Exploring New Horizons in Treatment: The Potential of Radiation-induced Neuromodulation to Enhance Psychological Therapies in Refractory Obsessive Compulsive Disorder

Francesco Camponeschi

Utrecht University - UMC Utrecht

Thesis is prepared in accordance with the demands of the Master's degree in Science and Business Management

June 2023

Internal Supervisor: dr Joost Verhoeff (UMC Utrecht - Radiotherapy department)
External Supervisor: dr Metten Somers (UMC Utrecht - Psychiatry department)

Abstract

Obsessive-compulsive disorder (OCD) poses a significant challenge in psychiatric treatment, with a considerable number of patients exhibiting limited response to conventional therapies. As a result, neuromodulatory and neuroablative approaches for treatment-resistant OCD are gaining popularity. Stereotactic radiosurgery (SRS) presents a minimally invasive neuroablative approach that targets specific brain regions and has some advantages over other neuromodulatory strategies. This narrative review examines the promise of radiosurgical neuromodulation, focusing on Gamma Knife SRS. Due to its non-invasiveness and excellent focal precision, SRS neuroablation techniques have drawn significant interest for the treatment of refractory OCD, mainly when targeting the anterior limb of the internal capsule through a technique referred to as capsulotomy. Capsulotomy studies have shown encouraging results for treating refractory OCD, however, most of them report the risk of severe adverse effects such as development of brain cysts related to higher radiation doses. Thus, the concept of radiation-induced neuromodulation with repeated lower, sub-ablative doses is explored in this paper. Additionally, Personalized Ultra-fractionated Low-dose Stereotactic Adaptive Radiotherapy (PULSAR) is introduced as a novel radiotherapy approach to combine with SRS capsulotomy for achieving radiation-induced neuromodulation without neural tissue ablation. Based on a careful evaluation of literature evidence, the historical growth and improvements in psychiatric radiosurgery are highlighted, emphasizing the possibility of non-invasive, radiation-induced neuromodulation approaches in modulating aberrant brain circuits in treatment-resistant OCD. The key impact of this research is to provide a strong foundation for creating future protocols designed to test the effectiveness of PULSAR-induced neuromodulation-assisted psychological treatment for refractory OCD patients.

Keywords: ‘Obsessive-compulsive disorder’, ‘Refractory’, ‘Capsulotomy’, ‘Anterior limb of the internal capsule’, ‘Gamma Knife’, ‘ Gamma Knife capsulotomy’, ‘Personalized ultrafractionated low-dose stereotactic adaptive radiotherapy’.

Plain Language Summary (Layman Summary)

Obsessive-compulsive disorder (OCD) is a common mental health condition affecting many people globally. While therapy and medication are effective for most individuals with OCD, there is a significant group of patients who do not respond well to these treatments. Scientists are now exploring alternative approaches to help these individuals, one of which is stereotactic radiosurgery (SRS). SRS is a non-invasive treatment that utilizes radiation to target specific areas of the brain, aiming to modify brain activity and reduce OCD symptoms. One type of SRS, called Gamma Knife SRS, is of particular interest in OCD treatment.

SRS offers several advantages. It is a non-invasive procedure, eliminating the need for extensive surgery, and it provides precise targeting of specific brain regions requiring treatment. Studies have shown that by using SRS to target the anterior limb of the internal capsule, a key brain area involved in behavior, symptoms in severe OCD patients can be improved. However, using high radiation doses can pose risks, such as the development of brain cysts. To minimize these risks, this review proposes an investigation into personalized and lower radiation doses tailored to each individual patient.

This review examines several important factors in the use of Gamma Knife SRS for treating OCD, including radiation dose and associated adverse effects. It is crucial to strike a balance between delivering enough radiation to achieve the desired therapeutic effect while minimizing any potential harm or side effects. Concerning this, this research paper discusses the concept of modulating brain activity by using non-lesioning, low-dose radiation. Instead of relying on the conventional rationale of destroying brain tissue in order to modulate brain activity, lower doses of radiation can be used to alter brain functioning, potentially offering a safer approach with valuable therapeutic effect and minimal brain damage. This personalized treatment strategy may offer a more effective way to help individuals with severe OCD who have not responded well to other treatments.

In summary, we investigate the potential of personalized, non-lesioning radiation doses in Gamma Knife SRS as a treatment for individuals with OCD who have not seen improvement with other therapies. By tailoring the radiation dose to each patient, researchers aim to achieve positive effects while minimizing the risk of adverse effects associated with higher radiation doses. This study provides hope for finding a safer and more effective treatment option for treatment-resistant psychiatric patients.

1. Introduction

1.1 OCD as Circuito Pathology

Obsessive-compulsive disorder (OCD) is a prevalent, chronic, and debilitating mental health disorder which involves recurrent and uncontrollable thoughts referred to as obsessions, combined with excessive urges to perform repeated actions denoted as compulsions[1,2]. Although OCD can develop at any age, it typically manifests during childhood and adolescence, with symptoms frequently beginning around the age of ten[3]. Functional neuroimaging studies on individuals with OCD have consistently demonstrated altered functional connectivity within multiple brain networks, allowing us to potentially define OCD as a circuito-pathology, thus due to abnormal activity of brain networks that prevent proper interaction with the external environment[4]. The definition of OCD as circuito-pathology highlights the concepts of connectome and neuroplasticity, emphasizing the significance of targeting connectome activity for potential OCD treatments. This approach aims to normalize the connectome towards a more functional state, ultimately contributing to the improvement of OCD symptoms. Current standard treatments for OCD include pharmacological medications, such as selective serotonin reuptake inhibitors (SSRIs), and cognitive behavioral therapy (CBT). However, an overall 20%-30% of OCD patients are estimated to be refractory to available psychological and pharmacological treatments[5,6], emphasizing the need for understanding the circuitry model responsible for OCD.

1.2 Connectome and OCD Circuitry Model

The human brain consists of diverse interconnected brain networks, collectively forming the connectome, which represents the comprehensive wiring diagram of the brain. The individual variability of the connectome, including its connectivity, cortical function, and structure, contributes to the development of unique personalities and influences the manifestation of psychiatric disorders[7,8]. In the context of OCD, the connectome plays a crucial role in shaping the abnormal patterns of neural activity observed in affected individuals. The dysregulation within specific circuits, particularly the cortico-striato-thalamo-cortical (CSTC) loop, has been implicated in the circuitry model of OCD[9].

Meta-analyses can help to draw more consistent conclusions about the structural and functional features underlying OCD pathology. Klugah-Brown and his colleagues performed a voxel-based meta-analysis[10] comparing gray matter volume (GMV) in OCD patients and healthy controls (HCs). They reported that OCD patients showed a reduced GMV in the inferior frontal gyrus (IFG) and an increased GMV in the striatal area of the putamen compared to HCs. Similarly, other meta-analyses have shown the presence of volumetric and cortical thickness differences in OCD patients compared to HCs, particularly in specific brain areas such as the orbitofrontal cortex (OFC), the anterior cingulate cortex (ACC), and the caudate[11,12,13,14]. Diffusion tensor imaging studies have indicated abnormalities in white matter physiology, including reduced fractional anisotropy in specific regions such as the lenticular nucleus (part of the basal ganglia), a key component of the CSTC[15]. Functional neuroimaging studies have consistently implicated altered brain activity in the fronto-limbic network, thalamus, and striatum in OCD[16]. Resting-state functional neuroimaging meta-analyses have supported the triple network model hypothesis, indicating reduced functional connectivity between the frontoparietal network, salience network, and default-mode network in OCD[17]. Dysfunction within the default-mode network contributes to increased self-referential processing and impaired attention shifting, both behavioral deficits which play a significant role in the manifestation of OCD symptoms[18,19]. Functional imaging studies consistently report hyperactivity in the OFC, the ACC, and the head of the caudate nucleus of individuals with OCD[20]. Overall, literature from studies investigating the circuitry involved in OCD pathology led to the definition of several models which differ in details, but they all share the idea that obsessions and compulsion result from malfunctioning neural circuits that include the OFC, the ACC, the basal ganglia, and the thalamus, key brain areas of the CSTC circuit (Figure 1). It is clear that abnormalities in the connectome of OCD patients lead to the symptoms of such disorder, thus research is shifting interest towards a connectome modulation approach targeting the CSTC.

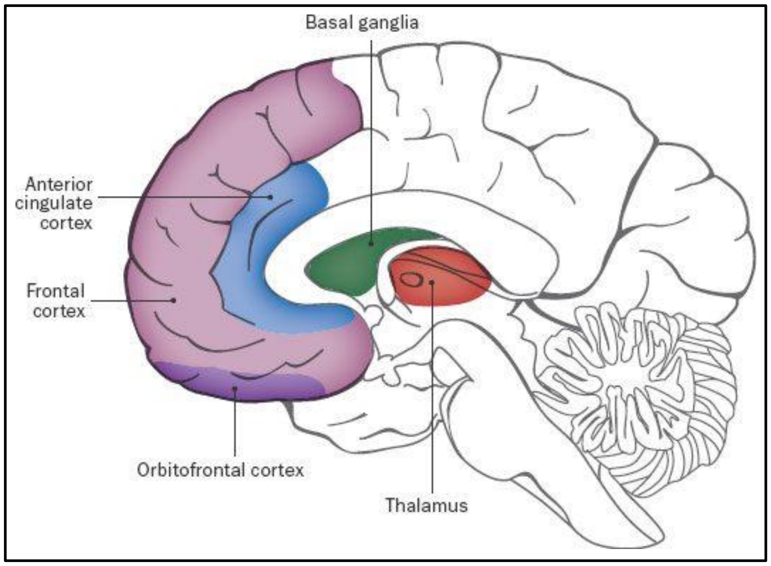


Figure 1: Representation of some of the key brain areas of the CSTC circuit.

The connectome is constantly shaped and influenced throughout life by external and internal stimuli through the process of neuroplasticity. Neuroplasticity refers to the brain's ability to alter its structure and function in response to experience, involving the formation, strengthening, or weakening of neural connections, and processes of neurogenesis, synapse formation, and network remodeling[21]. Given the observed hyperactivity in the CSTC circuit[22] and the ongoing advancement in our understanding of the neural circuitry underlying OCD, the field of neuromodulation is directed towards targeting brain regions within dysfunctional brain networks. The primary objective is to restore neural activity to a healthier state, thereby normalizing the functioning of the target circuits.

1.3 Neuromodulatory Approaches for OCD

Neuromodulation techniques can be either reversible or non-reversible (ablative) depending on the method used to carry the stimulation or the surgical intervention. Reversible neuromodulatory approaches such as electroconvulsive therapy (ECT), repetitive transcranial stimulation (rTMS), and deep brain stimulation (DBS) have been explored concerning their therapeutic effect on psychiatric conditions. ECT involves the application of an electrical stimulus to the brain in order to depolarize neurons and produce a controlled seizure. The exact mechanism through which the seizure is spread is not yet clear, but it is thought that the antidepressant effect achieved by this technique largely depends on the intensity and site of seizure initiation[23]. This technique has proven effective for the treatment of OCD in some cases[24,25]; however, there is still limited evidence to recommend ECT for OCD[26]. rTMS is a non-invasive neuromodulation technique that has gained much interest as a possible alternative to ECT due to its excellent safety profile and non-invasive nature. rTMS involves placing a magnetic coil against the scalp, which generates short magnetic pulses directed to brain tissue and induces electrical currents in targeted brain areas, thus altering and affecting neuronal firing patterns and influencing brain connectome activity[27]. Many rTMS controlled trials investigating its use for treating depression were conducted, eventually leading to the approval of these techniques for treating such disorders in various parts of the world[27]. Concerning OCD, there is evidence of the effect of rTMS in improving OCD symptoms in various trials and meta-analyses, where the most promising targets are the supplementary motor area (SMA) and the dorsolateral prefrontal cortex (dlPFC)[28,29]. However, it does not provide the highest level of focal stimulation, particularly if compared with the anatomical specificity achieved by DBS and radiosurgical neuroablative techniques such as stereotactic radiosurgery (SRS). DBS uses brain-implanted electrodes which emit electrical impulses to stimulate and modulate neural functioning[30]. This process requires complex surgery and mechanical monitoring, thus presenting more complications than other neuromodulatory techniques. DBS was approved for the treatment of refractory OCD in 2009, and it has also been researched with regard to other disorders such as Parkinson's disease and refractory depression[31]. Considering refractory OCD, DBS has shown evidence of therapeutic effectiveness in regards to the following brain areas within the CSTC circuit: anterior limb of the internal capsule (ALIC), ventral striatum (VS), nucleus accumbens (NAcc), and subthalamic nucleus (STN)[32,33,34,35]. This evidence indicates that altering CSTC circuit activity potentially induces clinical improvements in refractory OCD patients.

1.4 Neuroablative Approaches for OCD – Historical Perspective

Neuroablation involves the destruction of neuronal tissue to achieve symptomatic relief in patients who have exhausted other therapeutic options. The fascination with causing brain lesions to achieve clinical improvements in psychiatric patients has captivated our ancestors throughout history. Ancient trials of trepanation involving the literal drilling of patients' skulls are dated back to 5100 BC[36]. The development of modern neurosurgical techniques for psychiatric treatment can be traced back to Burckhardt's pioneering work in 1888, when he performed the first topectomy, consisting of removing portions of the cortex through a scalp spoon[37]. However, these procedures faced criticism due to their brutality and adverse effects. Consequently, the field of psychosurgery received limited consideration in the years following World War I, and the first remarkable neurosurgical approach that paved the way for this field was done by the work of the Portuguese neurologist António Egas Moniz (Figure 2) and the neurosurgeon Pedro Almeida Lima. In 1936, they introduced the concept of prefrontal leucotomy and performed the first modern neurosurgical procedure on a 63-year-old woman suffering from anxiety and paranoid symptoms[38,39]. The operation involved injecting alcohol into the frontal white matter tracts, leading to observed improvements in anxiety symptoms during a psychiatric evaluation two months later. Afterwards, Egas Moniz developed a new surgical instrument called leucotome, which he used to mechanically disrupt frontal lobes by creating circular lesions to separate white matter fibers. His neurosurgical operations proved to have a therapeutic effect on treating many cases of severe psychiatric conditions, as reported by his work in 1937[40]. Egas Moniz was awarded the Nobel Prize in 1949 in acknowledgment of his remarkable contributions to the field.

Figure 2: António Egas Moniz, considered the father of psychosurgery.

