechanisms involve eating and satiety patterns along with reward and compulsive aspects of food intake. On these bases, DBS targets proposed to treat obesity include the hypothalamus and the NAc [118,119]. The structures involved are the arcuate nucleus, the dorsal medial nucleus, the paraventricular nucleus, the lateral hypothalamus, and the ventral medial
nucleus; the NAc instead should play a role in rewarding aspects of food intake and compulsive feeding. NAc-DBS could, therefore, modulate the food craving and compulsive eating [119]. The theoretical explanation about the DBS in eating disturbances is related to the modulation of hypothalamic satiety centers [120]. Although neuromodulation for eating disorders represents, currently, mainly an experimental intervention, the progressive understanding of the potential pathophysiological mechanisms, along with the growing number of studies in this area, could provide further indications for invasive treatment of alimentary disturbances (Table 6).

| Eating Disorder | Procedure | Author (Year) | Study Design | Targets | Patients | Outcomes | Comments |
|-----------------|-----------|---------------|--------------|---------|----------|----------|----------|
| AN              | DBS       | Wu (2013)     | OLS          | NAc     | 4        | Average weight increase of 65% | Comorbid OCD in 3/4. Menstruation cycle restored in all patients in an average of 6.8 months |
| AN              | DBS       | Lipsman (2013)| OLS          | SCG     | 6        | After 9 months, 3/6 increased BMI | Improvement in quality of life in three patients after 6 months |
| AN              | DBS       | Lipsman (2017)| OLS          | SCG     | 16       | Mean BMI increased from 13.83 to 17.34 at 1 year | Significant improvements in depression and anxiety |
| AN              | DBS       | Villalba Martínez (2020) | Double-blind randomized controlled crossover trial | SCG, NAc | 8        | After 6 months, 5/8 showed an increase of ≥10% in BMI | Target (SCG or NAc) selected according to comorbidities (affective or anxiety disorders) |

### 8. Addictions

The mesolimbic system is involved in the early stage of addiction, during which the substance abuse causes a sense of reward, along with VTA, MFB, hypothalamus, olfactory tubercle, and NAc. Dopamine plays a primary role in addiction, and dopaminergic excitability increases with prolonged substance use [121]. Following substance withdrawal, the “addiction system” is affected by a decrease of such dopaminergic activity, with subsequent depressive state and anhedonia; the “extended amygdala” (BNST, central nucleus of the amygdala, the shell of the NAc) also plays a role in this system [122].

A first human addiction model can be the dopamine dysregulation syndrome, which is often encountered in Parkinson’s disease patients submitted to dopamine-replacement therapy, who develop pathological gambling, hypersexuality, mood alterations, and, above all, pathological dopamine-seeking behavior. NAc DBS for OCD also resolved coexistent drug addiction [123,124]. According to a recent systematic review of DBS for substance use disorder [125], 13 publications were identified on this subject (reports or case series involving addiction to alcohol, cocaine, nicotine, heroin, and methamphetamine). DBS targets included the NAc, and in two cases also ALIC was targeted (Table 7)
Table 7. Instrumental therapeutics in addiction.

| Author          | Addiction | Outcome                                                        | Adverse Effects                      |
|-----------------|-----------|----------------------------------------------------------------|--------------------------------------|
| Kuhn (2007)     | Alcohol   | Reduction of consumption from 10 (or more) drinks per day to 0–2 drinks per day | -                                    |
| Muller (2009)   | Alcohol   | All patients experienced loss of cravings; 2/5 pts maintained abstinence for 6–8 years; 2/5 pts maintained abstinence for 15–20 months followed by relapses; 1/5 pt reduced consumption with multiple short relapses | Hypomanic episode; migration of electrodes |
| Voges (2013)    | Alcohol   | All patients experienced loss of cravings; 2/5 pts maintained abstinence for 6–8 years; 2/5 pts maintained abstinence for 15–20 months followed by relapses; 1/5 pt reduced consumption with multiple short relapses | Hypomanic episode; migration of electrodes |
| Muller (2016)   | Alcohol   | All patients experienced loss of cravings; 2/5 pts maintained abstinence for 6–8 years; 2/5 pts maintained abstinence for 15–20 months followed by relapses; 1/5 pt reduced consumption with multiple short relapses | Hypomanic episode; migration of electrodes |
| Kuhn (2009)     | Nicotine  | 3/10 patients stopped smoking at first attempt after surgery, maintaining cessation at 2-years FU | -                                    |
| Gonçalves-Ferreira (2016) | Cocaine | Reduced use at 6 months and 24 months post-surgery; reduced severity of dependence at 2.5 years FU | Diminished libido; weight gain |
| Zhou (2011)     | Heroin    | Mantained abstinence 6-years FU                                  | Weight gain                          |
| Valencia-Alfonso (2012) | Heroin | Mantained abstinence 6-months FU                                 | -                                    |

Parameters varied between 130 and 185 Hz, 90–240 µs, 1.5–7 V [124,126–130]. Interestingly, there was also an improvement in neuropsychological outcomes [131]. The discrepancies between inclusion criteria, evaluation scales, time of follow-up, and stimulation parameters among the different studies could limit our capacity to draw any conclusions, but it appears that NAc could be an effective target.

