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Radiation Therapy for Non-Malignant Central Nervous System Tumors, Disorders, and Illnesses — Current Applications and Future Directions

Felix Ehret,[*,†,‡] Charles Leland Rogers,[§] James Fontanesi,[‖] George D. Wilson,[‖] Bhargava S. Chitti,[¶,#] John Starner,[**] Baho Sidiqi,[**] Anuj Goenka,[**] Michael Schulder,[††] Anna M.E. Bruynzeel,[‡‡] Joost J.C. Verhoeff,[‡‡] Alexander C. MacDonagh,[*] Hannah I. Park,[*] Helen A. Shih,[*] and Lawrence Kleinberg[§§]

Radiation therapy has a central role in the treatment of various malignant central nervous system tumors, including gliomas, high-grade meningiomas, and brain metastases. This also applies to a plethora of non-malignant central nervous system lesions, such as vestibular schwannomas and arteriovenous malformations, and, in specific situations, for selected functional and psychiatric disorders. In patients with these conditions, the goal of radiation therapy is generally to preserve and stabilize function. In addition, as these illnesses, with some exceptions such as arteriovenous malformations, are rarely life-threatening, the risks of radiation therapy must be interpreted in a different context than for patients with malignancy. Given the continuous and growing interest in the use of radiation therapy for non-malignant tumors and functional conditions, this review summarizes the current and future directions in central nervous system applications, addressing its use for the management of vestibular schwannomas, arteriovenous malformations, trigeminal neuralgia, tremor, Alzheimer's disease, and other psychiatric conditions, such as obsessive-compulsive disorder, addiction, and eating disorders.
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Introduction

The use of radiation therapy, including stereotactic radiosurgery (SRS) and conventionally fractionated radiation therapy, for the treatment of malignant central nervous system tumors has a long-standing history. This also applies to a variety of non-malignant lesions, such as vestibular schwannomas, pituitary adenomas, and arteriovenous malformations (AVMs), as well as functional diseases like trigeminal neuralgia (TN). With the recent advances in imaging, radiation techniques, and understanding in functional neuroanatomy, the use of radiation therapy for other diseases,

[*]Department of Radiation Oncology, Massachusetts General Hospital, Mass General Brigham, Harvard Medical School, Boston, MA
[†]Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Radiation Oncology, Berlin, Germany
[‡]German Cancer Consortium (DKTK), partner site Berlin, a partnership between DKFZ and Charité – Universitätsmedizin Berlin, Berlin, Germany
[§]Radiation Oncology, Utah Cancer Services, Salt Lake City, UT
[‖]Department of Radiation Oncology, Corewell Health, Royal Oak, MI
[¶]Department of Radiation Oncology, New York City Health and Hospitals/Kings County, Brooklyn, NY
[#]SUNY Downstate Health Sciences University, Brooklyn, NY
[**]Department of Radiation Medicine, Northwell, Lake Success, NY
[††]Department of Neurosurgery, Northwell, Lake Success, NY
[‡‡]Department of Radiation Oncology, Amsterdam UMC, Cancer Center Amsterdam, Amsterdam, the Netherlands
[§§]Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University School of Medicine, Baltimore, MD
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Address reprint requests to Felix Ehret, MD, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Radiation Oncology, Augustenburger Platz 1, 13353, Berlin, Germany. E-mail: felix.ehret@charite.de

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such as Alzheimer's disease (AD), addiction, obsessive-compulsive disorder (OCD), and tremor, is emerging and merits further investigation.

In this article, we focus on several established and investigational indications for radiation therapy in non-malignant, though life-altering conditions, where the treatment decision is primarily driven by the goal of preserving function. The primary treatment goal for vestibular schwannoma is to preserve hearing, balance, and facial nerve function, while also preventing symptoms of brainstem compression. Appropriately treated, this tumor is rarely life-threatening. AVM patients endure the stress of living with a lifelong risk of sudden catastrophic bleeding at any time that may result in permanent disability or death. When used in the treatment of TN, radiosurgery is administered purely to control a pain syndrome. Two novel potential applications of radiation therapy are to delay the progression of AD and to disrupt brain pathways driving psychiatric disorders. Although potentially of great benefit, radiation therapy for these 2 fields has been challenging to study due to barriers related to ethics, informed consent, treatment safety, and our limited understanding of the underlying pathophysiology and radiobiology. However, the work is ongoing, and further insights and advances are eagerly awaited.

Vestibular Schwannomas

Vestibular schwannomas are benign nerve sheath tumors of the vestibular branch of the vestibulocochlear nerve (cranial nerve VIII), representing the most common tumor in the cerebellopontine angle.[1] Often referred to as "acoustic neuroma," a historical misnomer, they account for approximately 8% of all intracranial tumors and around 75% of all nerve sheath tumors in the central nervous system.[1,2] The incidence of vestibular schwannomas increases with age, with an overall age-adjusted annual incidence of 1.52 per 100.000.[2] In most patients, the tumors are sporadic, while approximately 5% are linked to neurofibromatosis type 2-related schwannomatosis (NF2).[3,4] Bilateral vestibular schwannomas are a diagnostic hallmark distinctive of NF2, occurring in 90%-95% of affected patients.[3] Vestibular schwannomas typically cause gradual hearing loss, tinnitus, vertigo, and dizziness.[5] Significant neuropathy of cranial nerves V and VII is less common but possible.[5] The diagnosis is primarily based on the typical imaging findings on magnetic resonance imaging (MRI) in conjunction with the clinical presentation.[6]

The indication for treatment is based on several factors, including tumor size and growth rate, symptoms, cranial nerve status, patient age and preferences, and comorbidities. In general, the treatment decision-making should be based on an interdisciplinary consensus. While surgical resection may be indicated for tumors causing brainstem mass effect, radiation therapy, particularly with SRS, plays a central role in managing vestibular schwannomas, given its excellent local tumor control and favorable safety profile.[6-9] Therefore, the paragraph will focus on SRS, which may be used for small- and medium-sized (a)symptomatic tumors, as well as selected larger tumors without a mass effect, to prevent further tumor growth and associated symptoms.[6,7,9,10] SRS also plays a role after a planned subtotal microsurgical resection for cranial nerve sparing in large tumors.[11]