American scientists Walter Freeman and James Watts, contemporaries of Moniz, were inspired by his work and began performing prefrontal leucotomies shortly thereafter. Freeman believed that psychiatric disorders were caused by disrupted brain network interaction. In his opinion, it was possible to alter the brain towards a positive change through neurosurgery[41]. Building upon Moniz's work, Freeman and Watts introduced the concept of standard prefrontal lobotomy, which replaced the leucotome with a blade. Freeman's experiments were reported to bring clinical improvements in 63% of patients, as highlighted in one of his major case series studies[42]. During this period, the field of psychosurgery demanded continuous efforts to enhance procedure effectiveness and minimize side effects. One notable

Figure 3: Walter Freeman performing a transorbital lobotomy.

contribution came from Amarro Fiamberti, an Italian psychiatrist who introduced the concept of transorbital lobotomy. This technique, also adopted by Freeman (Figure 3), involved using an ice-pick-like instrument (transorbital leucotome) to cut projections within the prefrontal cortex[36]. Although it offered greater precision, it faced criticism for its crude nature. This criticism, together with the advent of pharmacological treatments like chlorpromazine, which were perceived as safer and more effective, led to a decline in interest in psychosurgery[43,44]. Nevertheless, ongoing research focused on creating precise subcortical lesions resulted in the development of stereotaxis, enabling precise targeting of inner brain areas with minimal disruption and invasiveness.

Swedish neurosurgeon Lars Leksell revolutionized the field in 1951 with the introduction of Stereotactic Radiosurgery (SRS)[45], eliminating the need for craniotomy. Although the main downside of SRS is its non-reversibility and ablative nature, this technique presents specific advantages compared to other neuromodulatory techniques like ECT, rTMS, and DBS. Its high level of focality and non-invasiveness allow for the precise induction of neurolesions within the human brain without the need for craniotomy. Various procedures such as cingulotomy, capsulotomy, subcaudate tractotomy, and limbic leucotomy[46] (Figure 4) gained popularity for treating refractory OCD, with capsulotomy demonstrating the highest effectiveness[50]. The stereotactic target site for capsulotomy is located within the ALIC, a portion of the internal capsule located between the head of the caudate and the lenticular nucleus which represents a key hub carrying cortical white matter fibers from the PFC to the subcortical structures of the CSTC[47,48]. Procedures involving the lesioning of the internal capsule have shown effectiveness and clinical improvements higher than DBS[49]. A meta-analysis by Brown and his team[50] compared the efficacy of two prominent neuroablative procedures for treating severe refractory OCD, namely capsulotomy and cingulotomy, targeting the ALIC and cingulum, respectively. This study found a higher effectiveness of the former compared to the latter, indicating the ALIC as a potentially more effective target to induce therapeutic effects in intractable OCD.

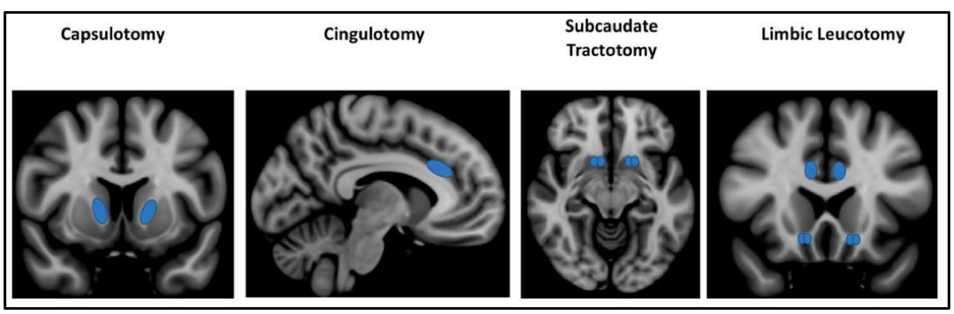


Figure 4: Four of the psychourgical techniques which gained significant popularity for treating refractory OCD: capsulotomy, cingulotomy, subcaudate tractotomy, limbic leucotomy (from left to right).

While SRS capsulotomy studies targeting the ALIC have shown promising outcomes in treating refractory OCD, it is essential to acknowledge that certain cases have reported severe adverse effects, including the development of brain cysts[51,52], particularly associated with the use of higher radiation doses. It is worth noting that using high radiation doses is a conventional practice in SRS capsulotomy studies as the primary objective is to induce a lesion in the neural tissue of the ALIC to modulate brain activity. This approach aligns with the etymology of the term "capsulotomy," derived from the Greek word "tomia," which signifies "cutting". However, emerging evidence suggests the potential for radiation-induced neuromodulation to occur before ablation[53], indicating the possibility of reducing the radiation dose used in SRS capsulotomy studies. This reduction aims to mitigate the adverse effects associated with neural tissue destruction.

1.5 Radiomodulation and Personalized Ultra-fractionated Low-dose Stereotactic Adaptive Radiotherapy

Interestingly, it has been noted that neuromodulation of a specific brain circuit might be achieved without ablating the neural tissue, as hypothesized by scientists Jean Regis and Bret Schneider, the pioneers of the field of radiomodulation[53,54,55]. Radiomodulation is introduced as the use of focally-delivered radiation at sub-ablative doses that can alter neural activity (Figure 5). At the brain's cellular level, various types of cells react differently when exposed to radiation, thus it is possible to modulate the proliferation and polarization activity in the neural environment by using sub-ablative radiation doses[54]. In order to get insights into targeting and dosing plans for applying radiomodulation approaches to treat refractory psychiatric patients, it is helpful to look at radiation-induced acute neural changes in animal and human studies.

Studies using sub-ablative GK radiation at doses of 40 Gy significantly reduced or eliminated seizures in temporal lobe epilepsy rat models starting from 1-month post-irradiation[56]; results also corroborated by other studies showing the promising dose-dependent effect of radiation on reducing kainic acid-induced epilepsy models when using similar (30Gy) or higher radiation doses (60 Gy)[57,58]. Overall, preclinical animal studies indicate radiation-induced neuromodulation through hyperpolarization of neurons, reduced synaptic connectivity, inhibition of sodium channels, and shortened action potential[53]. In human cases of trigeminal neuralgia and arteriovenous malformation (AVM) induced seizures, irradiation of the target area has resulted in immediate pain relief[59,60] and seizure reduction prior to AVM ablation[61,53], respectively. These cases provide evidence of the acute neuromodulatory effects exerted by radiation on neural tissue. In addition, a pilot study using subgenual cingulate irradiation (with a prescription dose of 75 Gy) in patients with severe depression and bipolar disorder reported acute therapeutic effects and clinical

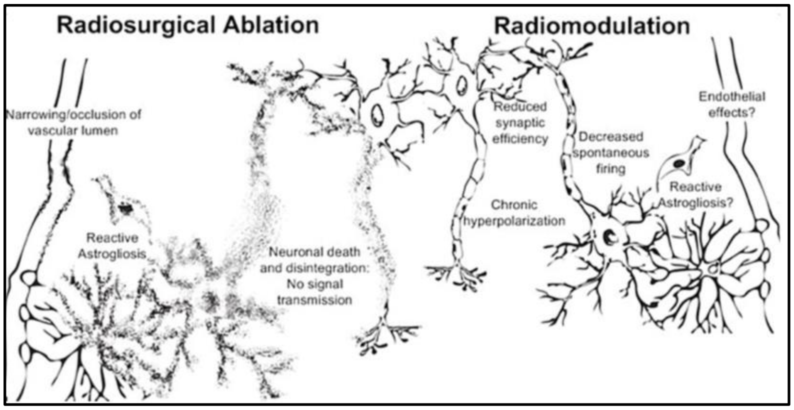


Figure 5: Representation of radiosurgical ablation, where there is an ocurrence of neuronal tissue destruction which leads to loss of signal transmission, and radiomodulation, where there is modulation of neuronal environment without any cell death occurring.

improvements within one week[62]. These findings hold promise for a low-dose, sub-ablative SRS application for psychiatric disorders and acute symptom relief.

The groundbreaking radiotherapy (RT) approach named Personalized Ultra-fractionated Low-dose Stereotactic Adaptive Radiotherapy (PULSAR)[63], pioneered by Dr. Timmerman and his team in 2021, presents a promising solution to achieve the optimal low-dose required for sub-ablative radiation-induced neuromodulation. PULSAR involves the use of large doses of radiation ("pulses" > 8 Gy) separated by longer time intervals compared to conventional RT methods, to treat lung tumors. Standard stereotactic ablative radiotherapy (SAbR) treatments are carried over 1-2 weeks, allowing few possibilities of changes to occur within the patient's biology with regards to tumor shrinkness or shape, thus presenting no opportunities to change and adapt the treatment based on the patient's body response. Instead, PULSAR makes a step forward to adaptive personalized treatment by separating pulses with more extended periods of time (3-4 weeks), eventually allowing changes to occur, be observed, and adapt the next steps of the ongoing therapy[63] (Figure 6). PULSAR is considered less toxic and allows more time for changes to occur and be assessed, thus enabling the oncologists to adapt the treatment depending on how the patient responds to it[64]. PULSAR has shown its potential to provide an improved tumor control compared to hyperfractionated RT[65].

The potential combination of PULSAR with psychiatric SRS holds promise for inducing sub-ablative radiation-induced neuromodulation and monitoring neuroplastic processes over specific time intervals. These intervals are valuable for visualizing the neuromodulatory effects of PULSAR in psychosurgery, investigating its properties in altering circuit connectivity, and planning the next step of the neuromodulatory treatment based on the individual patient's response. This adaptive approach is not only necessary due to the heterogeneity of OCD, but it also ensures that the treatment is customized and optimized for each patient, maximizing its effectiveness in attaining the desired outcomes.

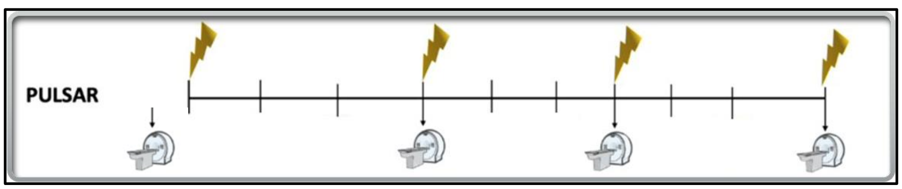


Figure 6: Schematic representation of the PULSAR RT approach, based on radiation treatment followed by imaging assessment which can then be used to plan the next step of the on-going therapy.

1.6 Aim of the Research

Psychotherapy for OCD mainly involves CBT, which has exhibited neuromodulatory effects on brain activity across different areas and the capacity to induce changes in regional brain function[66,67,68]. Furthermore, the possibility of enhancing the effectiveness of psychotherapy treatments by combining these with neuromodulatory approaches has been shown by different studies[69,70,71]. In view of the potential for increased effectiveness of psychotherapy when combined with neuromodulatory techniques, and the superior precision offered by SRS, this paper will discuss the potential of augmenting the therapeutic efficacy of psychological interventions through their integration with SRS. In particular, this paper will explore the possibility of achieving radiation-induced neuromodulation without ablation of the neural tissue by adopting the newly developed PULSAR approach. The potential of this approach to transition the radiosurgical capsulotomy intervention for refractory psychiatric disorders from SRS neuroablation to SRS neuromodulation will be carefully discussed. By avoiding neural tissue destruction, this approach shows promise in promoting brain connectivity normalization while mitigating the severe adverse effects observed in SRS capsulotomy studies[53].

This paper presents a narrative review on the use of Gamma Knife stereotactic radiosurgery (GK-SRS) capsulotomy for treating refractory OCD patients, mainly investigating factors such as radiation dose, adverse effects, and efficacy of such a technique. The narrative review will be used to explore the application of radiosurgical approaches for psychiatric disorders, to discuss the concept of radiation-induced neuromodulation, and finally to lay the groundwork for the development of a protocol for a study involving PULSAR-induced neuromodulation-assisted psychological treatment for refractory OCD patients. The importance of this research is dual; firstly, this paper sheds light on the field of psychiatric SRS, which is gaining increased attention due to technological and methodological advancements like PULSAR. Secondly, the authors will discuss the potential of employing non-lesioning, radiation-induced neuromodulation for treating refractory OCD patients, highlighting the promise of this technique to modify abnormal brain circuits in psychiatric patients, potentially facilitating psychological-assisted neuromodulation.

2. Materials & Methods

2.1 Narrative Reviews

Narrative reviews are a type of literature review that combines data from several sources to provide a thorough overview of a particular subject, serving many purposes such as tying up new findings and providing an outline of ideas that have not been discussed in depth yet. The authors conducted a narrative review on the use of GK capsulotomy for the treatment of refractory OCD, in order to report insights and evidence about the effectiveness of such technique in neuromodulating the key brain circuits of OCD pathology. A narrative review can provide a valuable set of educational articles and present a broad perspective on a given subject, in this case the use of GK capsulotomy for refractory OCD and the concept of radiomodulation. By providing a set of information coming from different sources on the use of radiosurgical capsulotomy, this narrative review not only presents an updated depiction of the literature in a single source, which can be very useful for students and researchers, but also facilitates the presentation of controversies and foster thoughts and brainstorming. The author's evaluation and synthesis of the information is one of the major downsides related to bias, and this will be discussed later in the "*Limitations and Future Directions*" paragraph in the "*Discussion*" section. Here we review what has been learned from the implementation of radiosurgical GK capsulotomy for the treatment of refractory OCD, and we speculate about the use of radiosurgery as a neuromodulation technique that can assist and foster the effectiveness of psychotherapy through a radiation-induced neuromodulatory effect.

2.2 Database, Search Terms

The authors reviewed the literature on the use of radiosurgical GK capsulotomy for refractory OCD by using a combination of optimal search strategies and the words: "Obsessive Compulsive Disorder" AND/OR "gamma knife" AND/OR "capsulotomy" AND/OR "radiosurgery", in the following databases: Worldcat Utrecht University, Pubmed, Scopus & Google Scholar. The most recent update of this search was on 31st of May 2023. The terms combined were inserted in each database and results were screened in a yearly range fashion considering the introduction of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score in 1989 as an essential year for the development of an OCD-specific scale evaluating the effectiveness of such techniques (1989-2023). The search output obtained by strategically combining the four keywords mentioned above yielded 45 papers from UU Worldcat, 51 papers from Pubmed, 49 from Scopus, and 605 from Google Scholar (n = 750). The overall flow chart representing the study selection process is shown in Figure 7. The research aimed at collecting and analyzing report studies investigating the effectiveness of GK capsulotomy on refractory OCD patients. All the duplicates were manually identified and removed (n = 127). The title and abstract of the remaining 623 studies were screened by applying inclusion and exclusion criteria (see 2.3), and the ones not related to this research topic were removed (n = 593). The remaining 30 papers were carefully read, and after a further analysis a total of 14 papers were selected to be discussed in the following narrative review.