9. Summary and Future Perspectives

Invasive procedures for psychiatric disorders present several concerns, both due to the fact that the first questionable methodologies used during the middle of the twentieth century, such as prefrontal lobotomy, caused severe deficits in emotional responsiveness, and to the lack of information about the exact neurophysiopathological mechanisms involving different cortical and subcortical structures. Experimental neuromodulation via brain electrodes was first tried in patients with schizophrenia during the 1950s [4,132]. However, the functional neurosurgical procedures have been successfully investigated and applied to movement disorders like Parkinson’s disease and dystonia, starting from the late 80s and the early 90s [27,133], then spreading to intractable somatic and cephalic pain of various nature [134], and finally to psychiatric disorders [55,99].

Nowadays, there are more clear indications also for some psychiatric disorders amenable to invasive procedures, comprising MDD, OCD, pathological aggressive behavior, Tourette’s syndrome, anorexia nervosa, schizophrenia, and addiction. The patients submitted to invasive procedures have to be treatment-resistant, that is to say, resistant to conservative measures, and criteria to define treatment resistance depend on the disease. In the last decade, much attention has been paid to investigating the mechanisms of action of the neuromodulatory procedures (DBS) and the lesional procedures (RF, GK, MRgFUS) on psychiatric disorders. Neurophysiological and functional neuroimaging data helped to assess this issue in the past; the technological evolution applied to neuroradiological investigations should also be helpful in the next years to better clarify the complexity of the structures involved in psychiatric disorders. Moreover, it is of foremost importance to individuate, at a laboratory level, the critical mechanism altered in such diseases; the so-called “key-structures” could probably only be a node in the context of very complex and reverberating systems, which could feed each other through whole-brain dynamics involving many, if not all, cortical and subcortical structures. Different targets have been used for lesional (surgical or not approaches) and neuromodulation procedures. For example, a meta-analysis reported that, for OCD-DBS, ALIC, VC/VG, NAc, STN, and ITP determined the same results in terms of Y-BOCS [69]: the different targets did no show significant differences in terms of efficacy and clinical response.
The explanation underlying these results may be obtained by introducing the concept of “connectome”: different targets may modulate the same neural network responsible for clinical improvement. In movement disorders, DBS has experienced a paradigm-shift from stimulation of specific brain nuclei to a real modulation of brain networks, which can be evaluated through resting state functional MRI (rsFMRI).

As far as MDD is concerned, there is substantial evidence that functional connectivity (FC) disruption, as investigated with rsFMRI, is a very frequent finding in MDD patients. Dysfunction in FC involving the salience network (comprising ACC), as well as in FC of structure mediating attention (such as dorsolateral prefrontal cortex and amygdala) are very frequent findings in this disease [135]. Dysfunction in the reward-learning system involving VTA and its projections to ACC, NAc, and medial prefrontal cortex could contribute to anhedonia; at rsFMRI, an excessive functional dominance of Default Mode Network, comprising medial prefrontal cortex and posterior cingulate cortex over Task-Positive-Network, which includes associative frontal and parietal cortices, could facilitate a depressive state trough excess of negative self-referential information [6].

In a study by Cano et al. [136], comprising 86 OCD patients and 104 healthy controls, rsFMRI with seed-based analysis focused on STN and on BNST was employed. In comparison with controls, patients with OCD showed an increased FC between the left STN and the right premotor cortex, decreased FC between the right STN and the lenticular nuclei, and increased FC between the left BNST and the right frontopolar cortex. A negative association between clinical severity and FC between the right STN and lenticular nucleus was thus revealed. About TS, already in 2009 Rickards, using fMRI, reported an increased connectivity between striatum and insula, orbitofrontal cortex, cerebellum and motor cortex, thus confirming that TS is a disease involving both emotional and motor systems [137]. In patients with TS comorbid with OCD, strong connectivity has been reported between insula and inferior and middle temporal gyri, between the putamen and superior and middle temporal gyri, and between orbitofrontal cortex and anterior cingulate cortex.