Prescription doses between 11 and 13 Gy for single-fraction SRS are well established, with numerous studies demonstrating excellent outcomes.[6,8] For hypofractionated SRS, 3 × 6 Gy and 5 × 5 Gy are commonly used.[12-14] The question of fractionation is the subject of ongoing debate and research. The recently published ACOUNEU trial compared single-fraction and hypofractionated SRS regarding hearing preservation.[15] No differences were found between both treatment arms, which is in agreement with previous retrospective reports and reviews.[13,16,17] In summary, there is no clear evidence of superiority with fractionation, although some institutions have historically preferred hypofractionated SRS.[15-17] Therefore, single-fraction SRS remains the most common and widely used treatment approach. Nevertheless, the underlying radiobiological rationale may favor fractionated treatments in specific scenarios such as reirradiation. A case-based guide for the management of vestibular schwannomas, including details on the treatment planning and dose constraints for organs at risk, is reported elsewhere.[7] Figure 1 shows a typical SRS treatment plan and treatment response. The treatment-associated toxicity is usually limited, potentially consisting of transient symptom worsening, progressive hearing loss, or edema. High-grade toxicity, such as permanent facial nerve weakness or trigeminal neuropathy, occurs rarely.[18] Malignant transformation or radiation-induced malignancy after SRS is extremely rare.[19,20]

The follow-up after SRS typically includes serial MRI, audiometry, and physical examinations, with the recommendation for structured quality of life assessments.[6] Pseudoprogression, i.e., transient increase in size of the tumor, may be substantial, and must be anticipated during the first 2-3 years of follow-up, whereas actual early progression is unlikely.[21] However, cases of pseudoprogression have also been reported after 3 years, highlighting the need for a careful assessment.[21,22] Approximately one-third of patients can have pseudoprogression after radiosurgery, which should not be categorized as treatment failure.[23-25] Actual local tumor progression must be carefully confirmed, considering the time since SRS, longitudinal volumetric changes, and symptoms.[21,22] A continuous, uninterrupted tumor volume increase over 2-4 years after radiosurgery with worsening symptoms, such as impaired hearing, is indicative of actual tumor progression.[7,21] An initial increase in tumor volume, followed by a decrease, i.e., pseudoprogression, in the first years after SRS, succeeded by further tumor growth and true progression, is observed in a smaller proportion of patients.[21] The outcomes after radiosurgery are favorable. Local tumor control is typically achieved in over 90% of cases without the need for further treatment.[18,26] There is limited prospective data addressing whether there is a benefit of early intervention for selected vestibular schwannoma versus observation. The recently reported V-REX trial

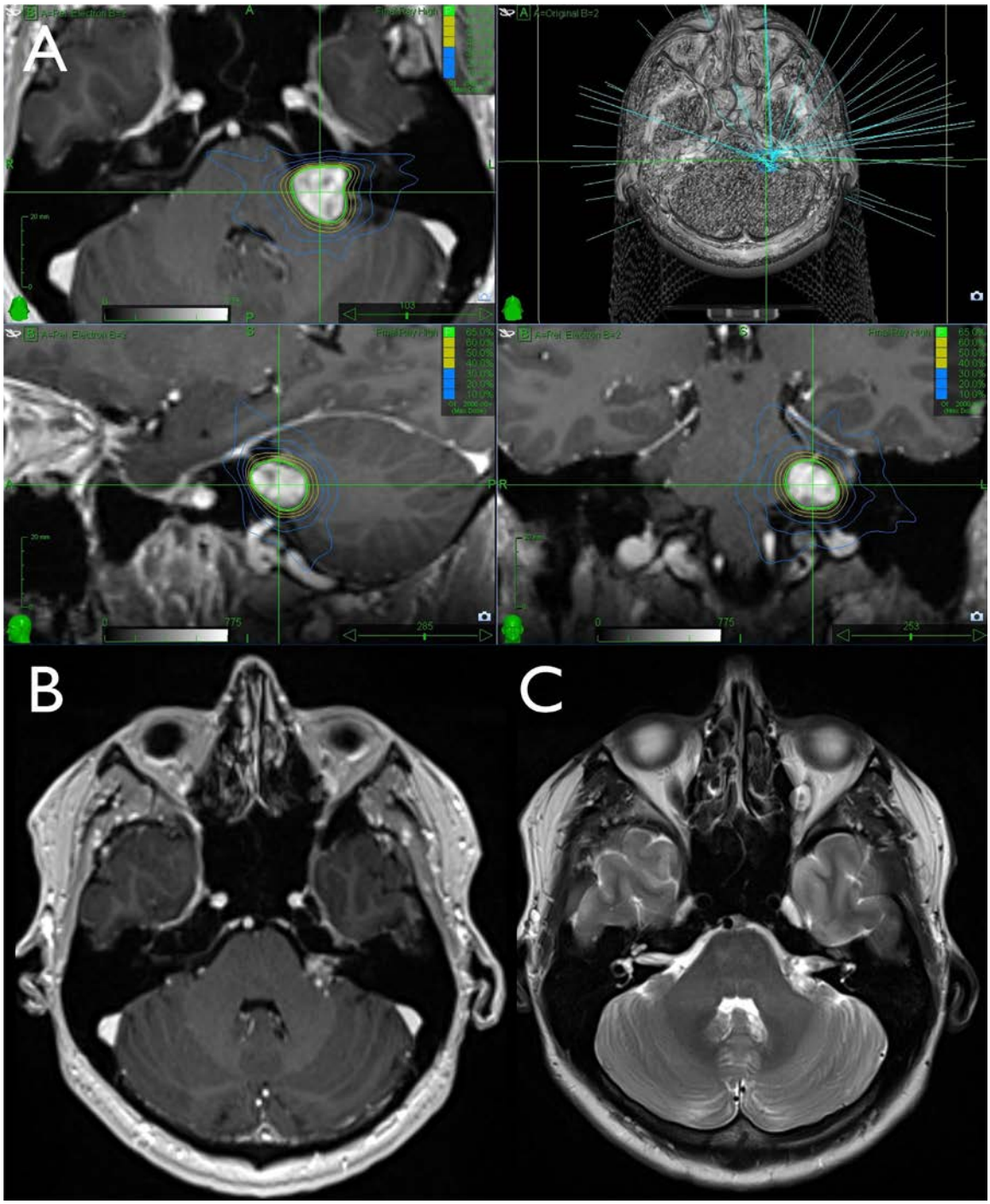

Figure 1 (A) Treatment plan for a left vestibular schwannoma. Single-fraction stereotactic radiosurgery, prescription dose 13 Gy, prescription isodose line 65%, planning target volume 1.83 cm^3. (B/C) Magnetic resonance imaging, T1-weighted contrast-enhanced (left) and T2-weighted images (right), 17 months after treatment, demonstrating treatment response and loss of contrast enhancement.

investigated whether radiosurgery for small- and medium-sized vestibular schwannomas is superior compared to a wait-and-scan approach in terms of tumor control.[27] The primary endpoint was the tumor volume ratio at the end of the trial, after the four-year follow-up, and the start of the trial. Secondary endpoints included 26 outcomes, including patient-reported outcomes and quality of life assessments. The trial showed excellent tumor volume control with SRS. Only 3 patients in the radiosurgery arm required treatment for further tumor growth, while 22 patients in the wait-and-scan arm underwent additional treatment. Notably, 25 out of the 26 secondary outcomes demonstrated no significant differences. These findings align well with the VISAS-K1 and VISAS-K2 studies, two retrospective, propensity score-matched multicenter analyses, comparing SRS for Koos grade 1 and 2 tumors with active surveillance.[28-30] Based on

the available evidence, the findings suggest that either an early intervention with SRS or observation for selected small vestibular schwannomas is appropriate.[31] Nevertheless, further prospective research is vital to refine the management of vestibular schwannomas, including the optimal timing for treatment.