2.3 Inclusion – Exclusion Criteria & Data Extraction

It was chosen to select papers published between the introduction of the Y-BOCS assessment scale for OCD until May 2023. The inclusion criteria focused on selecting studies that: 1. reported human studies assessing the effectiveness of GK capsulotomy for OCD 2. reported patient selection details, 3. reported neurophysiological results in Y-BOCS score, where "responders", "partial responders", and "nonresponders" were defined based on the extent of reduction in the total Y-BOCS score at the final follow-up compared to the baseline (responders demonstrates a reduction of ≥ 35%, partial responders show a reduction of 25% to less than 35%, and nonresponders exhibits a reduction of less than 25% in their total Y-BOCS score), 4. use neuroablation by GK radiation, 5. were reported in English. On the other hand, the exclusion criteria focused on avoiding papers that: 1. used any form of ablation other than radiosurgery, 2. lacked stereotactic MRI guidance during ablation, 3. did not reach a minimum follow-up (FU) of 6 months 4. animal studies, 5. literature reviews, reviews, commentary and meta-analysis. As mentioned above, 14 papers reporting GK capsulotomy for refractory OCD were selected for the narrative review after applying the inclusion & exclusion criteria. Each study was analyzed and divided into the respective case series when data for each patient were available.

2.4 Assessment Scale and Patient Selection

The Y-BOCS is the assessment scale used by the selected studies to measure capsulotomy's therapeutic effectiveness on OCD patients. It consists of 10 items, with five domains related to obsessive thoughts and five domains related to compulsive behavior[72]. A rating scale ranging from 0 (no symptoms) to 4 (extreme symptoms) assesses each domain, resulting in a maximum score of 40. Total Y-BOCS scores from 0 to 7 indicate "subclinical" OCD symptoms, while scores from 8 to 15 indicate the presence of "mild" symptoms. Scores falling between 16 and 23 correspond to "moderate" symptoms. Scores within the range of 24 to 31 suggest "severe" symptoms; and lastly, scores from 32 to 40 represent the presence of "extreme" symptoms[73]. The patients eligible for the GK radiosurgical intervention were refractory OCD patients. Refractory OCD patients are defined as individuals with a Y-BOCS score higher than 28, with a prolonged history of disorder, and who do not exhibit a positive response to all available treatment options for OCD. These treatment options typically include: SSRIs either alone or in combination with CBT, combination therapies involving two or three SSRIs along with CBT, and a combination of multiple SSRIs, CBT and adjunctive treatments such as clomipramine, psychoeducation, or benzodiazepines. The lack of response to these diverse treatment approaches highlights the need to explore alternative strategies such as psychosurgery to manage symptoms in refractory OCD patients[74]. Note that the definition of refractory OCD is inconsistent, but in general it is referred to these patients who do not demonstrate a favorable response to all available treatment approaches for their condition.

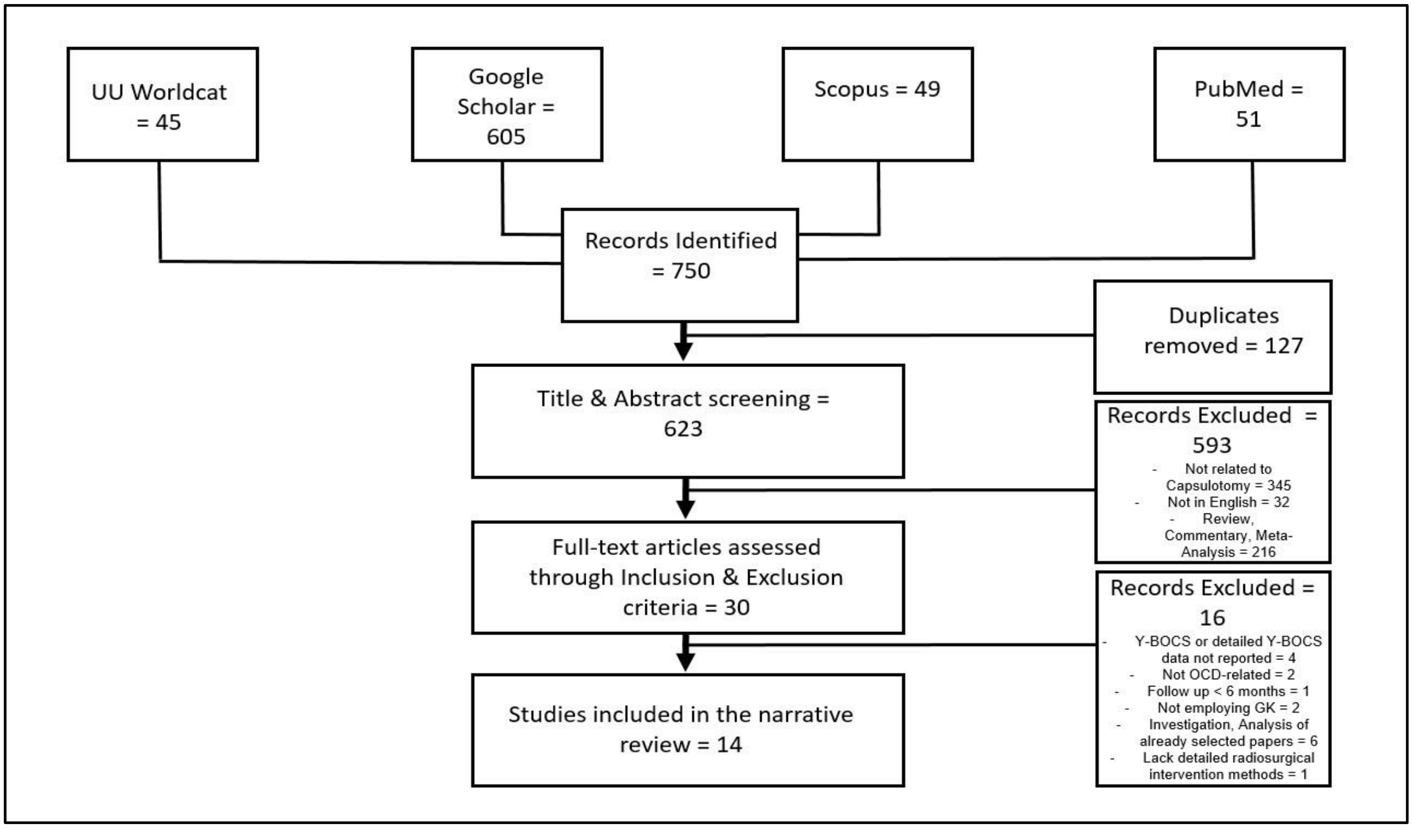


Figure 7: Flowchart providing a condensed summary of the search results and the study selection process.

3. Results

The output from the databases UU Worldcat, Pubmed, Scopus and Google Scholar after applying the Inclusion and Exclusion criteria led to the selection of 14 GK capsulotomy studies for refractory OCD. Studies reporting individual clinical details were further divided, eventually including in the dataset a total of 142 patients (48 entries); the selected cases are reported in Table 1 in the "*Supplements*" section.

3.1 Y-BOCS/pre & Y-BOCS/last FU

Table 2 lists the improvements in Y-BOCS scores noticed in almost all (≈ 96%) of the radiosurgical studies examined. These results show that GK capsulotomy significantly improves symptoms in resistant OCD patients, as shown by their overall lower Y-BOCS score at last FU (LFU) compared to the preoperative Y-BOCS score. These outcomes highlight the possibility of GK capsulotomy as a valuable treatment strategy, especially in light of the poor preoperative condition of these patients.

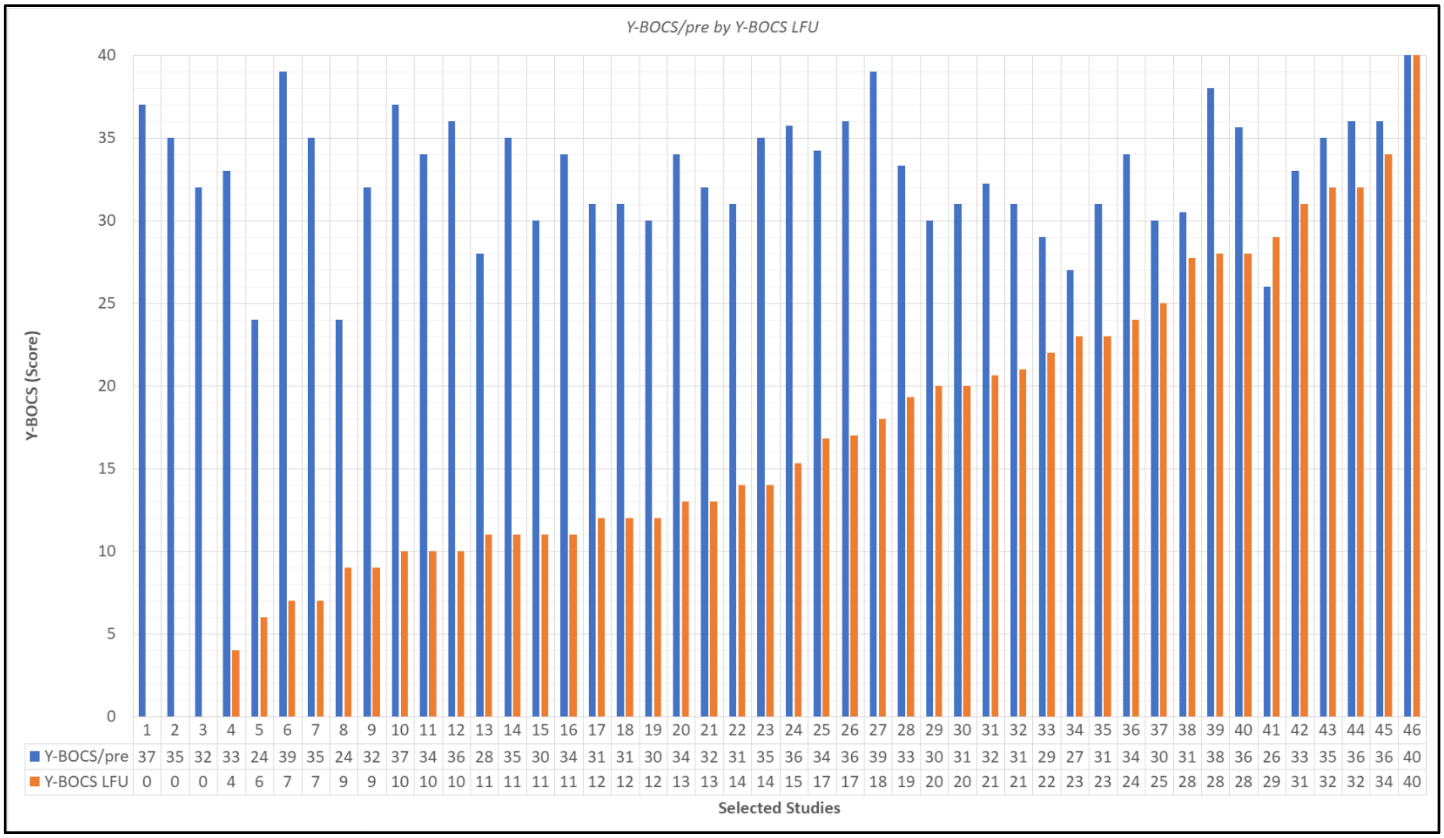


Table 2: Comparative analysis of Y-BOCS/pre and Y-BOCS LFU scores. The table offers a detailed evaluation of the change in obsessive-compulsive symptom severity, highlighting the impact of surgery on the reduction of symptoms in patients undergoing GK. Y-BOCS 0-7: 'subclinical' OCD symptoms. Y-BOCS 8-15: 'mild' OCD symptoms. Y-BOCS 16-23: 'moderate' OCD symptoms. Y-BOCS 24-31: 'severe' OCD symptom. Y-BOCS 32-40: 'extreme' OCD symptoms.

3.2 Y-BOCS/last FU by Prescription Dose (Gy)

Table 3 reports the impact of various prescription radiation dosages on Y-BOCS scores, showing the heterogeneity of OCD. Utilizing bilateral, double-shot GK capsulotomy with high doses (90 Gy), individuals exhibited varying outcomes. Some achieved remission, as evidenced by two out of twelve patients in the study conducted by Lopes[75], the participant in the double-blind, placebo-controlled trial conducted by Gouvea[76], and the individual treated in the study by Spofford and his colleagues[77]. Conversely, others experienced only partial improvement, as reported by five patients in Lopes's study[75], who achieved Y-BOCS scores indicating 'moderate' symptom levels (Y-BOCS: 8-15). Finally, one patient in Lopes's study[75] and one patient in Ertek et al.'s study[78] did not exhibit significant improvements and continued to be assessed with Y-BOCS scores within the 'extreme' range (Y-BOCS: 32-40). The results of bilateral, double-shot GK capsulotomy utilizing radiation doses lower than 90 Gy (ranging between 60-84 Gy) demonstrated comparable positive effects, with a subset of patients experiencing significant relief from symptoms. Specifically, in a study conducted by Spatola in 2018[79], six out of ten patients treated with double-shot GK capsulotomy with a prescription dose of 84 Gy reported a substantial improvement in their Y-BOCS score, achieving scores ranging from 4 to 11 (preoperative Y-BOCS scores ranged between 24 and 37). Two patients reported postoperative Y-BOCS scores of 17 and 22 (indicating "moderate" OCD), compared to preoperative scores of 36 and 29, respectively. Two other patients out of ten reported postoperative Y-BOCS score of 28 and 29, starting with a preoperative "extreme" (Y-BOCS score: 38) and "severe" (Y-BOCS score: 26) condition, respectively. Considering the employment of bilateral single shots with prescription doses of 80 Gy, a study reported two patients with a starting Y-BOCS score of 31 and 32, that achieved a Y-BOCS score of 12 and 13 at LFU, respectively[80]. In the same study, three patients treated with prescription doses of 70 Gy showed various results. Two achieved "mild" OCD symptoms (Y-BOCS LFU ranging between 12 and 13) starting from an "extreme" condition (preoperative Y-BOCS ranging between 31 and 34), whereas one patient changed his Y-BOCS score from 33 before the operation to 31 at LFU. Other studies[78,81] investigated the effect of double-shot, triple shot and five-shot capsulotomies employing a prescription dose of 80 Gy, achieving clinical improvements in most of these cases (preoperative Y-BOCS ranged between 30 and 31, Y-BOCS LFU ranged between 20 and 23).

