Psychiatric Disorders

Subjects: Clinical Neurology

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Psychiatric disorders refer to the behavior or psychological pattern that can lead to significant distress or functional impairment.

addiction deep-brain stimulation major depressive disorder Obsessive-Compulsive Disorder OCD

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.

Table 1. Overview of the 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 sterotactic 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-emittingCobalt 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. 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 coeruleus, 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 ≥ 30 years, a score ≥ of 20 at Hamilton Depression Rating Scale (HDRS), a score ≥ 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.

2.1. 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.

2.1.1. 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.

2.1.2. 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 deposing 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%.

2.1.3. 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.

2.1.4. Limbic Leucotomy

Limbic Leucotomy (LL) is a combination of anterior cingulotomy and subcaudate tractotomy initially described by Kelly and Richardson in 1972. 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%).

2.2. 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.

2.3. 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].

2.4. 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 therapeutical 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][34][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].

3. 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 cortico-striatal-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.

3.1. 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][57][58][59][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][64][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. 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, is it 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 32.3 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.

3.2. 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.

3.3. 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.

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