Patients with confirmed tumor progression have several treatment options, depending on the tumor size, comorbidities, personal preferences, and previous treatments. It must be acknowledged that treatment algorithms for local tumor progression are less well-defined. This underlines the necessity for a careful, interdisciplinary approach. Microsurgical resection after prior irradiation has been associated with a high risk of facial nerve injury, and this risk is considered in the decision of some patients as a "risk" of the selection of radiosurgery in the initial management. Based on the limited evidence available, reirradiation with SRS of truly progressive tumors after initial radiosurgery represents a viable salvage treatment, with an acceptable safety profile.[32]

In summary, radiation therapy, especially SRS, is a central treatment modality for vestibular schwannomas. Based on the plethora of studies and reports, SRS provides an excellent long-term tumor control with a low risk of significant and persistent treatment-associated toxicity. The role of reirradiation, potential differences between single-fraction and hypofractionated SRS, timing of treatment, and further approaches to preserve hearing and cranial nerve function in patients are some of the topics that will most likely be addressed by future research in the field.

Arteriovenous Malformations

In 1967, Lars Leksell had advanced the concept of SRS that he initially proposed in 1951 with the deployment of the first Gamma Knife.[33] Based on the observation that conventional radiation used for tumors could induce vascular narrowing, Steiner in 1970 used the first Gamma Knife in an attempt to ablate an AVM.[34] Using planar angiography to guide the treatment, SRS was delivered to the feeding vessels of the malformation. Although no changes were observed on the 4-month follow-up angiography, an angiogram obtained 19 months later demonstrated complete resolution of the AVM.

Since that pioneering experience, there has been considerable interest in elucidating the biological processes responsible for the gradual obliteration of AVMs, which typically unfolds over several years.[35-37] The earliest observed changes include endothelial cell injury, which becomes apparent within days of irradiation. This is followed by the circumferential proliferation of smooth muscle cells, and subsequently, the progressive deposition of hyaline material and dense collagen that gradually occludes the small muscularized vessels of the nidus, occurring over a period of years. It remains unclear whether the therapeutic ratio of radiosurgery is determined solely by precise targeting or whether intrinsic structural and functional abnormalities within AVM vasculature also contribute to radiosensitivity. Additionally, it is intriguing to consider whether similar vascular effects may underlie the effectiveness of high-dose radiosurgery in the treatment of certain tumors.

The motivation for the treatment of patients with AVM is the risk of brain hemorrhage that can be fatal or result in disability. Cerebral AVMs can present with a variety of signs and symptoms, including headaches, seizures, transient focal neurologic deficits, and hemorrhage. Once the abnormality is identified, the future risk of bleeding is estimated to be 2%-4% for each year of life, with each bleeding event associated with a 20%-30% fatality risk and a 20%-40% rate of permanent disability.[38-41] Significant risk factors for future hemorrhage of untreated lesions in individual patients include prior bleeding, deep brain location, and entirely deep vein drainage.[42] Patients with none of these risk factors appeared to have a less than 1% risk of bleeding per year of follow-up without treatment, whereas those with all factors had a risk of 34% per year. Interestingly, the size of the AVM itself may not always be an essential factor.

There is no disagreement that surgical resection, or, in a small number of patients, endovascular obliteration are the treatments of choice to prevent AVM hemorrhage. However, for patients with AVMs that cannot be resected or obliterated safely due to their volume, location, and venous drainage, radiosurgery is an effective non-invasive treatment option for ablating AVMs. Nevertheless, a substantial disadvantage is that the risk of hemorrhage persists for several years, occasionally stretching over a decade, until complete resolution, i.e., obliteration, of the AVM. Radiosurgery is most successful for lesions smaller than 3-4 cm in size, with geometry and location in the brain that allow for a dose of 18 Gy or higher to be administered without unacceptable risk of injury. The response is dose-related.[43] When 18 Gy or higher can be given to a volume including the periphery of the AVM, the ablation rate is 80% or higher.[43-45] The obliteration rate appears to plateau at approximately 90% at a dose of roughly 20-22 Gy, with marginal benefits with increases beyond that. The imprecision of angiography in identifying the entire extent of the AVM nidus in some patients may be the cause of the cap on success with increasing dose. For doses between 14 and 16 Gy, the resolution rate ranges from 50% to 60%.

The decision on the dose to be administered, with the goal of at least 18-20 Gy, depends upon the maximum that can be given with appropriate safety, and which becomes a challenging goal as lesion size reaches 3-4 cm. However, considerable injury from radiosurgery has not been most closely correlated with the size of the lesion treated with a high dose, but with the volume of brain, including normal tissue exposed to 12 Gy or more, and the eloquence of that region.[46,47] Flickinger reported the specific risk of injury related to dose based on eloquence location in the brain, which provides guidance on the appropriate safety of the planned radiation dose.[47] The highest risk regions of the brain included the brainstem, thalamus, and corpus callosum. However, a nuanced consideration of the function of

the localized area of the brain is critical, such as the motor strip and visual cortex. Pretreatment embolization may be used to reduce the size of a lesion to enable higher dose radiosurgery, but has actually been associated with inferior outcome, perhaps because of an impact on radiation dosimetry of the material and/or on visualization of the lesion on the angiogram to define a true target.