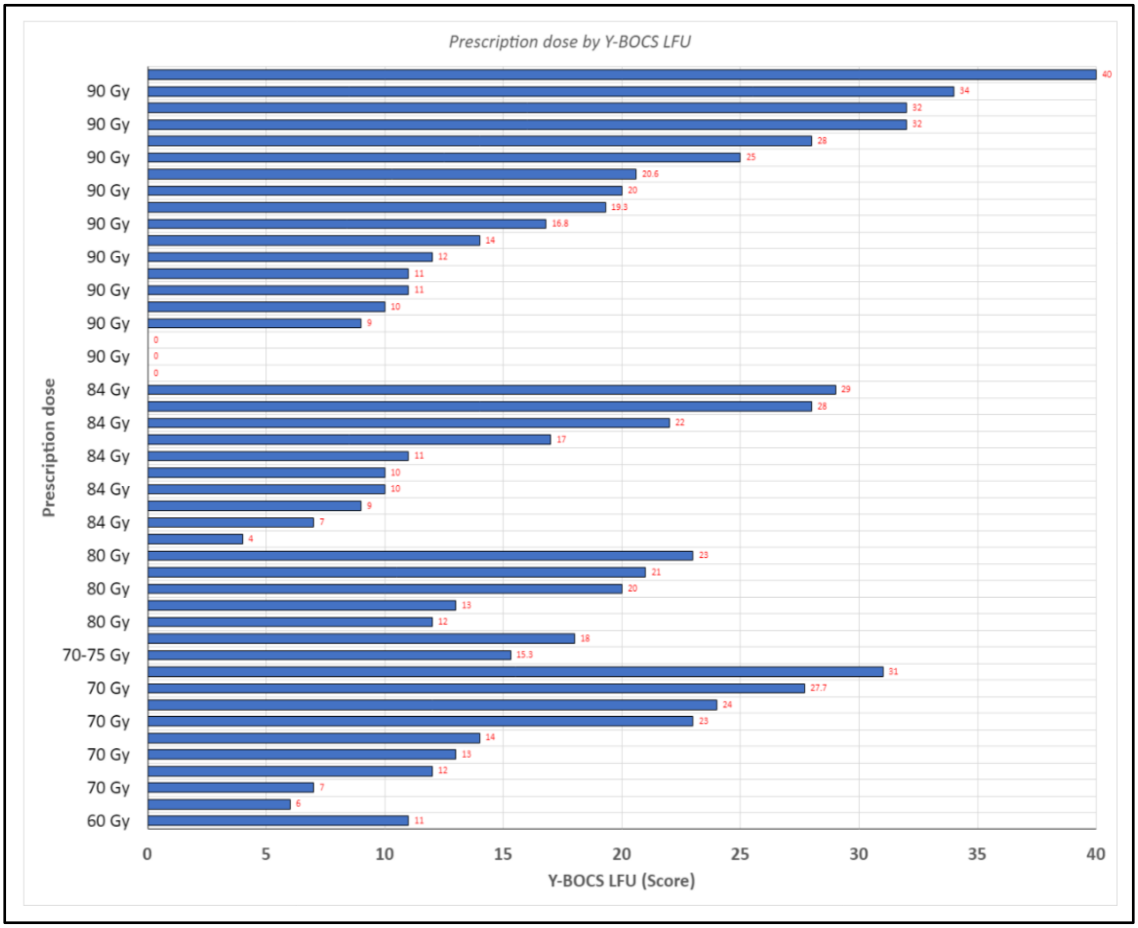
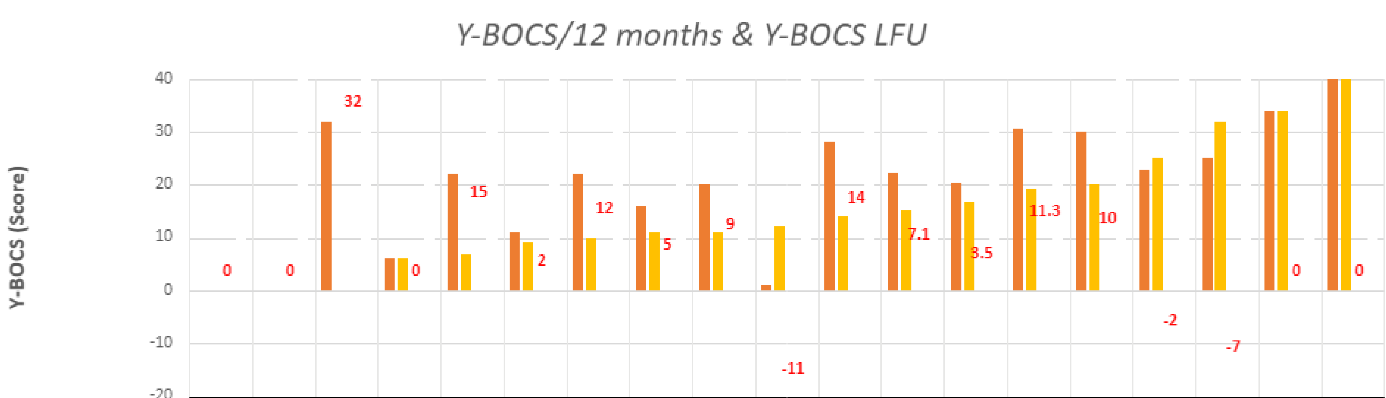


Table 3: Comprehensive comparative analysis of the effects of different prescription radiation doses on Y-BOCS scores in patients included in the selected GK capsulotomy studies. The table highlights the heterogeneity of treatment response and sheds light on the limited exploration of prescription doses lower than 60 Gy in this field.

Kondziolka and his colleagues explored the effect of bilateral, double-shot GK capsulotomy using prescription doses of 70 Gy and 75 Gy. One patient treated in 2008[82] was a 55-years old male with a severe skin-picking obsessive disorder which came with different problems like severe wounding and blood infections, who was in remission from OCD at 30-months FU, when his Y-BOCS score was 4. The two patients treated in 2011[83] by the same study group reached a Y-BOCS score of 18 and 24, starting with a preoperative Y-BOCS score of 39 and 34, respectively. The studies performed by the research teams of Richieri[84] and Pattankar[81] reported a therapeutic effect of bilateral, double-shot GK capsulotomy using prescription doses of 65 Gy and 60 Gy, respectively. Both of these patients were classified as responders and had a Y-BOCS score at LFU which was within the "subclinical" and "mild" symptoms range.

3.3 Y-BOCS/12 months & Y-BOCS/last FU: Potential of Permanent Improvements

At long-term follow-up, several cases had stable Y-BOCS scores, demonstrating that radiosurgical capsulotomy can have long-lasting effects and can be used as a one-time treatment for a better quality of life. Table 4 shows the GK capsulotomy studies reporting Y-BOCS score at 12 months, then compared with the Y-BOCS score at LFU. The authors analyzed cases where the difference in Y-BOCS score at the two selected time points (12/month and LFU) is significantly low. .Four cases of the study performed by Lopes and his colleagues[75] reported a Y-BOCS improvement at 12-month, which was kept stable for a significant amount of time at FU (ranging from 51 to 82 months). Furthermore, the patient involved in the study performed by Richieri[84] reported a Y-BOCS score of 6 at 12-months, which was kept stable also at 24-months FU.



	Gouvea et al., 2010	Lopes et al., 2014	Lopes et al., 2014	Richieri et al. 2018	Kondziolka et al., 2008	Lopes et al., 2014	Lopes et al., 2014	Lopes et al., 2014	Spofford et al., 2014	Lopes et al., 2014	Lopes et al., 2014	Peker et al. 2020	Rasmussen et al. 2018	Rasmussen et al. 2018	Lopes et al., 2014	Lopes et al., 2014	Lopes et al., 2014	Lopes et al., 2014	Lopes et al., 2014
Y-BOCS/12 months	0	0	32	6	22	11	22	16	20	1	28	22.4	20.3	30.6	30	23	25	34	40
Y-BOCS LFU	0	0	0	6	7	9	10	11	11	12	14	15.3	16.8	19.3	20	25	32	34	40
Difference	0	0	32	0	15	2	12	5	9	-11	14	7.1	3.5	11.3	10	-2	-7	0	0
LFU time (months)	12	82	67	24	42	51	48	56	36	56	86	36	36	36	72	65	55	12	12

Table 4: Comparative analysis of Y-BOCS scores at 12 months post-surgery with Y-BOCS scores at last follow-up (LFU), aiming to assess the lasting effects of GK surgery on OCD symptoms. The table emphasizes cases in which Y-BOCS scores at 12 months show stability at LFU, suggesting the sustained therapeutic benefits of GK surgery in effectively managing OCD symptoms over an extended duration.

3.4 Prescription Dose by Number of Patients

The prescribed radiation doses applied in GK capsulotomy studies are summarized in Table 5. The most frequent dose used was 90 Gy, however, the previous tables suggest that by examining lower radiation doses it may be possible to achieve similar or better therapeutic effects. This table points out that all GK capsulotomy studies for the treatment of refractory OCD have been strictly limited and related to neuroablative biological processes, without exploring the possibility of achieving therapeutic effects without lesioning human neuronal tissue.

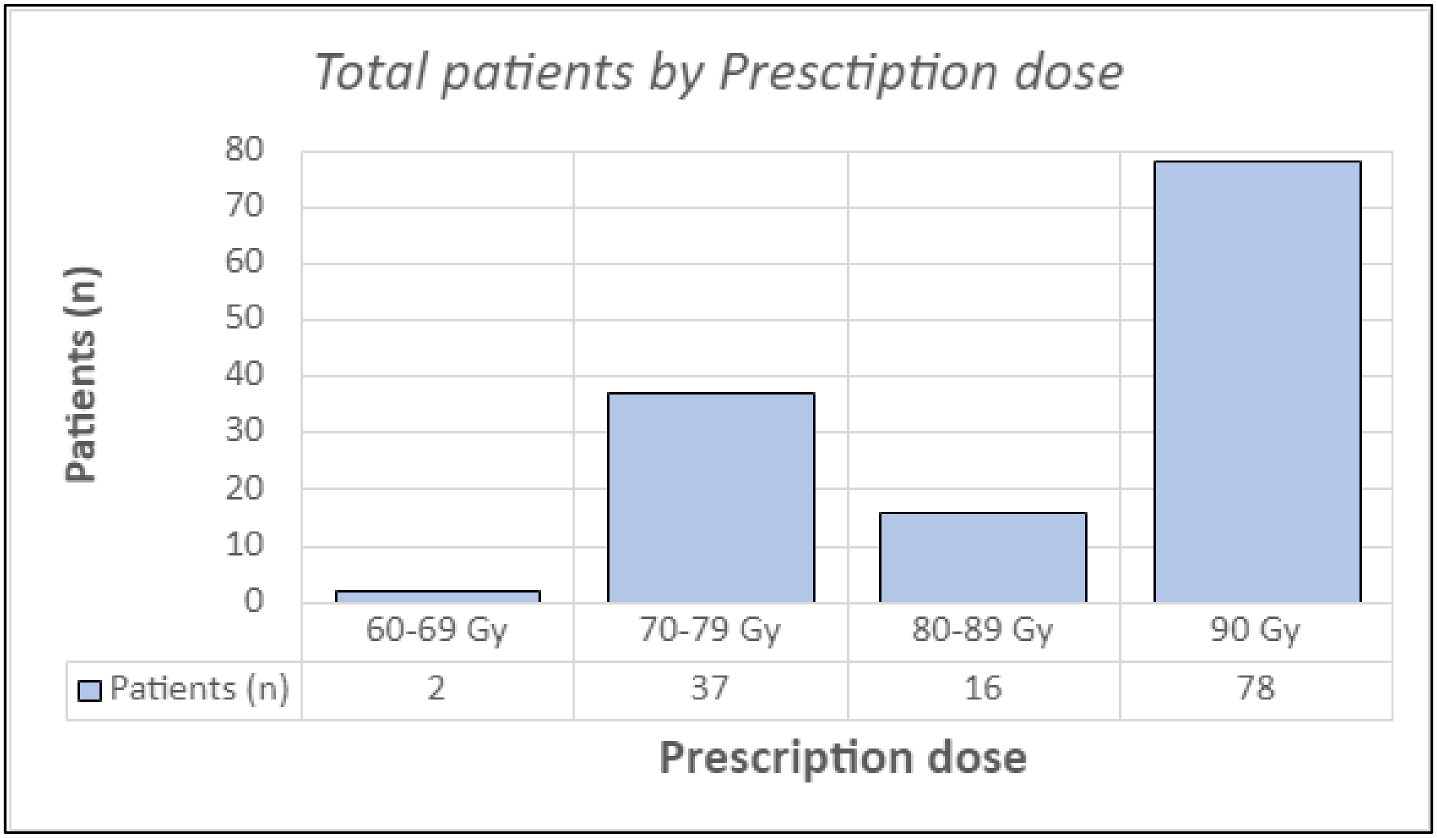


Table 5: Comprehensive overview of the prescription doses employed in selected GK capsulotomy studies for refractory OCD. The analysis indicates a predominant focus on prescription doses equal to or exceeding 60 Gy, with no exploration of doses below this threshold. Consequently, the potential therapeutic advantages associated with lower, repeated, sub-ablative radiation using lower dose approaches remain unexplored within the context of OCD treatment.

4. Discussion

4.1 The Potential of Gamma Knife SRS

The narrative review performed in this research reports several studies demonstrating that SRS capsulotomy performed through GK can considerably lessen OCD symptoms in individuals with severe, treatment-resistant types of the disease, as shown in Table 2. In addition to the significant effectiveness of GK capsulotomies in reducing symptoms of intractable OCD patients, it is important to consider the specific advantages presented by this technique compared to its counterpart DBS. Of particular interest, the non-invasive nature of SRS is a significant advantage when compared to the complex surgical procedures involved in DBS.