Li and coauthors of a multicentric international group analyzed four cohorts of OCD patients submitted to DBS of DBS targets, using a connectomic approach [66]: the same results were obtained with ALIC-DBS or STN-DBS cohort. These two regions are involved in a network comprising dorsal ACG, ventrolateral prefrontal cortices, and antero-medial STN. Therefore, the overall connectivity of STN- and ALIC-DBS modulates how different brain areas interconnected. A potential consequence is to evaluate post-operative connectomic maps acquired with advanced neuroimaging or metabolic tracers to analyze the exact changes of all networks involved and modulated, also coupling individualized MRI data with normative connectomes atlases of average brain connectivity acquired from large cohorts of subject [66,138].

A new advancement in DBS technology is potentially represented by closed-loop stimulation, employing neural (such as abnormal electrographic discharges) or neurochemical feedback to modulate the stimulation parameters to the fluctuations and paroxysms of the clinical manifestations [139]. This so-called adaptive DBS (aDBS) evaluates specific neural patterns, recorded by electrodes, and recognized to be related to specific symptoms (e.g., TS tics or the onset of obsessive-compulsive episodes), and dynamically and automatically calibrates the stimulation to suppress the events. Although this is just an experimental therapy at its beginning, it could result in a promising approach to customize psychiatric patients’ treatment in real-time.

10. Conclusions

Despite the efficacy of DBS and other instrumental therapeutics not yet being established for some psychiatric disorders, there are several premises for the future applications of “unclassical” treatments in psychiatry. A more in-depth knowledge of such disorders’ neuroanatomical bases, also thanks to advanced neuroimaging, could better let us understand why neuromodulation determines similar effects across various psychiatric disorders. The new technologies, applied to new stimulation techniques, may improve the current
results to personalize each specific patient’s treatment. However, despite the good results reported, the need to prolong psychotherapy and pharmacotherapy should be established for each single patient.

11. Key Questions
1. Have the right targets for each disease been individuated? Is neuroimaging sufficient to address this point?
2. Is a single target sufficient to control all of the symptoms, given the emerging concept of altered connectivity between different structures?
3. How can the connectomic approach help us in refining and improving surgical approach?
4. Will aDBS improve results and be more effective in these patients?
5. How can we solve the problem of non-responders? Is it possible to predict lack of efficacy and to find a biological hallmark for non-responsiveness for each disease?

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Abbreviations
ACC: anterior cingulate cortex; ACG: anterior cingulate gyrus; aDBS: adaptive deep brain stimulation; aGPi: anterior globus pallidus internus; ALIC: anterior limb of internal capsule; AN: anorexia nervosa; BDI: beck depression inventory scale; BMI: body mass index; BNST: bed nucleus of stria terminalis; CGI: clinical global improvement; CGPSS: current global psychiatric-social status scale; CSTC: cortico-striatal-thalamo-cortical; DBS: deep brain stimulation; DTI: diffusion tensor imaging; ED: eating disorder; FC: functional connectivity; FDA: food and drug administration; FU: follow-up; FUS: focused ultrasound; GK: gamma knife; GPi: globus pallidus internus; HARS: Hamilton anxiety rating scale; HB: habenula; HDRS: Hamilton depression rating scale; IC: internal capsule; imMFB: inferomedial branch of the medial forebrain bundle; ITP: inferior thalamic peduncle; Hb: lateral habenular complex; LL: limbic leucotomy; MADRS: Montgomery-Åsberg depression rating scale; MDD: major depressive disorder; MFB: medial forebrain bundle; MRgFUS: magnetic resonance-guided focused ultrasound; MRI: magnetic resonance imaging; NAc: nucleus accumbens; OCD: obsessive-compulsive disorder; OLS: open label study; PAG: periaqueductal gray; PANSS: positive and negative symptoms scale; pGPi: posterior globus pallidus internus; RCT: randomized controlled trial; RF: radiofrequency; rsFMR: resting state functional MRI; SCG: subcallosal cingulate gyrus; SGC: subgenual cortex; SI: substantia innominata; slMFB: superiorolateral branch of the medial forebrain bundle; SN: substantia nigra; ST: subcaudate tract; STN: subthalamic nucleus; TRS: treatment-resistant schizophrenia; TS: Tourette’s syndrome; US: ultrasound; VC/VS: ventral capsule/ventral Striatum; Vo-CM-Pf: Voi centromedian-parafascicular thalamic complex; Voi: nucleus ventro-oralis internus of the thalamus; VTA: ventral tegmental area; Y-BOCS: Yale-Brown obsessive-compulsive Scale; YGTSS: Yale global tic severity scale.
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