Importantly, there are strategies to use radiosurgery effectively as an alternative to surgery, even when a dose likely to be curative cannot be administered in a single fraction. First, there is extensive experience in safely retreating high-dose AVMs that were treated with curative intent, generally after allowing a 3-year or longer interval to confirm that there has been no adequate response to the initial treatment. The obliteration rate is approximately 60% despite failure of the initial treatment, and the radiation injury rate is around 10%.[48-51] Staged treatments, however, include treating part of an AVM to an effective dose with a plan to treat the remainder at a planned interval of generally 6-12 months.[38,48,52-54] With this strategy, an obliteration rate of 60%-70% is anticipated if a dose of 17 Gy or greater is ultimately administered to the entire nidus. Other approaches use low-dose treatment of 10-14 Gy to the entirety of a large lesion with an understanding that retreatment, as described above, will be required.[55,56] The ARUBA trial has raised the question of whether lower-risk AVMs that have not ruptured should be treated.[57,58] Participants were randomized to either medical management alone or medical management with an intervention selected by the treating physicians. The study was closed after enrollment of 226 of 800 planned patients, as treated patients had an inferior early outcome of stroke or death. With a mean follow-up of 50.4 months, the hazard ratio of 0.31 was superior for medical management alone.[58] Still, concerns have been raised about the general applicability based on issues related to design and conduct of the study including selection bias, participating-site characteristics, high inclusion of embolization in therapy, lack of standardized approaches to therapy selection, no stratification for important risk factors, worse than expected outcomes for interventions, and short length of follow-up for a lifelong condition in which further toxicity is not likely once obliterated with treatment.[38,39,59-61] In contrast, the morbidity and mortality of untreated lesions are likely to continue increasing over time. Therefore, decisions for this group should continue to be personalized based on the risk of future bleeding and the suitability of different therapeutic options.

Although SRS has a well-documented effectiveness in treating AVMs, multidisciplinary involvement in decision-making is critical. Important factors include the lifetime risk of monitoring, whether immediate surgical cure is feasible and safe, patient goals, and whether a sufficient dose of radiation can be given, sometimes over several treatments, to result in an ablation of the lesion. The delayed resolution of the lesion with irradiation and continued risk of bleeding during that interval is an important consideration, especially for patients at high risk of future hemorrhage. The Spetzler-Martin grading system, based on adverse features such as large size, location in eloquent brain areas, and deep venous drainage, has been used to categorize patients based on predicted surgical outcome, and is used not only to guide selection among management options but also to divide patients into more homogeneous groups, facilitating comparison of outcomes of different strategies.[62] Several comparative studies and meta-analyses of relevant literature suggest that the cure rate is higher with surgical intervention, but that the risks of radiosurgery are lower.[59,63-67] However, there are many undefined factors beyond the Spetzler-Martin grade that are unique to the anatomy of each patient's AVM and their clinical circumstances, which determine whether the patient will be triaged to surgical resection or radiosurgery. The Virginia grading system has been developed to similarly categorize patients treated with radiosurgery based on adverse factors such as age above 65 years, large AVM size, eloquent brain location, and prior embolization.[68]

Trigeminal Neuralgia

TN is a prototypical paroxysmal facial pain disorder, affecting approximately 4-13 per 100,000 persons per year.[69,70] Drug therapy, such as carbamazepine or oxcarbazepine, remains first-line, but 30%-50% of patients eventually require additional intervention.[71-73] Contemporary options include microvascular decompression (MVD), radiofrequency rhizotomy, balloon compression, glycerol rhizolysis, and SRS. Compared with open or percutaneous techniques, SRS is a non-invasive procedure and is performed as an outpatient treatment with minimal adverse effects, making it an attractive choice for elderly or medically frail patients.[74-76]

Historical Perspective

Dandy's 1930s observation that arterial loops compressing the trigeminal root-entry zone could be surgically mobilized marked the beginning of the modern era of MVD.[77] Jannetta later refined the procedure, reporting durable pain relief in more than 80% of carefully selected patients.[78] Meanwhile, Spiegel and Wycis's stereotactic frame (1947) and Leksell's Gamma Knife (1968) paved the way for an incision-less treatment.[74,79] In 1992, the Karolinska group published one of the first clinical reports of Gamma Knife rhizotomy, showing that a single 70-90 Gy shot to the trigeminal root-entry zone could reduce pain without craniotomy.[80] Régis and colleagues confirmed long-term efficacy in a 497-patient European cohort.[81] Image-guided, mask-based linear accelerator and CyberKnife solutions appeared in the 2000s, broadening access and facilitating prospective studies.[76,82]

Pathophysiology and Target Selection

Episodes of TN are believed to arise from cross-talk between demyelinated fibers at the dorsal root entry zone. High-resolution diffusion-weighted imaging shows that the radiosurgically responsive target is the ~3 mm root-entry zone, where central (oligodendrocytes) myelin transitions to peripheral (Schwann cells) myelin.[83] Tractography-based planning

helps center the 4-mm isocenter on this vulnerable zone while sparing adjacent fibers.[84]

Current Interventional Paradigm

MVD remains the gold standard for young, medically fit patients with demonstrable vascular conflict, offering the highest long-term cure rate (>80% at 10 years).[85] Percutaneous intervention yields rapid relief but carries a 10%-30% risk of dysesthesia or anesthesia dolorosa, especially after repeat procedures.[74] In contrast, SRS has a different post-treatment course: pain relief typically begins after 4-8 weeks, while severe sensory morbidity is <5%.[81,86] Notably, focused ultrasound is still investigational for TN, and unlike SRS, it is limited by skull-density constraints.

Radiosurgical Technique

Thin-slice constructive interference in steady state (CISS) or fast imaging employing steady-state acquisition (FIESTA) MRI and computed tomography (CT) are used to delineate the cisternal trigeminal nerve. On Gamma Knife, a single 4-mm collimator typically receives 80-90 Gy at the 100% isodose, with the 20%-30% isodose kept outside the pontine border (<15 Gy). Linear accelerator and CyberKnife systems use cones or multi-leaf collimators to produce similar dose distributions with submillimeter image guidance.[76,82,87]

Efficacy and Toxicity

TN-associated pain is often graded with the Barrow Neurological Institute (BNI) scale, with documentation of the medication use.[88] A pooled analysis of more than 1100 published cases shows that 60%-75% achieve complete pain freedom without medication (BNI I) by 12 months, while an additional 10%-15% enjoy worthwhile improvement on reduced drug doses.[86] The median latency to initial response is 6 weeks. The five-year pain-free durability rate is approximately 50%. Late recurrence can often be salvaged with a second radiosurgical rhizotomy, which restores durable control in two-thirds of cases.[89] In cases of patients with bilateral TN, staged SRS performed ≥12 months after the initial treatment achieved ≤BNI IIIb pain relief in 87% of first-treated nerves and in 95% of second-treated nerves. Estimated durability after the repeat procedure was 89% at 1 year and 62% at 5 years, with bothersome numbness in ≤20% and no cases of anesthesia dolorosa.[90] Patients are typically examined at 6 weeks, 3 months, and 1 year, with further follow-up visits depending on the control of clinical symptoms and the effectiveness of medical management. SRS is the least morbid of all procedural options for TN. Mild, non-bothersome facial numbness occurs in 7%-20% of patients. The rate of troublesome dysesthesia is <5%, and objective corneal reflex loss is <1% when the pontine dose is limited. Anesthesia dolorosa and brainstem injury are exceedingly rare with modern planning constraints. Importantly, quality of life studies show that even patients who develop mild numbness rate their outcome as favorable because pain relief outweighs sensory changes.[81,86] Extrapolation from the literature on essential tremor (ET), end-to-end cost analyses indicate that single-fraction SRS is more cost-effective than MVD for unilateral disease, as it involves no hospital stay.[91]