Table 4 suggests that radiosurgical capsulotomy has the potential to induce lasting improvements in OCD symptomatology. This highlights the potential for reduced hospitalization periods in comparison to alternative neuromodulatory modalities such as ECT and DBS. It is important to note that although long hospitalization might not be required for SRS, follow-up appointments and monitoring may be necessary to assess treatment response and manage any potential side effects or complications. Additionally to the high potential of SRS in treating refractory OCD, Table 3 shows that lower radiation dosages like 60 Gy or 70 Gy can be as effective as higher radiation dosages such as 90 Gy, further stressing the heterogeneous nature of OCD which results in a heterogeneity of treatment response. The variability observed in both the therapeutic and adverse effects associated with GK capsulotomy for OCD prevents the identification of a consistent treatment-induced effect attributable to specific dosages. This heterogeneity indicates that there is a need for a personalized and individualized approach, thus allowing better treatment responses with lower radiation doses in some patients, eventually reducing toxicity and increasing the safety of the treatment.

4.2 GK Capsulotomy Adverse Effects

Despite encouraging findings from GK-SRS capsulotomy experiments, large prescription radiation doses have been linked to the occurrence of adverse effects. By reviewing the selected studies, it was shown that these adverse effects commonly manifest as headaches lasting for days to weeks, vertigo, weight changes, and episodic episodes of nausea. The study conducted by Lopes and his team in 2009[85] reported that most of these were mild and transient, without permanent implications. Similarly, the study performed by Rasmussen in 2018[52] revealed that acute adverse effects encompassed nausea, vomiting, and headaches, which were generally well-tolerated by the patients, allowing for their discharge on the same day. Importantly, no signs of cognitive decline were observed in any patient, highlighting the overall safety of GK capsulotomy on patients' neuropsychology. These findings align with previous studies, including Batistuzzo[86] and Paiva[87], which demonstrated that GK capsulotomy did not induce deleterious effects on personality, or negatively impact cognitive and motor functioning. The limited severity of side effects is significant when compared with the therapeutic effect achieved by GK capsulotomy to previously intractable patients, however, the investigation into the occurrence of acute and severe adverse effects remains an area that requires further exploration.

Prior to addressing the occurrence of more severe complications, it is important to examine two fundamental concepts. In the context of SRS, the central radiation dose refers to the prescribed dose deliered to the specific target area, which, in the case of capsulotomy, is the ALIC. Conversely, the peripheral radiation dose refers to the dose received by the surrounding healthy tissue adjacent to the target. The aim is to minimize the maximum dose received by these peripheral areas to limit the risk of radiation-related complications. The GK capsulotomy study by Ruck et al.[88] highlights the potential toxicity and increased likelihood of adverse effects associated with administering maximal doses of 200 Gy doses. Once again, this finding emphasizes the need for caution in applying high radiation doses to the human brain, and indicates the necessity to investigate the therapeutic efficacy of lower radiation dosages for alleviating symptoms of OCD. Indeed, the development of brain cysts has been reported as an adverse effect following high doses of radiation in the studies performed by Peker in 2020[89] and Kasabkojian in 2021[51], as well. Similarly, as mentioned above, the study performed by Rasmussen in 2018[52] revealed that most adverse effects were mild and well-tolerated by patients (both responders and non-responders), however three patients who underwent the double-shot procedure eventually developed brain cysts 3 to 5 years after surgery. These findings warrant consideration of brain cysts development as a potential complication of GK SRS which significantly impacts the risk-benefit ratio of such operation technique, thus pushing future studies to explore the relationship between radiation dose and this type of complication.

To sum up, high-dose GK capsulotomy for intractable OCD presents the risk of a range of adverse effects. Optimizing treatment outcomes necessitates careful consideration of radiation dose and its potential impact on both efficacy and safety. The utilization of lower, modulative, radiation doses presents a potential method for mitigating the risk of severe complications associated with GK capsulotomy while still maintaining significant effectiveness in reducing OCD symptoms.

4.3 Radiation-induced Neuromodulation as an Adjunct to Psychological Therapies

Given the risk of severe adverse effects associated with high prescription doses and the need for an individualized method due to the heterogeneity of response in GK SRS capsulotomy studies (Table 3), we propose integrating the PULSAR RT approach to personalize the procedure. This integration could facilitate a transition from an "ablative" outcome to a personalized and "modulative" approach. The constant need for innovation and improvement in any scientific field has led us to hypothesize whether it might be possible to treat severe, refractory OCD patients more effectively by using lower, repeated, sub-ablative radiation doses that might "modulate" rather than "lesion" the neuronal tissue. The implementation of lower radiation doses with a modulative approach offers a potential strategy to mitigate the occurrence of severe complications linked to GK capsulotomy, while simultaneously preserving substantial efficacy in the reduction of OCD symptoms. Notably, there is a limited depth of research in this area, as evidenced by Table 5, which shows that the majority of patients were administered a prescription dose of 90 Gy, and no patients received prescription doses below 60 Gy.

As previously mentioned, the combination of psychological treatments with neuromodulatory approaches has demonstrated an enhanced effectiveness compared to the individual use of psychological treatments[69,70,71]. Considering that SRS can provide some advantages compared to other brain stimulation techniques, such as higher focality and lower invasiveness, this paper suggests the application of sub-ablative, neuromodulatory SRS combined with psychotherapy. Irradiation of brain tissue strongly affects the composition of the neuronal environment to different extents by changing the presence of astrocytes and glial cells. These changes impact distant brain regions through messenger protein processes, thus inducing an overall change of brain connectome composition, which is then followed by neuroplasticity processes. This research's main suggestion is how to drive such neuroplastic processes and foster a normalization of brain connectome activity. It is critical to remember that these patients are severe cases with a long history (e.g. >15yrs) of disorder and an extremely low QoL that prevents them from living a normal life, working, or socializing with others. In light of those, this research aims to draw attention to whether the neuroplasticity processes brought about by psychological treatments may be enhanced by combining those interventions with radiation-induced neuromodulatory approaches like GK.

This means that a patient's initial poor therapeutic response to available psychological treatments may be improved when such treatments are aided by radiomodulation, which may induce specific brain areas to be more likely and prone to healthy neuroplastic processes. Regarding this, the study by Spofford[77] investigated in the present narrative review reveals that three months after undergoing GK capsulotomy, the patient reported a qualitative difference in his behavioral therapy sessions compared to prior surgery. He stated that the CBT sessions were easier to apprehend, and defined them as ‘‘..an easier process to understand..’’. This indicates that a patient who was previously refractory to psychological treatments may become responsive to those following radiation-induced neuromodulation of the ALIC.

4.4 PULSAR-induced Neuromodulation: Potential for Radiomodulation Multifocal Targeting

The application of PULSAR in GK capsulotomies for psychiatric disorder treatment is proposed in this paper. PULSAR-induced neuromodulation may enhance receptivity to first-line therapies like CBT, which is often continued alongside and after radiosurgery. This technique offers the advantage of mitigating treatment toxicity by utilizing lower radiation doses (e.g., 8-20 Gy) compared to previous studies on GK capsulotomy. Given the varying reactivity of neural tissue to radiation in individual patients, a personalized approach is essential. The implementation of the PULSAR method within GK capsulotomy treatment plans involves image and psychological assessments at specific intervals, facilitating the visualization of biological changes following brain tissue irradiation. This allows for adaptive therapy steps based on individualized patient responses. Further investigations are needed to understand the neurobiological effects of specific radiation doses on brain tissues and to optimize treatment by avoiding unnecessarily high radiation doses.

By employing irradiation treatments at lower dosages, it is possible to modulate activity within the CSTC circuit without causing tissue damage. SRS and DBS have shown the ability to achieve this neuromodulation effect by targeting different brain areas within the CSTC. For instance, cingulotomy targets a different brain region than ALIC, and limbic leucotomy combines targets from cingulotomy and subcaudate tractotomy. This indicates that the CSTC circuit can be modulated by selectively targeting different brain regions, suggesting the potential for a multifocal approach to enhance therapeutic modulation within this neural circuit. SRS stands out as a suitable option for performing such multi-targeting treatment due to its non-invasiveness and high precision. Combining PULSAR and SRS capsulotomy presents a promising opportunity for precise targeting and modulation of brain activity in multiple pivotal hubs within the aberrant neuronal circuitry associated with OCD pathology. This multitargeting approach might achieve a better neuromodulatory effect on CSTC circuit activity.

4.5 Ethics of Psychosurgery

Significant advancements have been made in the field of psychosurgery by allowing more precise targeted and refined procedures, particularly when comparing it with the first brutal surgical approaches such as lobotomies, however, the ethical considerations behind this treatment technique are still debated and worthy of consideration. The first issue is that there is not enough evidence showing the efficacy of SRS in treating psychiatric disorders, thus the risk-benefit ratio of this approach has to be carefully considered[90,91]. It is essential to understand that psychosurgical approaches should be considered only for severe, long-term, intractable psychiatric patients, as a last-resort treatment option. This cohort of patients must have first tried all available psychological and pharmacological treatment available because such methods could permanently fix the disorder by being less invasive and dangerous than psychosurgical approaches. However, the patients who do not respond to those treatments live a life characterized with a long (e.g. >15 years) history of disorder which makes them completely unable to socialize, carry out daily activities, find a stable job, thus making them unable to live a proper life. For the application of psychosurgical approaches such as SRS for those patients, an increase in the number of randomized controlled trials (RCTs) is required. However, achieving this objective is not always feasible due to logistical constraints such as long waiting times required for the "sham" groups, the high level of risk and harm which could follow such procedures, and the limited patient pool willing to undergo such interventions. Additionally, a research study comparing the effect of DBS and capsulotomy procedures in terms of personality changes would be valuable to further understand the impact on personality and behavior.

This underlies a second ethical concern: whether it is justifiable to intervene directly in the brain of those mentally ill patients to change their behavior or not. The concept of patient selection is also strictly related to this. Psychosurgical techniques are intended to address the drastic situations confronted by patients with intractable psychiatric illnesses who have severe limits in their capacity to live. These interventions aim to change their behaviors and way of living, giving them hope and a chance for better health. The primary question that arises is whether patients are willing to undergo treatments aimed at altering their personality and behavior. Other ethical concerns are related to this aspect, for instance determining the appropriate authority to decide the eligibility of patients for such treatments when the patient's own autonomy may be in question. It has to be considered that refractory OCD patients often have a drastically low QoL, which has a profound impact on their closely related individuals, such as their family members, leading to a notable decrease in their overall well-being as well. Patients should be carefully informed about the treatment's advantages, risks and alternatives, particularly if considering the permanent changes that psychosurgical approaches might induce. The concept of obtaining informed consent should be guided by a multidisciplinary team of psychiatrists, neurosurgeons, psychologists and bioethicists, eventually ensuring the patient's capacity to consent and understand the rationale of the therapy. The preliminary evidence of SRS is the reason why these ethical questions must be discussed. For instance, there are studies in which patients achieve positive personality improvement such as a reduction in neuroticism and an improvement in extroversion after GK capsulotomy interventions[87].

Overall, given the clear need for effective treatments for refractory psychiatric patients, and the promising effectiveness shown by SRS, further research is needed to widely explore this treatment modality in order to get clear insights and report reliable evidence in terms of efficacy and safety. Strict guidelines and regulations should be implemented in order to increase awareness on these approaches. In addition, the concept of guided neuroplasticity also requires careful ethical guidelines, avoiding unethical uses of such approaches in order to induce behavioral improvements besides psychiatric conditions. Understanding and improving the field and application of psychosurgery would induce many advantages such as providing a valuable option that can improve the QoL of patients who cannot live properly for a significant, prolonged life period.

4.6 Limitations and Future Directions

There are two major drawbacks in this research study: one is associated to the use of a narrative review approach, and the other relates to limitations within the field of psychosurgery itself. As previously mentioned, an advantage of narrative reviews approaches is to provide a compact, flexible synthesis on a given scientific topic, however, the author's interpretation of data and literature can be a limitation, due to a lack of standardized methodology which questions the validity and reliability of the results. Differently from systematic review approaches like meta-analysis, which follow predetermined methodologies, narrative reviews are susceptible to the reviewer's subjective interpretation and judgment, potentially resulting in an incomplete coverage of the literature and a bias towards studies supporting the authors' opinions. Along with this, the inclusion of studies with low sample sizes presents another limitation of this narrative review, which significantly compromises the generalizability of the findings. In addition to the limitations of narrative reviews, it is important to acknowledge the inherent limitations of psychosurgery as a field. A comprehensive cost-effectiveness analysis comparing psychosurgical interventions with conventional approaches is necessary to determine the extent of benefits this field can offer the scientific community. Furthermore, the ethical concerns mentioned above present the most prominent limitations of this field, which slow down its development and innovation, for instance limiting the availability of evidence by delaying the conduction of RCTs. Overall, it is crucial to take into account the factors that influence the validity of this research study, carefully considering the limitations of narrative reviews and the ethical concerns related to psychosurgery.

Future studies should investigate the underlying neurobiological mechanisms of PULSAR-induced neuromodulation, determining optimal dosing parameters, identifying appropriate brain targets, exploring synergistic effects with other treatments, and conducting rigorous clinical trials. Concerning this, the implementation of RCTs with larger sample sizes would help to establish robust evidence regarding the effectiveness of lower radiation doses while reducing treatment toxicity and maintaining therapeutic benefits. The conduction of RCTs must include design trials which maintian patient interest and engagement, also when partecipating in the 'control' groups. For instance, the employment of crossover design would be an effective RCT type to address motivation, allowing partecipants to receive both active treatment and control interventions, eventually fostering engagement throughout the study and facilitating its successful completion. The conduction of sham trials investigating radiation-induced neuromodulation is possible using SRS procedures like GK, as seen in the study by Lopes in 2014[75]. Developing a PULSAR-induced neuromodulation RCT requires a balance between frequent and long-term assessments, with primary assessment outcomes such as Y-BOCS and fMRI playing a crucial role. Patient selection should focus on refractory cases that have not responded to conventional treatments, and collaboration between academia and industry must ensure patient care after the study, as personality changes and potential adverse effects need careful evaluation. The goal is to selectively alter the brain activity in specific areas, making them more susceptible to neuroplastic changes induced by psychological therapies.