Future Directions and Conclusion

Ongoing studies are investigating the role of hypofractionated radiosurgery, such as 72 Gy in 6 fractions, in reducing facial numbness associated with single-fraction radiosurgery.[92] Integration of magnetic resonance-linear accelerator technology promises real-time imaging and adaptive dosimetry, while connectome-based targeting aims to personalize the isocenter to each patient's fiber anatomy. Ultimately, predictive radiobiological modeling may enable proactive reirradiation schedules that extend pain freedom beyond the current 5- to 7-year plateau. In summary, SRS provides durable pain control for most medication-refractory TN patients, with a favorable safety profile among ablative procedures. Its non-invasive nature, outpatient workflow, and compatibility with anticoagulation make it the interventional choice for the elderly, the medically fragile, and those who decline open surgery, while leaving MVD available as a future therapeutic option.

Tremor

Tremor is a highly prevalent movement disorder, affecting about 7 million people in the United States and roughly 6% of adults older than 65 years.[93,94] ET constitutes the majority of cases, followed by tremor-dominant Parkinson's disease and the less frequent symptomatic tremors of multiple sclerosis, stroke, or trauma. First-line medications include propranolol or primidone.[95] However, approximately 30%-50% of patients fail to respond to these drugs.[95] For this population, interventional therapy becomes necessary. Contemporary options include deep brain stimulation (DBS) of the ventral-intermediate nucleus (VIM), radiofrequency thalamotomy, magnetic resonance-guided focused ultrasound thalamotomy, and SRS.[96-100] Among them, SRS is the only non-invasive technique that requires neither general anesthesia nor interruption of anticoagulation, making it particularly attractive for older and frail patients, as well as non-surgical candidates.[100] Patients being considered for such treatment should be under the care of a neurologist and neurosurgeon with demonstrated expertise in the management of movement disorders.

Historical Perspective

The search for a safe and effective treatment method spans nearly a century. Early open cortical or pyramidal tract surgeries performed in the 1930s reduced tremor but left unacceptable motor deficits.[97] Progress accelerated when Spiegel and Wycis introduced the first human stereotactic frame in 1947, creating a reproducible three-dimensional coordinate system for deep targets.[79] Seven years later, Hassler and Riechert electrophysiologically mapped the thalamus and identified the VIM as the critical relay for tremor.[101] Subsequent

decades produced a parade of innovations: Velasco's description of the posterior subthalamic area in 1972, Benabid's demonstration of high-frequency VIM stimulation in 1987, the birth of DBS, and Duma's landmark 1998 report of Gamma Knife thalamotomy for tremor.[100,102] Linear-accelerator thalamotomy became feasible in 2004, while pilot and randomized trials by Elias and colleagues between 2013 and 2016 validated thermal lesioning with magnetic resonance-guided focused ultrasound thalamotomy.[98,99,103] A cost-utility analysis later showed that both SRS and focused ultrasound thalamotomy were more economical than DBS for unilateral ET, supporting its use in the treatment of this disease, even as a first-line therapy in selected patients.[91]

Pathophysiology and Target Selection

Functional imaging, diffusion-tensor tractography, and electrophysiology converge on a cerebello-thalamo-cortical network: Oscillations initiated in the dentate nucleus travel along the dentato-rubro-thalamic tract (DRT), synapse within the VIM, and reverberate to the primary motor cortex.[104] Lesioning or stimulating the VIM interrupts this loop and reliably suppresses tremor. In modern practice, patient-specific tractography can delineate the DRT and adjacent internal capsule, allowing millimetric refinement of the radiosurgical isocenter.[105]

Current Interventional Paradigm

The choice of treatment modality for medication-refractory ET is tailored to the individual patient. DBS offers reversible, adjustable control and remains the gold standard for long-term control of bilateral disease in medically fit patients, yet it requires craniotomy and implanted hardware with infection and maintenance risks.[96] Radiofrequency thalamotomy provides immediate relief but is invasive and carries a ≤ 10% rate of permanent neurological deficits, especially if performed bilaterally.[97] Magnetic resonance-guided focused ultrasound thalamotomy delivers real-time MRI guidance and rapid benefit, but excludes patients with unfavorable skull density and still lacks long-term data.[106] SRS is unique in being completely outpatient, frame-based, or mask-based, and compatible with anticoagulation, while its main drawbacks are the 6-12 week latency to effect, the absence of intraoperative confirmation, and the required latency period of 12-24 months, following treatment of one side, to treat the other.[100]

Radiosurgical Technique

SRS is offered for medication-refractory ET, tremor-dominant Parkinson's disease, and carefully selected symptomatic tremors. It plays an especially valuable role when open surgery is undesirable or not feasible. Mask- or frame-based radiosurgical techniques are available. On stereotactic MRI, the VIM is located approximately 11 mm lateral to the third ventricle wall, 2-3 mm superior to the plane of the anterior and posterior commissures, and is positioned 1/4th of the way anteriorly from the posterior commissure toward the anterior commissure. A single 4-mm isocenter is treated with 130-140 Gy on the Gamma Knife or a biologically matched 110-140 Gy on linear accelerators, while sparing the internal capsule and sensory thalamus.[107-110]

Efficacy and Safety

Neurological examination and Fahn-Tolosa-Marín (FTM) scoring are typically performed at 3, 6, and 12 months, with MRI at 6-12 months used to document the signature lesion. Across prospective studies and large series, unilateral SRS achieves significant tremor reduction in 70%-90% of patients, with responder definitions ranging from ≥50% FTM improvement to complete arrest.[106-119] Benefit typically begins 8-12 weeks after treatment and plateaus by 6-12 months. Long-term follow-up shows durable control beyond 5 years in most responders.[114] Adverse events are predominantly mild and transient. Sensory disturbance and gait ataxia each occur in <10% of cases; permanent disabling deficits are uncommon, ≤4%−8% across contemporary series.[119] A network meta-analysis of 464 focused ultrasound and 62 SRS thalamotomies for ET found equivalent 12-month tremor suppression but a four-fold higher rate of persistent adverse effects after focused ultrasound − imbalance (10.5%) and sensory disturbance (8.3%) − compared with SRS − transient hemiparesis (2.7%) and dysarthria (2.4%). The authors linked focused ultrasound toxicity to larger, ellipsoid thermal lesions and skull-density constraints, whereas SRS lesions are smaller, spherical, and evolve slowly, sparing adjacent capsule fibers. These data reinforce SRS as a safer, non-invasive treatment option when long-term tolerability is paramount.[120] Cost-utility analyses favor SRS and focused ultrasound thalamotomy over DBS for unilateral ET, primarily because hardware and postoperative programming costs are absent.[91]

Future Directions and Conclusion

Connectome-guided targeting personalizes the isocenter to each patient's DRT, and optimized dose de-escalation studies designed to minimize hyper- and hyporesponders are anticipated developments in the field. Finally, staged bilateral SRS, which is already showing approximately 80% contralateral control without excess toxicity in small series, may expand options for patients unsuited to DBS.[121] In summary, SRS thalamotomy delivers durable tremor suppression in most medication-refractory patients while avoiding operative morbidity and implanted hardware. Contemporary evidence supports a lower toxicity for SRS compared with focused ultrasound. Ongoing advances in imaging, radiobiology, and delivery will help refine radiosurgery as an important tool for individualized tremor care.

Alzheimer's Disease

AD was initially described in 1906 by the German psychiatrist Alois Alzheimer, who then published the results of an

autopsy study that identified neurofibrillary tangles and plaques.[122] That report initiated an ever-expanding effort to identify the exact reason for the development of these findings. However, the efforts made since then in search of an effective treatment have yielded mixed results. In 2024, it is estimated that nearly 7 million Americans age 65 or older are suffering from AD, with the median lifespan from AD diagnosis to death of 7-10 years.[123,124] It also notably increased healthcare expenditures, not only in direct costs of approximately $384 billion, but also in indirect costs of $413.5 billion, including unpaid caregiving, as well as significant productivity losses.[123] In the future, it is estimated that the number of patients in the United States with AD will more than double and will be responsible for ever-increasing competition for healthcare dollars from governmental, self-pay, and non-reimbursed perspectives.[125] Disappointingly, up to this point, there has been limited progress in stopping or slowing the symptoms of AD.

Pharmaceutical Developments

The pharmaceutical industry has taken an active interest in developing pharmaceuticals addressing AD, with billions of dollars spent to date. Several phase 3 trials are ongoing or have been recently completed, assessing the effectiveness of amyloid−targeting therapies. The monoclonal antibodies aducanumab, donanemab, and lecanemab each target different epitopes or have different binding affinities to the various forms of amyloid beta (Aβ). Aducanumab targets aggregated forms of Aβ, and the EMERGE phase 3 trial demonstrated a statistically significant reduction in clinical decline, whilst a second trial, the ENGAGE phase 3 study, did not replicate this finding.[126] Although the drug was controversially approved by the Food and Drug Administration (FDA) in 2021, it was later discontinued by the manufacturer. Lecanemab targets soluble Aβ protofibrils, which are intermediate structures formed during the aggregation of Aβ peptides that are believed to be toxic. Lecanemab was granted approval by the FDA in 2023 after showing a 27% lower Clinical Dementia Rating-Sum of Boxes in the experimental arm after 18 months in a phase 3 trial.[127] Donanemab targets a modified form of deposited Aβ and received FDA approval in 2024 after results from the TRAILBLAZER-ALZ 2 trial.[128] The primary endpoint of the study, the integrated Alzheimer's Disease Rating Scale, exhibited a 35.1% delay in clinical decline at 76 weeks in the donanemab group compared with the placebo group. Yet, even though the FDA has approved certain drugs, none have demonstrated a significant long-term impact in delaying the progression of AD or overall survival, and only a few have shown a slight slowing of symptoms based on neurocognitive scores when compared to matched cohorts.[129-131]

The pharmaceutical companies and research institutions have taken multiple approaches. They have included targeting various points along the development lines for both amyloid and tau. However, while animal models have demonstrated effectiveness for some of these drugs, this has not translated well to humans, highlighting the multifactorial nature of causation. Despite the disappointing effectiveness of current agents, approved drug therapy is expensive, whereas a short course of radiation therapy, if durably effective and safe, would be cost-effective and readily available in most healthcare systems worldwide.

Origins of the Low-Dose Radiation Concept to Treat Alzheimer's Disease

About 15 years ago, the initial concepts for low-dose radiation as a potential treatment for AD developed from family experience of the disease and curiosity about a peripherally related population of children, namely those with Down syndrome who had received whole-brain irradiation for acute lymphocytic leukemia. It is expected that up to 90% of these children would have developed AD.[132] However, discussion with their treating physicians and review of the literature failed to find any mention of plaques in these children at the time of death. This led to the hypothesis that low-dose radiation therapy might have a beneficial effect on the development of AD plaques.

Initial Studies and Proof of Concept

To test this theory, a series of animal studies was performed using a well-characterized double transgenic mouse model expressing a chimeric mouse/human amyloid precursor protein (Mo/HuAPP695swe) and a mutant human presenilin 1 (PS1-dE9) (APP/PS1) to determine whether radiation could favorably impact the development and/or clearance of amyloid plaques. Utilizing a hemi-brain irradiation technique, which allows for the direct comparison of irradiated and unirradiated brain in the same histological section, initial experiments investigated single doses of 5, 10, and 15 Gy and found a dose-response relationship in the reduction of Aβ plaques (Fig. 2). However, subsequent experiments with fractionated doses showed a greater reduction in plaques as a function of biologically effective dose, providing the first indication that the effect was not classical cell killing, as seen in oncology.[133] From these second-generation hemi-brain experiments, 5 fractions of 2 Gy emerged as a preferred radiation therapy schedule. This was used in subsequent experiments involving whole-brain irradiation in older animals exhibiting significant cognitive deficiencies. Using a standard Morris water maze test, the irradiation resulted in cognitive improvements measured by latency accessing a concealed platform.[133] Furthermore, the improvement in cognition correlated with a reduction in plaque burden confirmed on post-water maze testing histological samples.[133] Later, the same effect on Aβ plaque reduction was demonstrated in the B6;129-Tg(APPSwe,tauP301L)1Lfa Psen1^{tm1Mpm}/Mmjax (3xTg-AD) model, which harbors both amyloid and tau mutations; changes in tau expression were also observed.[134]

Development of a Phase I Trial

After several years of animal model studies, the logical conclusion was to move forward with a single-arm phase 1 clinical trial in patients with moderate AD. After careful