The main rationale behind PULSAR includes the use of large 'pulses' of radiation; here, the authors suggest a first treatment of 8-10 Gy. A Y-BOCS, fMRI, and neuropsychological evaluation should be conducted, ideally at 3-4 weeks after the initial radiation treatment. During this time, the patient should be kept on medications and psychotherapy (based on individual prescriptions prior to radiomodulation treatment). An initial Y-BOCS and fMRI assessment prior to treatment is needed to visualize any changes occurring after radiation-induced neuromodulation. Of practical importance, the next step of the treatment must be planned depending on the 3-4 weeks assessment results. A careful and considerate collaboration between a team of experts like neurosurgeons, psychiatrists, radiation oncologists and bioethicists is needed, in order to precisely define how the patient might gain benefits from the next treatment step if a lower, same, or higher dose is employed. Here, a careful and considerate collaboration between a team of experts like neurosurgeons, psychiatrists, radiation oncologists and bioethicists is needed, in order to precisely define how the patient might gain benefits from the next treatment step if a lower, same, or higher dose is employed. However, the therapeutic neuromodulatory effect of PULSAR lacks sufficient evidence, implying a careful evaluation of the radiation dose values and assessment waiting times above reported.

Promoting international collaboration in the field of neuromodulation research would promote the development of multi-center trials with large sample size, which would enhance the statistical power and generalizability of the results. Additionally, the development of guidelines and regulations is required to ensure the responsible and ethical implementation of psychosurgical techniques, safeguarding patient well-being throughout the process. Overall, continuous research efforts are needed to further explore the efficacy and safety of PULSAR-induced neuromodulation. Advancements in this area could revolutionize the treatment landscape not only for refractory psychiatric patients, but also for individuals with other neurological disorders such as addiction. These holds immense promises for the future of neurology, offering a new therapeutic approach to improve the lives of patients across various conditions.

5. Conclusion

In conclusion, this research paper provides a narrative review that focuses on the use of GK capsulotomy for treating refractory OCD. By examining factors such as radiation dose and adverse effects, the review sheds light on the concept of modulating brain activity without causing lesions, which holds immense interest for the field. The rationale presented in this publication lays the groundwork for considering radiation-induced neuromodulation without neuroablation, challenging the traditional capsulotomy approach based on lesioning neural tissue. By utilizing the PULSAR technique, the potential for inducing neuromodulation within the target brain area without ablating neuronal tissue emerges as a promising avenue. Moreover, this publication emphasizes the importance of combining radiation-induced neuromodulation with existing therapeutic modalities such as psychotherapy, highlighting the potential for guiding healthier neuronall cell reorganization following PULSAR-induced neuromodulation. This integrated approach offers a personalized GK-SRS strategy that could facilitate effective psychological-assisted neuromodulation. Overall, this research serves to lay the foundations for further investigations and the development of protocols to study the efficacy of combining PULSAR-induced neuromodulation with psychological treatments.

6. Supplements

6.1 Table of Selected Studies

Author (s)	Patients (n)	Mean Age (yrs)	Surgery Equipment	Collimators	Max Dose (100 % Gy)	Prescription dose	Lesions type	Y-BOCS/pre	Y-BOCS/6 months	Y-BOCS/12 months	Y-BOCS/24 months	Y-BOCS LFU	LFU time (months)
Ruck et al. 2008	5	45.2	Gamma Knife (different models)	4-mm	200 Gy	N/R	Bilateral, triple-shot	31.8	N/R	7.25	N/R	9.2	N/R
Ruck et al. 2008	4	42.25	Gamma Knife (different models)	4-mm	180 Gy	N/R	Bilateral, single-shot	35.5	N/R	27	N/R	22.6	N/R
Kondziolka et al., 2008	1	55	Gamma Knife (not specified)	4-mm	140 Gy	70 Gy	Bilateral, double-shot	39	N/R	22	N/R	7	42
Lopes et al. 2009	5	35	Gamma Knife model B	4-mm	180 Gy	90 Gy	Bilateral, double-shot	32.2	N/R	N/R	N/R	20.6	48
Gouvea et al., 2010	1	34	Gamma Knife model B	4-mm	180 Gy	90 Gy	Bilateral, double-shot	37	0	0	N/R	0	12
Kondziolka et al., 2011	1	39	Gamma Knife (not specified)	4-mm	150 Gy	75 Gy	Bilateral, double-shot	39	N/R	N/R	N/R	18	28
Kondziolka et al., 2011	1	37	Gamma Knife (not specified)	4-mm	140 Gy	70 Gy	Bilateral, double-shot	34	N/R	N/R	N/R	24	55
Sheehan et al., 2013	1	47	Gamma Knife Perfexion	4-mm	140 Gy	70 Gy	Bilateral, single-shot	31	N/R	N/R	N/R	12	15
Sheehan et al., 2013	1	36	Gamma Knife Perfexion	4-mm	160 Gy	80 Gy	Bilateral, single-shot	31	N/R	N/R	N/R	12	33

Sheehan et al., 2013	1	31	Gamma Knife Perfexion	4-mm	140 Gy	70 Gy	Bilateral, single-shot	34	13	N/R	N/R	13	6
Sheehan et al., 2013	1	26	Gamma Knife Perfexion	4-mm	160 Gy	80 Gy	Bilateral, single-shot	32	N/R	N/R	N/R	13	33
Sheehan et al., 2013	1	44	Gamma Knife Perfexion	4-mm	140 Gy	70 Gy	Bilateral, single-shot	33	N/R	N/R	31	31	24
Lopes et al., 2014	1	34	Gamma Knife model B	4-mm	180 Gy	90 Gy	Bilateral, double-shot	35	N/R	0	N/R	0	82
Lopes et al., 2014	1	25	Gamma Knife model B	4-mm	180 Gy	90 Gy	Bilateral, double-shot	32	N/R	32	N/R	0	67
Lopes et al., 2014	1	24	Gamma Knife model B	4-mm	180 Gy	90 Gy	Bilateral, double-shot	32	N/R	11	N/R	9	51
Lopes et al., 2014	1	35	Gamma Knife model B	4-mm	180 Gy	90 Gy	Bilateral, double-shot	36	N/R	22	N/R	10	48
Lopes et al., 2014	1	26	Gamma Knife model B	4-mm	180 Gy	90 Gy	Bilateral, double-shot	30	N/R	16	N/R	11	56
Lopes et al., 2014	1	21	Gamma Knife model B	4-mm	180 Gy	90 Gy	Bilateral, double-shot	30	N/R	1	N/R	12	56
Lopes et al., 2014	1	34	Gamma Knife model B	4-mm	180 Gy	90 Gy	Bilateral, double-shot	35	N/R	28	N/R	14	86

Lopes et al., 2014	1	34	Gamma Knife model B	4-mm	180 Gy	90 Gy	Bilateral, double-shot	31	N/R	30	N/R	20	72
Lopes et al., 2014	1	53	Gamma Knife model B	4-mm	180 Gy	90 Gy	Bilateral, double-shot	30	N/R	23	N/R	25	65
Lopes et al., 2014	1	55	Gamma Knife model B	4-mm	180 Gy	90 Gy	Bilateral, double-shot	36	N/R	25	N/R	32	55
Lopes et al., 2014	1	28	Gamma Knife model B	4-mm	180 Gy	90 Gy	Bilateral, double-shot	36	N/R	34	N/R	34	12
Lopes et al., 2014	1	38	Gamma Knife model B	4-mm	180 Gy	90 Gy	Bilateral, double-shot	40	N/R	40	N/R	40	12
Spofford et al., 2014	1	19	Gamma Knife (not specified)	4-mm	180 Gy	90 Gy	Bilateral, double-shot	34	26	20	N/R	11	36
Spatola et al., 2018	1	41.2	Gamma Knife model 4C/perfexion	4-mm	120 Gy	84 Gy	Bilateral, double-shot	33	N/R	N/R	N/R	4	116
Spatola et al., 2018	1	41.2	Gamma Knife model 4C/perfexion	4-mm	120 Gy	84 Gy	Bilateral, double-shot	35	N/R	N/R	N/R	7	106
Spatola et al., 2018	1	41.2	Gamma Knife model 4C/perfexion	4-mm	120 Gy	84 Gy	Bilateral, double-shot	24	N/R	N/R	N/R	9	21
Spatola et al., 2018	1	41.2	Gamma Knife model 4C/perfexion	4-mm	120 Gy	84 Gy	Bilateral, double-shot	37	N/R	N/R	N/R	10	37

Spatola et al., 2018	1	41.2	Gamma Knife model 4C/perfexion	4-mm	120 Gy	84 Gy	Bilateral, double-shot	34	N/R	N/R	N/R	10	17
Spatola et al., 2018	1	41.2	Gamma Knife model 4C/perfexion	4-mm	120 Gy	84 Gy	Bilateral, double-shot	35	N/R	N/R	N/R	11	14
Spatola et al., 2018	1	41.2	Gamma Knife model 4C/perfexion	4-mm	120 Gy	84 Gy	Bilateral, double-shot	36	N/R	N/R	N/R	17	25
Spatola et al., 2018	1	41.2	Gamma Knife model 4C/perfexion	4-mm	120 Gy	84 Gy	Bilateral, double-shot	29	N/R	N/R	N/R	22	27
Spatola et al., 2018	1	41.2	Gamma Knife model 4C/perfexion	4-mm	120 Gy	84 Gy	Bilateral, double-shot	38	28	N/R	N/R	28	6
Spatola et al., 2018	1	41.2	Gamma Knife model 4C/perfexion	4-mm	120 Gy	84 Gy	Bilateral, double-shot	26	N/R	N/R	N/R	29	41
Richieri et al. 2018	1	47	Gamma Knife (not specified)	4-mm	130 Gy	65 Gy	Bilateral, double-shot	24	N/R	6	6	6	24
Rasmussen et al. 2018	40	32.8	Gamma Knife model U/C	4-mm	180 Gy	90 Gy	Bilateral, double-shot	34.2	23.9	20.3	17.8	16.8	36
Rasmussen et al. 2018	15	35.87	Gamma Knife model U/C	4-mm	180 Gy	90 Gy	Bilateral, single-shot	33.3	30.8	30.6	24.1	19.3	36

Peker et al. 2020	20	32.8	Gamma Knife 4C	4-mm	140-150 Gy	70-75 Gy	Bilateral, double-shot	35.7	29.9	22.4	17.7	15.3	36
Ertek et al., 2021	6	31.3	Gamma Knife Perfexion	4-mm	140 Gy	70 Gy	Bilateral, double-shot	31	14	N/R	N/R	14	6
Ertek et al., 2021	2	27.5	Gamma Knife Perfexion	4-mm	160 Gy	80 Gy	Bilateral, double-shot	30	20	N/R	N/R	20	6
Ertek et al., 2021	3	31.3	Gamma Knife Perfexion	4-mm	180 Gy	90 Gy	Bilateral, single-shot	35.6	28	N/R	N/R	28	6
Ertek et al., 2021	1	32	Gamma Knife Perfexion	4-mm	180 Gy	90 Gy	Bilateral, double-shot	35	32	N/R	N/R	32	6
Pattankar et al., 2022	1	19	Gamma Knife (not specified)	4-mm	120 Gy	60 Gy	Bilateral, double-shot	28	N/R	N/R	N/R	11	30
Pattankar et al., 2022	1	52	Gamma Knife (not specified)	4-mm	160 Gy	80 Gy	Bilateral, triple-shot	31	N/R	N/R	N/R	21	60
Pattankar et al., 2022	1	35	Gamma Knife (not specified)	4-mm	140 Gy	70 Gy	Bilateral, double-shot	27	N/R	N/R	N/R	23	3
Pattankar et al., 2022	1	34	Gamma Knife (not specified)	4-mm	160 Gy	80 Gy	Bilateral, five-shots (9)	31	N/R	N/R	N/R	23	60
Pattankar et al., 2022	4	26	Gamma Knife (not specified)	4-mm	140 Gy	70 Gy	Bilateral, triple-shot	30.5	N/R	N/R	N/R	27.7	27

Table 1: Table of selected GK capsulotomy studies for refractory OCD included in the review.

7. References

1. Stein, D. J., Costa, D. L. C., Lochner, C., Miguel, E. C., Reddy, Y. C. J., Shavitt, R. G., van den Heuvel, O. A., & Simpson, H. B. (2019). Obsessive-compulsive disorder. Nature reviews. Disease primers, **5**(1), 52. https://doi.org/10.1038/s41572-019-0102-3
2. Greenberg, B. D., Rauch, S. L., & Haber, S. N. (2010). Invasive circuitry-based neurotherapeutics: stereotactic ablation and deep brain stimulation for OCD. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, **35**(1), 317–336. https://doi.org/10.1038/npp.2009.128
3. Chabane, N., Delorme, R., Millet, B., Mouren, M.-C., Leboyer, M., & Pauls, D. (2005). Early-onset obsessive-compulsive disorder: a subgroup with a specific clinical and familial pattern? Journal of Child Psychology and Psychiatry, **46**(8), 881–887. https://doi.org/10.1111/j.1469-7610.2004.00382.x
4. Yazdi-Ravandi, S., Akhavanpour, H., Shamsaei, F., Matinnia, N., Ahmadpanah, M., Ghaleiha, A., & Khosrowabadi, R. (2018). Differential pattern of brain functional connectome in obsessive-compulsive disorder versus healthy controls. EXCLI journal, **17**, 1090–1100. https://doi.org/10.17179/excli2018-1757
5. Math, S. B., & Janardhan Reddy, Y. C. (2007). Issues in the pharmacological treatment of obsessive-compulsive disorder. International journal of clinical practice, **61**(7), 1188–1197. https://doi.org/10.1111/j.1742-1241.2007.01356.x
6. Balachander, S., Arumugham, S. S., & Srinivas, D. (2019). Ablative neurosurgery and deep brain stimulation for obsessive-compulsive disorder. Indian journal of psychiatry, **61**(Suppl 1), S77–S84. https://doi.org/10.4103/psychiatry.IndianJPsychiatry_523_18
7. Van Essen, D. C., & Barch, D. M. (2015). The human connectome in health and psychopathology. World psychiatry : official journal of the World Psychiatric Association (WPA), 14(2), 154–157. https://doi.org/10.1002/wps.2022
8. Sha, Z., Xia, M., Lin, Q., Cao, M., Tang, Y., Xu, K., Song, H., Wang, Z., Wang, F., Fox, P. T., Evans, A. C., & He, Y. (2017). Meta-connectomic analysis reveals commonly disrupted functional architectures in network modules and connectors across Brain Disorders. Cerebral Cortex, **28**(12), 4179–4194. https://doi.org/10.1093/cercor/bhx273
9. Milad, M. R., & Rauch, S. L. (2012). Obsessive-compulsive disorder: Beyond segregated cortico-striatal pathways. Trends in Cognitive Sciences, **16**(1), 43–51. https://doi.org/10.1016/j.tics.2011.11.003
10. Klugah-Brown, B., Jiang, C., Agoalikum, E., Zhou, X., Zou, L., Yu, Q., Becker, B., & Biswal, B. (2021). Common abnormality of gray matter integrity in substance use disorder and obsessive-compulsive disorder: A comparative voxel-based meta-analysis. Human Brain Mapping, **42**(12), 3871–3886. https://doi.org/10.1002/hbm.25471