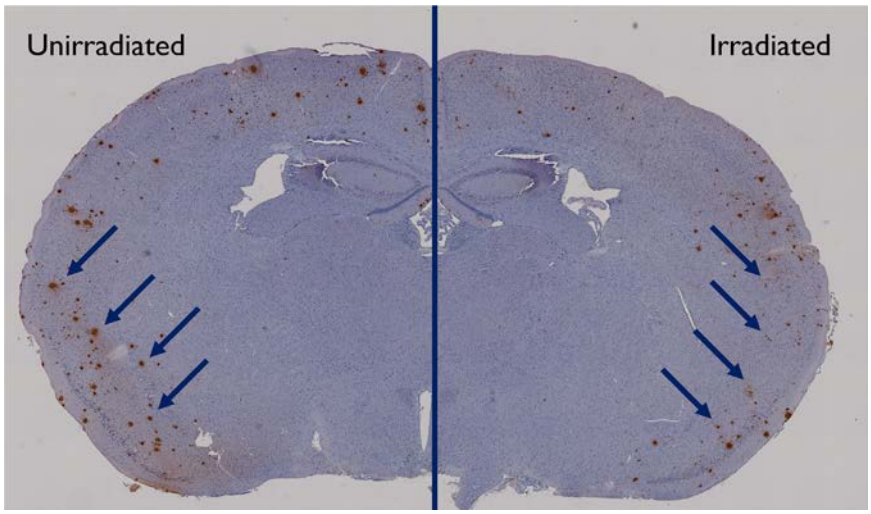

Figure 2 Section of APP/PS1 mouse brain treated with hemi-brain irradiation of 5 × 2 Gy, sacrificed 8 weeks later. Blue arrows highlight the reduction of Aβ plaques in the irradiated hemi-brain.

consideration of the preclinical data and low-dose regimens used in pediatric hematologic cancers for whole-brain prophylactic cranial irradiation with low risk of later malignancy, a dose of 5 × 2 Gy was selected.[135] This AD trial design was shared with several other groups and investigated the optimal irradiation scheme observed in the preclinical studies, which involved 5 × 2 Gy as consecutive fractions administered over a single week.

Unfortunately, the study was terminated due to poor accrual resulting from the challenges of patient recruitment during the COVID-19 outbreak. However, two centers, one in Virginia and one in Geneva, were able to accrue enough patients to allow for neurocognitive testing to be completed for up to 18 months after treatment completion. It appeared that the selected radiation dose had a positive impact on stabilizing or even improving symptoms in patients with early AD.[136]

Expansion of Low-Dose Radiation Therapy Studies

In the intervening years between the original observations and the present day, numerous experimental studies have pursued this line of investigation, demonstrating a spectrum of potentially beneficial effects of low-dose radiation treatment for AD.[134,136-144] Some major questions persist, including what is the optimum dosing schedule, how long does the radiation effect persist, and whether retreatment is possible and efficacious? Several mechanisms have been suggested for the effect of low-dose radiation in this disease and have been reviewed in various publications.[145-148] A definitive mechanism has yet to be identified. It would seem that the effect is pleotropic and may open up opportunities for novel combinations with current and new other available or yet-to-be-developed treatment modalities.

The Implications for Radiation Therapy

The potential of this treatment strategy has obvious ramifications for the radiation oncology community and the manufacturers of linear accelerators. This has led to the formation of a collaborative trial group, comprising multiple centers in Europe and the United States, to develop an international phase 2 clinical trial addressing this opportunity in greater detail. There are frequent and ongoing discussions among members of a multidisciplinary, international steering group. A three-arm trial, which includes observation with standard of care and two separate low-dose irradiation cohorts, enjoys great enthusiasm. The two proposed low-dose dose arms are 5 × 2 Gy delivered consecutively over 5 days or 5 × 0.5 Gy over the same timescale. Additionally, a comparable Korean trial is currently underway.[149] Efforts such as this will help define whether low-dose radiation is effective in slowing the progression of AD, but in the words of Albert Szent-Györgyi, “research is to see what everybody else has seen and to think what nobody else has thought." In many ways, the concept of treating a neurodegenerative disease with radiation falls into this realm, and the potential success would be significant for countless patients and families, and in essence, every healthcare system worldwide.

Psychiatric Disorders

Approaches to understanding and treating psychiatric disorders have evolved throughout history in response to shifting hypotheses of pathophysiology, treatment paradigms, and societal attitudes. Texts from ancient civilizations reveal an appreciation for the biological bases of psychiatric disorders, as Hippocrates proposed that melancholy (from Greek $\mu\acute{\varepsilon}\lambda\alpha\iota\nu\alpha\ \chi o\lambda\acute{\eta}$ (melaina chole), translated as “black bile”) was the result of an imbalance of the 4 bodily humors in 450 BCE.[150,151]

In the late 19th century, various “somatic” approaches to treating psychiatric disorders were developed. By the 1930s, the increasing trend towards hospitalization of patients with these disorders and subsequent severe overcrowding in public institutions opened the door to surgical treatment.[152,153] Egas Moniz, a Portuguese neurologist, partnered with

neurosurgeon Almeida Lima to perform "frontal leucotomies."[154] The reported results were sufficient to spark international interest in this approach, and Moniz was awarded the Nobel Prize in Physiology or Medicine in 1949.[155] Walter Freeman, an American neurologist, worked with neurosurgeon James Watt and altered Moniz' technique to perform "frontal lobotomies."[156]

Neurosurgeons around the world, with enthusiastic support from psychiatrists, continued to modify ablative surgical approaches for patients with mental disorders. The most common diagnoses treated were OCD and schizophrenia.[157] Ultimately, the emergence of neuroleptic medications in the mid-1950s, paired with growing social pressure over abuses in psychiatric surgery, led to its decline.[155] However, a small number of practitioners around the world continued to work on minimally invasive stereotactic procedures for these patients.[158] In fact, the US government-commissioned Belmont Report recommended, in 1979, that psychiatric surgery continue to be offered to select psychiatric patients.[156]

Recent advances in neuroimaging, stereotactic techniques, and ethical frameworks, combined with the persistence of treatment-resistant psychiatric disorders, have renewed interest in alternative therapeutic modalities for neuromodulation.[159-161] Today, FDA-approved indications for invasive intracranial neuromodulation are quite limited.[162] Interventions for other indications remain at an investigational stage, and the role of invasive procedures such as DBS or radiofrequency ablation versus non-invasive methods such as SRS or focused ultrasound remains a subject of debate.[163] Given the historical context and implications of irreversible brain interventions, SRS has correspondingly been studied with great caution. Here, we review the evidence for radiation therapy, SRS in particular, in defined, intractable psychiatric disorders.