11. Radua, J., van den Heuvel, O. A., Surguladze, S., & Mataix-Cols, D. (2010). Meta-analytical comparison of Voxel-based morphometry studies in obsessive-compulsive disorder vs other anxiety disorders. Archives of General Psychiatry, **67**(7). https://doi.org/10.1001/archgenpsychiatry.2010.70

12. Rotge, J.-Y., Guehl, D., Dilharreguy, B., Tignol, J., Bioulac, B., Allard, M., Burbaud, P., & Aouizerate, B. (2009). Meta-analysis of brain volume changes in obsessive-compulsive disorder. Biological Psychiatry, **65**(1), 75–83. https://doi.org/10.1016/j.biopsych.2008.06.019

13. Boedhoe, P. S., Schmaal, L., Abe, Y., Ameis, S. H., Arnold, P. D., Batistuzzo, M. C., Benedetti, F., Beucke, J. C., Bollettini, I., Bose, A., Brem, S., Calvo, A., Cheng, Y., Cho, K. I., Dallaspezia, S., Denys, D., Fitzgerald, K. D., Fouche, J. P., Giménez, M., Gruner, P., van den Heuvel, O. A. (2017). Distinct Subcortical Volume Alterations in Pediatric and Adult OCD: A Worldwide Meta- and Mega-Analysis. The American journal of psychiatry, **174**(1), 60–69. https://doi.org/10.1176/appi.ajp.2016.16020201

14. Fouche, J. P., Groenewold, N. A., Sevenoaks, T., Heany, S., Lochner, C., Alonso, P., Batistuzzo, M. C., Cardoner, N., Ching, C. R. K., de Wit, S. J., Gutman, B., Hoexter, M. Q., Jahanshad, N., Kim, M., Kwon, J. S., Mataix-Cols, D., Menchon, J. M., Miguel, E. C., Nakamae, T., Phillips, M. L., Stein, D. J. (2022). Shape analysis of subcortical structures in obsessive-compulsive disorder and the relationship with comorbid anxiety, depression, and medication use: A meta-analysis by the OCD Brain Imaging Consortium. Brain and behavior, **12**(10), e2755. https://doi.org/10.1002/brb3.2755

15. Zhang, Z., Ping, L., Zhai, A., & Zhou, C. (2021). Microstructural white matter abnormalities in obsessive-compulsive disorder: A coordinate-based meta-analysis of diffusion tensor imaging studies. Asian Journal of Psychiatry, **55**, 102467. https://doi.org/10.1016/j.ajp.2020.102467

16. Liu, J., Cao, L., Li, H., Gao, Y., Bu, X., Liang, K., Bao, W., Zhang, S., Qiu, H., Li, X., Hu, X., Lu, L., Zhang, L., Hu, X., Huang, X., & Gong, Q. (2022). Abnormal resting-state functional connectivity in patients with obsessive-compulsive disorder: A systematic review and meta-analysis. Neuroscience & Biobehavioral Reviews, **135**, 104574. https://doi.org/10.1016/j.neubiorev.2022.104574

17. Gürsel, D. A., Avram, M., Sorg, C., Brandl, F., & Koch, K. (2018). Frontoparietal areas link impairments of large-scale intrinsic brain networks with aberrant fronto-striatal interactions in OCD: A meta-analysis of resting-state functional connectivity. Neuroscience & Biobehavioral Reviews, **87**, 151–160. https://doi.org/10.1016/j.neubiorev.2018.01.016

18. Rasgon, A., Lee, W. H., Leibu, E., Laird, A., Glahn, D., Goodman, W., & Frangou, S. (2017). Neural correlates of affective and non-affective cognition in obsessive compulsive disorder: A meta-analysis of functional imaging studies. European Psychiatry, **46**, 25–32. https://doi.org/10.1016/j.eurpsy.2017.08.001

19. Koch, K., Reeß, T. J., Rus, O. G., Gürsel, D. A., Wagner, G., Berberich, G., & Zimmer, C. (2018). Increased Default Mode Network Connectivity in Obsessive-Compulsive Disorder During Reward Processing. Frontiers in psychiatry, **9**, 254. https://doi.org/10.3389/fpsyt.2018.00254

20. Maia, T. V., Cooney, R. E., & Peterson, B. S. (2008). The neural bases of obsessive-compulsive disorder in children and adults. Development and psychopathology, **20**(4), 1251–1283. https://doi.org/10.1017/S0954579408000606

21. Kays, J. L., Hurley, R. A., & Taber, K. H. (2012). The dynamic brain: Neuroplasticity and mental health. The Journal of Neuropsychiatry and Clinical Neurosciences, **24**(2), 118–124. https://doi.org/10.1176/appi.neuropsych.12050109

22. Goodman, W. K., Storch, E. A., & Sheth, S. A. (2021). Harmonizing the neurobiology and treatment of obsessive-compulsive disorder. American Journal of Psychiatry, **178**(1), 17–29. https://doi.org/10.1176/appi.ajp.2020.20111601

23. Kellner, Charles H.. Brain Stimulation in Psychiatry: ECT, DBS, TMS and Other Modalities. The Journal of ECT **29**(1):p 78, March 2013. | DOI: https://doi.org/10.1097/YCT.0b013e318283908a

24. Fukuchi, T., Okada, Y., Katayama, H., Nishijima, K., Kato, S., Netsu, S., & Fukuda, H. (2003). Seishin shinkeigaku zasshi = Psychiatria et neurologia Japonica, **105**(7), 927–932.

25. Strassnig, M., Riedel, M., & Müller, N. (2004). Electroconvulsive therapy in a patient with Tourette's syndrome and co-morbid Obsessive Compulsive Disorder. The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry, **5**(3), 164–166. https://doi.org/10.1080/15622970410029930

26. Fontenelle, L. F., Coutinho, E. S., Lins-Martins, N. M., Fitzgerald, P. B., Fujiwara, H., & Yücel, M. (2015). Electroconvulsive therapy for obsessive-compulsive disorder: a systematic review. The Journal of clinical psychiatry, **76**(7), 949–957. https://doi.org/10.4088/JCP.14r09129

27. McNamara, B., Ray, J. L., Arthurs, O. J., & Boniface, S. (2001). Transcranial magnetic stimulation for depression and other psychiatric disorders. Psychological medicine, **31**(7), 1141–1146. https://doi.org/10.1017/s0033291701004378

28. Zhou, D. D., Wang, W., Wang, G. M., Li, D. Q., & Kuang, L. (2017). An updated meta-analysis: Short-term therapeutic effects of repeated transcranial magnetic stimulation in treating obsessive-compulsive disorder. Journal of affective disorders, **215**, 187–196. https://doi.org/10.1016/j.jad.2017.03.033

29. Liang, K., Li, H., Bu, X., Li, X., Cao, L., Liu, J., Gao, Y., Li, B., Qiu, C., Bao, W., Zhang, S., Hu, X., Xing, H., Gong, Q., & Huang, X. (2021). Efficacy and tolerability of repetitive transcranial magnetic stimulation for the treatment of obsessive-compulsive disorder in adults: A systematic review and network meta-analysis. Translational Psychiatry, **11**(1). https://doi.org/10.1038/s41398-021-01453-0

30. De Jesus, O., Fogwe, D. T., Mesfin, F. B., & M Das, J. (2023). Neuromodulation Surgery for Psychiatric Disorders. In StatPearls. StatPearls Publishing.

31. Sullivan, C. R. P., Olsen, S., & Widge, A. S. (2021). Deep brain stimulation for psychiatric disorders: From focal brain targets to cognitive networks. NeuroImage, **225**, 117515. https://doi.org/10.1016/j.neuroimage.2020.117515

32. Abelson, J. L., Curtis, G. C., Sagher, O., Albucher, R. C., Harrigan, M., Taylor, S. F., Martis, B., & Giordani, B. (2005). Deep brain stimulation for refractory obsessive-compulsive disorder. Biological psychiatry, **57**(5), 510–516. https://doi.org/10.1016/j.biopsych.2004.11.042

33. Greenberg, B. D., Malone, D. A., Friehs, G. M., Rezai, A. R., Kubu, C. S., Malloy, P. F., Salloway, S. P., Okun, M. S., Goodman, W. K., & Rasmussen, S. A. (2006). Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, **31**(11), 2384–2393. https://doi.org/10.1038/sj.npp.1301165

34. Chabardes, S., Krack, P., Piallat, B., Bougerol, T., Seigneuret, E., Yelnik, J., Fernandez Vidal, S., David, O., Mallet, L., Benabid, A. L., & Polosan, M. (2020). Deep brain stimulation of the subthalamic nucleus in obsessive-compulsives disorders: long-term follow-up of an open, prospective, observational cohort. Journal of neurology, neurosurgery, and psychiatry, **91**(12), 1349–1356. https://doi.org/10.1136/jnnp-2020-323421

35. Liebrand, L. C., Zhutovsky, P., Tolmeijer, E. K., Graat, I., Vulink, N., de Koning, P., Figee, M., Schuurman, P. R., van den Munckhof, P., Caan, M. W. A., Denys, D., & van Wingen, G. A. (2021). Deep brain stimulation response in obsessive-compulsive disorder is associated with preoperative nucleus accumbens volume. NeuroImage. Clinical, **30**, 102640. https://doi.org/10.1016/j.nicl.2021.102640

36. Robison, R. A., Taghva, A., Liu, C. Y., & Apuzzo, M. L. (2012). Surgery of the mind, mood, and conscious state: an idea in evolution. World neurosurgery, **77**(5-6), 662–686. https://doi.org/10.1016/j.wneu.2012.03.005

37. Joanette, Y., Stemmer, B., Assal, G., & Whitaker, H. (1993). From theory to practice: The unconventional contribution of Gottlieb Burckhardt to Psychosurgery. Brain and Language, **45**(4), 572–587. https://doi.org/10.1006/brln.1993.1061

38. Gross, D., & Schäfer, G. (2011). Egas Moniz (1874-1955) and the "invention" of modern psychosurgery: a historical and ethical reanalysis under special consideration of Portuguese original sources. Neurosurgical focus, **30**(2), E8. https://doi.org/10.3171/2010.10.FOCUS10214

39. Tan, S. Y., & Yip, A. (2014). António Egas Moniz (1874-1955): Lobotomy pioneer and Nobel laureate. Singapore medical journal, **55**(4), 175–176. https://doi.org/10.11622/smedj.2014048

40. Moniz, E. (1937). Prefrontal leucotomy in the treatment of mental disorders. American Journal of Psychiatry, **93**(6), 1379–1385. https://doi.org/10.1176/ajp.93.6.1379

41. Getz, M. J. (2009). The Ice Pick of Oblivion: Moniz, Freeman and the development of Psychosurgery. Trames. Journal of the Humanities and Social Sciences, **13**(2), 129. https://doi.org/10.3176/tr.2009.2.03

42. Caruso, J. P., & Sheehan, J. P. (2017). Psychosurgery, ethics, and media: A history of Walter Freeman and the lobotomy. Neurosurgical Focus, **43**(3). https://doi.org/10.3171/2017.6.focus17257

43. Winkelman NW. Chlorpromazine in the treatment of neuropsychiatric disorders. JAMA. 1954;**155**(1):18–21. https://doi.org/10.1001/jama.1954.03690190024007

44. López-Muñoz, F., Alamo, C., Cuenca, E., Shen, W. W., Clervoy, P., & Rubio, G. (2005). History of the discovery and clinical introduction of chlorpromazine. Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists, **17**(3), 113–135. https://doi.org/10.1080/10401230591002002

45. Harris, L., & M Das, J. (2022). Stereotactic Radiosurgery. In StatPearls. StatPearls Publishing.

46. Mustroph, M. L., Cosgrove, G. R., & Williams, Z. M. (2022). The Evolution of Modern Ablative Surgery for the Treatment of Obsessive-Compulsive and Major Depression Disorders. Frontiers in integrative neuroscience, **16**, 797533. https://doi.org/10.3389/fnint.2022.797533

47. Kihlström, L., Hindmarsh, T., Lax, I., Lippitz, B., Mindus, P., & Lindquist, C. (1997). Radiosurgical lesions in the normal human brain 17 years after Gamma Knife capsulotomy. Neurosurgery, **41**(2), 396–402. https://doi.org/10.1097/00006123-199708000-00011

48. Tripathi, M., & Sadashiva, N. (2022). Gamma Capsulotomy: A Valid Option for Refractory Obsessive Compulsive Disorder. Journal of neurosciences in rural practice, **13**(2), 167–168. https://doi.org/10.1055/s-0041-1742119

49. Pepper, J., Hariz, M., & Zrinzo, L. (2015). Deep brain stimulation versus anterior capsulotomy for obsessive-compulsive disorder: a review of the literature. Journal of neurosurgery, **122**(5), 1028–1037. https://doi.org/10.3171/2014.11.JNS132618

50. Brown, L. T., Mikell, C. B., Youngerman, B. E., Zhang, Y., McKhann, G. M., & Sheth, S. A. (2016). Dorsal anterior cingulotomy and anterior capsulotomy for severe, refractory obsessive-compulsive disorder: A systematic review of Observational Studies. Journal of Neurosurgery, **124**(1), 77–89. https://doi.org/10.3171/2015.1.jns14681

51. Kasabkojian, S. T., Dwan, A. J., Maziero, M. P., de Salles, A., Gorgulho, A., Miguel, E. C., Fillipo de Queiroz Vattimo, E., & Lopes, A. C. (2021). Delayed Brain Cyst Formation After Gamma Knife Anterior Capsulotomy. World neurosurgery, **145**, 298–300. https://doi.org/10.1016/j.wneu.2020.07.199

52. Rasmussen, S. A., Noren, G., Greenberg, B. D., Marsland, R., McLaughlin, N. C., Malloy, P. J., Salloway, S. P., Strong, D. R., Eisen, J. L., Jenike, M. A., Rauch, S. L., Baer, L., & Lindquist, C. (2018). Gamma Ventral Capsulotomy in Intractable Obsessive-Compulsive Disorder. Biological psychiatry, **84**(5), 355–364. https://doi.org/10.1016/j.biopsych.2017.11.034

53. Schneider, M. B., Walcott, B., & Adler, J. R., Jr (2021). Neuromodulation via Focal Radiation: Radiomodulation Update. Cureus, **13**(4), e14700. https://doi.org/10.7759/cureus.14700

54. Régis, J., Carron, R. & Park, M. Is radiosurgery a neuromodulation therapy?. J Neurooncol **98**, 155–162 (2010). https://doi.org/10.1007/s11060-010-0226-5

55. Régis, J. (2014). Gamma knife for functional diseases. Neurotherapeutics, **11**(3), 583–592. https://doi.org/10.1007/s13311-014-0276-z

56. Chen, Z.-F., Kamiryo, T., Henson, S. L., Yamamoto, H., Bertram, E. H., Schottler, F., Patel, F., Steiner, L., Prasad, D., Kassell, N. F., Shareghis, S., & Lee, K. S. (2001). Anticonvulsant effects of gamma surgery in a model of chronic spontaneous limbic epilepsy in rats. Journal of Neurosurgery, **94**(2), 270–280. https://doi.org/10.3171/jns.2001.94.2.0270

57. Mori, Y., Kondziolka, D., Balzer, J., Fellows, W., Flickinger, J. C., Lunsford, L. D., & Thulborn, K. R. (2000). Effects of stereotactic radiosurgery on an animal model of hippocampal epilepsy. Neurosurgery, **46**(1), 157–168.

58. Maesawa, S., Kondziolka, D., Dixon, C. E., Balzer, J., Fellows, W., & Lunsford, L. D. (2000). Subnecrotic stereotactic radiosurgery controls epilepsy produced by Kainic acid injection in rats. Journal of Neurosurgery, **93**(6), 1033–1040. https://doi.org/10.3171/jns.2000.93.6.1033

59. Smith, Z. A., De Salles, A. A., Frighetto, L., Goss, B., Lee, S. P., Selch, M., Wallace, R. E., Cabatan-Awang, C., & Solberg, T. (2003). Dedicated linear accelerator radiosurgery for the treatment of trigeminal neuralgia. Journal of Neurosurgery, **99**(3), 511–516. https://doi.org/10.3171/jns.2003.99.3.0511

60. Borchers, J. D., 3rd, Yang, H. J., Sakamoto, G. T., Howes, G. A., Gupta, G., Chang, S. D., & Adler, J. R., Jr (2009). Cyberknife stereotactic radiosurgical rhizotomy for trigeminal neuralgia: anatomic and morphological considerations. Neurosurgery, **64**(2 Suppl), A91–A95. https://doi.org/10.1227/01.NEU.0000340795.87734.70

61. Steiner, L., Lindquist, C., Adler, J. R., Torner, J. C., Alves, W., & Steiner, M. (1992). Clinical outcome of radiosurgery for cerebral arteriovenous malformations. Journal of neurosurgery, **77**(1), 1–8. https://doi.org/10.3171/jns.1992.77.1.0001

62. Adler, J [SRS Webinars] (2021, March 11). The Next Great Radiosurgical Frontier: Neuromodulation [Video]. Youtube. https://www.youtube.com/watch?v=WVWL5bIyYR0

63. Moore, C., Hsu, C. C., Chen, W. M., Chen, B. P. C., Han, C., Story, M., Aguilera, T., Pop, L. M., Hannan, R., Fu, Y. X., Saha, D., & Timmerman, R. (2021). Personalized Ultrafractionated Stereotactic Adaptive Radiotherapy (PULSAR) in Preclinical Models Enhances Single-Agent Immune Checkpoint Blockade. International journal of radiation oncology, biology, physics, **110**(5), 1306–1316. https://doi.org/10.1016/j.ijrobp.2021.03.047

64. UT Southwestern Medical Center. Pulsar: A paradigm for safer, more effective personalized radiotherapy: Clinical trials: Patient care: UT southwestern medical center. Clinical Trials | Patient Care | (n.d.). https://utswmed.org/cancer/cancer-answers/pulsar-paradigm-for-effective-radiotherapy/
65. Karanam, N. K., Shang, Z., Story, M. D., Timmerman, R. D., & Saha, D. (2022). Preclinical evaluation of tumor treating fields combined with personalized ultra-fractionated stereotactic adaptive radiotherapy (pulsar). International Journal of Radiation Oncology*Biology*Physics, **114**(3), 523. https://doi.org/10.1016/j.ijrobp.2022.07.2115
66. Saxena, S., Gorbis, E., O'Neill, J., Baker, S. K., Mandelkern, M. A., Maidment, K. M., Chang, S., Salamon, N., Brody, A. L., Schwartz, J. M., & London, E. D. (2009). Rapid effects of brief intensive cognitive-behavioral therapy on brain glucose metabolism in obsessive-compulsive disorder. Molecular psychiatry, **14**(2), 197–205. https://doi.org/10.1038/sj.mp.4002134
67. Yang, X. Y., Sun, J., Luo, J., Zhong, Z. X., Li, P., Yao, S. M., Xiong, H. F., Huang, F. F., & Li, Z. J. (2015). Regional homogeneity of spontaneous brain activity in adult patients with obsessive-compulsive disorder before and after cognitive behavioural therapy. Journal of affective disorders, **188**, 243–251. https://doi.org/10.1016/j.jad.2015.07.048
68. Li, P., Yang, X., Greenshaw, A. J., Li, S., Luo, J., Han, H., Liu, J., Zhong, Z., Guo, Z., Xiong, H., Yao, S., Chen, Y., Sun, J., & Li, Z. (2018). The effects of cognitive behavioral therapy on resting-state functional brain network in drug-naive patients with obsessive-compulsive disorder. Brain and behavior, **8**(5), e00963. https://doi.org/10.1002/brb3.963
69. Tan, O., Sayar, G.H., Ünsalver, B.Ö., Arat, M.M., & Karamustafalıoğlu, O. (2015). Combining transcranial magnetic stimulation and cognitive-behavioral therapy in treatment resistant obsessive-compulsive disorder. Anatolian Journal of Psychiatry, **16**, 180-188.
70. Adams, T. G., Jr, Badran, B. W., & George, M. S. (2014). Integration of cortical brain stimulation and exposure and response prevention for obsessive-compulsive disorder (OCD). Brain stimulation, **7**(5), 764–765. https://doi.org/10.1016/j.brs.2014.06.010
71. Tatti, E., Phillips, A. L., Paciorek, R., Romanella, S. M., Dettore, D., Di Lorenzo, G., Ruffini, G., Rossi, S., & Santarnecchi, E. (2022). Boosting psychological change: Combining non-invasive brain stimulation with psychotherapy. Neuroscience and biobehavioral reviews, **142**, 104867. https://doi.org/10.1016/j.neubiorev.2022.104867
72. López-Pina, J. A., Sánchez-Meca, J., López-López, J. A., Marín-Martínez, F., Núñez-Núñez, R. M., Rosa-Alcázar, A. I., Gómez-Conesa, A., & Ferrer-Requena, J. (2014). The Yale–Brown Obsessive Compulsive Scale. Assessment, **22**(5), 619–628. https://doi.org/10.1177/1073191114551954
73. Obsessive-Compulsive and Related Disorders, S. M. (n.d.). Diagnosis. Obsessive-Compulsive and Related Disorders. https://med.stanford.edu/ocd/about/diagnosis.html

74. Pallanti, S., Hollander, E., Bienstock, C., Koran, L., Leckman, J., Marazziti, D., Pato, M., Stein, D., Zohar, J., & International Treatment Refractory OCD Consortium (2002). Treatment non-response in OCD: methodological issues and operational definitions. The international journal of neuropsychopharmacology, **5**(2), 181–191. https://doi.org/10.1017/S1461145702002900

75. Lopes, A. C., Greenberg, B. D., Canteras, M. M., Batistuzzo, M. C., Hoexter, M. Q., Gentil, A. F., Pereira, C. A., Joaquim, M. A., de Mathis, M. E., D'Alcante, C. C., Taub, A., de Castro, D. G., Tokeshi, L., Sampaio, L. A., Leite, C. C., Shavitt, R. G., Diniz, J. B., Busatto, G., Norén, G., Rasmussen, S. A., Miguel, E. C. (2014). Gamma ventral capsulotomy for obsessive-compulsive disorder: a randomized clinical trial. JAMA psychiatry, **71**(9), 1066–1076. https://doi.org/10.1001/jamapsychiatry.2014.1193

76. Gouvea, F., Lopes, A., Greenberg, B., Canteras, M., Taub, A., Mathis, M., & Miguel, E. (2010). Response to sham and active gamma ventral capsulotomy in otherwise intractable obsessive-compulsive disorder. Stereotactic and functional neurosurgery, **88**(3), 177–182. https://doi.org/10.1159/000313870

77. Spofford, C. M., McLaughlin, N. C., Penzel, F., Rasmussen, S. A., & Greenberg, B. D. (2014). OCD behavior therapy before and after gamma ventral capsulotomy: case report. Neurocase, **20**(1), 42–45. https://doi.org/10.1080/13554794.2012.732083

78. Ertek, Irem & Uçar, Önder & Yaman, Mesut & Emmez, Ömer & Candansayar, Selçuk. (2021). Treatment Outcomes of Gamma-Knife Radio Surgery in Refractory Obsessive-Compulsive Disorder. Psychiatry and Clinical Psychopharmacology. **31**. 401-407. https://doi.org/10.5152/pcp.2021.21223

79. Spatola, G., Martinez-Alvarez, R., Martínez-Moreno, N., Rey, G., Linera, J., Rios-Lago, M., Sanz, M., Gutiérrez, J., Vidal, P., Richieri, R., & Régis, J. (2018). Results of Gamma Knife anterior capsulotomy for refractory obsessive-compulsive disorder: results in a series of 10 consecutive patients. Journal of neurosurgery, **131**(2), 376–383. https://doi.org/10.3171/2018.4.JNS171525

80. Sheehan, J. P., Patterson, G., Schlesinger, D., & Xu, Z. (2013). γ knife surgery anterior capsulotomy for severe and refractory obsessive-compulsive disorder. Journal of neurosurgery, **119**(5), 1112–1118. https://doi.org/10.3171/2013.5.JNS13201

81. Pattankar, S., Sankhe, M., & Chavda, K. (2022). Efficacy of Gamma Knife Radiosurgery in Refractory Obsessive-Compulsive Disorder: An Indian Experience. Journal of neurosciences in rural practice, **13**(1), 23–31. https://doi.org/10.1055/s-0041-1740453

82. Kondziolka, D., & Hudak, R. (2008). Management of obsessive-compulsive disorder-related skin picking with gamma knife radiosurgical anterior capsulotomies: a case report. The Journal of clinical psychiatry, **69**(8), 1337–1340. https://doi.org/10.4088/jcp.v69n0819c

83. Kondziolka, D., Flickinger, J. C., & Hudak, R. (2011). Results following gamma knife radiosurgical anterior capsulotomies for obsessive compulsive disorder. Neurosurgery, **68**(1) . https://doi.org/10.1227/NEU.0b013e3181fc5c8b

84. Richieri, R., Blackman, G., Musil, R., Spatola, G., Cavanna, A. E., Lançon, C., & Régis, J. (2018). Positive clinical effects of gamma knife capsulotomy in a patient with deep brain stimulation-refractory Tourette Syndrome and Obsessive Compulsive Disorder. Clinical neurology and neurosurgery, **170**, 34–37. https://doi.org/10.1016/j.clineuro.2018.04.018

85. Lopes, A. C., Greenberg, B. D., Norén, G., Canteras, M. M., Busatto, G. F., de Mathis, M. E., Taub, A., D'Alcante, C. C., Hoexter, M. Q., Gouvea, F. S., Cecconi, J. P., Gentil, A. F., Ferrão, Y. A., Fuentes, D., de Castro, C. C., Leite, C. C., Salvajoli, J. V., Duran, F. L., Rasmussen, S., & Miguel, E. C. (2009). Treatment of resistant obsessive-compulsive disorder with ventral capsular/ventral striatal gamma capsulotomy: a pilot prospective study. The Journal of neuropsychiatry and clinical neurosciences, **21**(4), 381–392. https://doi.org/10.1176/jnp.2009.21.4.381

86. Batistuzzo, M. C., Hoexter, M. Q., Taub, A., Gentil, A. F., Cesar, R. C., Joaquim, M. A., D'Alcante, C. C., McLaughlin, N. C., Canteras, M. M., Shavitt, R. G., Savage, C. R., Greenberg, B. D., Norén, G., Miguel, E. C., & Lopes, A. C. (2015). Visuospatial Memory Improvement after Gamma Ventral Capsulotomy in Treatment Refractory Obsessive-Compulsive Disorder Patients. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology, **40**(8), 1837–1845. https://doi.org/10.1038/npp.2015.33

87. Paiva, R. R., Batistuzzo, M. C., McLaughlin, N. C., Canteras, M. M., de Mathis, M. E., Requena, G., Shavitt, R. G., Greenberg, B. D., Norén, G., Rasmussen, S. A., Tavares, H., Miguel, E. C., Lopes, A. C., & Hoexter, M. Q. (2018). Personality measures after gamma ventral capsulotomy in intractable OCD. Progress in neuro-psychopharmacology & biological psychiatry, **81**, 161–168. https://doi.org/10.1016/j.pnpbp.2017.10.023

88. Rück, C., Karlsson, A., Steele, J. D., Edman, G., Meyerson, B. A., Ericson, K., Nyman, H., Asberg, M., & Svanborg, P. (2008). Capsulotomy for obsessive-compulsive disorder: long-term follow-up of 25 patients. Archives of general psychiatry, **65**(8), 914–921. https://doi.org/10.1001/archpsyc.65.8.914

89. Peker, S., Samanci, M. Y., Yilmaz, M., Sengoz, M., Ulku, N., & Ogel, K. (2020). Efficacy and Safety of Gamma Ventral Capsulotomy for Treatment-Resistant Obsessive-Compulsive Disorder: A Single-Center Experience. World neurosurgery, **141**, e941–e952. https://doi.org/10.1016/j.wneu.2020.06.098

90. Illes, J., & Hossain, S. (2017). Neuroethics: Anticipating the future. Oxford University Press. https://doi.org/10.1093/oso/9780198786832.001.0001

91. Müller, S., van Oosterhout, A., Bervoets, C., Christen, M., Martínez-Álvarez, R., & Bittlinger, M. (2022). Concerns about psychiatric neurosurgery and how they can be overcome: Recommendations for responsible research. Neuroethics, **15**(1). https://doi.org/10.1007/s12152-022-09485-z