Obsessive-Compulsive Disorder

With a lifetime prevalence of 1%-3%, OCD is characterized by obsessions, i.e., intrusive and disturbing thoughts, and/or compulsions, i.e., repetitive and obsessive behaviors.[164-168] In OCD, the cortico-striato-thalamo-cortical loop is dysregulated from hyperactive excitatory pathways and a hypoactive inhibitory pathway.[169] Approximately 30% of patients display an inadequate response to first-line therapies, including cognitive behavioral therapy and serotonin reuptake inhibitors, leading to their evaluation for alternative therapeutic modalities.[170,171] SRS is gaining interest as a treatment option for patients with severe treatment-refractory OCD. The anterior limb of the internal capsule, a hyperactive communicating white matter tract connecting the prefrontal areas and subcortical gray matter, has been investigated as a radiosurgical target since 1951.[172] A recent meta-analysis of 11 studies with 180 patients targeting this area with SRS determined that 60% of patients experienced a substantial improvement in OCD symptoms.[173] Encouragingly, remission was achieved in 18% of patients, and long-term follow-up data showed sustained post-SRS response at a mean of 10.9 years. In a separate 14-patient study, the most common adverse effects were headaches (15%), weight changes (14%), and mood changes (9%), with no significant changes in personality measures.[174]

While the ventral portion of the anterior limb of the internal capsule has emerged as the most studied target to date, additional considerations, such as optimization of dose, refinement of target, and customization for individual neuroanatomical heterogeneity, remain a subject of ongoing discussions to maximize treatment response and minimize adverse effects.[172,175,176] Anterior capsulotomies have been applied with doses ranging from 120 to 200 Gy in 1-4 fractions.[177] Dorsal anterior cingulotomies have also been investigated as alternatives.[175] Though SRS may not reduce the need for medications and psychiatric care, it presents a potential augmentation therapy for patients with severe OCD.[178,179]

Bipolar Disorder

Bipolar disorder (BD) is a mood disorder characterized by cycling episodes of mania or hypomania and depression and has a 1% lifetime prevalence in the United States.[167,180] BD arises from a complex pathophysiology, including disturbances in neuroinflammation, prefrontal and limbic network activity, and neurotransmitter signaling.[181,182] First-line treatments include mood stabilizers and antipsychotics.[183] However, many patients remain symptomatic with response rates around 50% for acute episodes and lower rates for maintenance and bipolar depression, highlighting the limited treatment options for refractory cases.[184] SRS represents an underexplored treatment avenue for treatment-resistant BD. Preliminary studies suggest potential therapeutic relevance through targeted modulation of neural circuits. One investigation utilized non-ablative SRS of 75 Gy targeting the subgenual cingulate cortex in treatment-resistant bipolar depression.[185] Two of 3 patients achieved a clinically significant response at the 6-month point, but their recoveries were complicated by discrete stressful circumstances. Nevertheless, these data suggest that radiosurgical modulation of dysfunctional circuits in BD may offer therapeutic benefits. These patients should only be considered for SRS in the context of a carefully vetted clinical trial.

Major Depressive Disorder

Major depressive disorder (MDD) is a heterogeneous mood disorder defined by at least 2 weeks of depressed mood or anhedonia accompanied by additional symptoms, such as sleep disturbances or suicide ideation.[167,186] Affecting approximately 20% of United States adults, MDD is a leading cause of disability and incurs a high societal burden due to its chronic, recurrent course.[187-189] While its neurobiology remains an area of active investigation, MDD has been associated with dysregulated neurotransmitter signaling, neuroplasticity, and structural and functional changes in multiple cortical and subcortical regions.[190-195] Psychotherapy and monoamine reuptake inhibitors, such as selective serotonin reuptake inhibitors, are the first-line treatments.[196] As the estimated prevalence of treatment-resistant depression is

30%, there is a critical need for novel therapeutic approaches.[197]

Mirroring OCD, SRS for treatment-resistant MDD has been reported for several targets. SRS with 140 Gy has recently been used to target the bilateral anterior limb of the internal capsule in 3 patients with depression.[198] Their depression had been present for over 50 years, and they had active suicidal ideation and were refractory to multiple medications and alternative therapy. Patients 1 and 2 improved from moderate depression scores to no depression and mild depression, respectively. Patient 3 similarly experienced reduced depressive symptoms, as she improved from moderately severe depression to moderate depression. In another study, SRS of 120 Gy was delivered to the anterior cingulate cortex in 5 patients with treatment-resistant MDD.[199] Overall, their depression symptoms improved by 65% at 24 months post-SRS. In a case report, a patient with a 30-year history of treatment-resistant depression and multiple suicide attempts was treated with SRS of 130 Gy targeted to the subcaudate region.[200] The patient's depression went into sustained remission beginning at 4 months post-SRS and continuing to 32 months, and antidepressant medications were discontinued. Importantly, no adverse effects, such as neurological or cognitive deficits, were noted in any of the 9 patients across the 3 studies. Together, these studies show promising outcomes in a small sample size and merit further investigation. As above, SRS remains an investigational treatment only for patients with MDD and must be evaluated alongside other methods of neuromodulation.

Eating Disorders

Eating disorders (EDs) are psychiatric conditions characterized by persistent disturbances in eating patterns and associated emotions. The primary forms include anorexia nervosa, bulimia nervosa, and binge-eating disorder.[201] Lifetime prevalence for all types of EDs is approximately 2%, with a higher rate in females.[202] ED pathophysiology reflects a whole-body disorder characterized by metabolic, endocrine, and neurobiological changes.[203,204] Treatment guidelines for EDs highlight outpatient psychological therapies as first-line interventions, with more severe cases involving nutritional interventions, antidepressant or antipsychotic pharmacotherapy, and multimodal day- and inpatient treatments.[205] Despite these evidence-based approaches, recovery rates remain suboptimal, with 20%-30% of anorexia nervosa and bulimia nervosa patients developing treatment-refractory conditions, driving the need for novel therapeutic interventions.[206]

Emerging evidence suggests that targeted neurosurgical and radiotherapeutic approaches may offer promising avenues for treating severe, treatment-resistant anorexia nervosa. Other neuroablative procedures, such as radiofrequency ablation targeted to the anterior limb of the internal capsule and the anterior cingulate cortex, have demonstrated potential clinical utility.[207-209] However, non-invasive approaches using ionizing radiation have received minimal research attention. A single study of 6 patients with treatment-refractory anorexia nervosa underwent SRS targeted to the bilateral anterior limb of the internal capsule.[199] A mean 40% increase in body mass index 6 months post-SRS was recorded, with sustained weight improvements during the available follow-up. Complementing this, another study demonstrated that progressive ablation of the right caudate nucleus in minipigs using combined SRS led to early changes in eating-related behaviors, including motivation and hedonism, with MRI confirming precise, localized effects.[210] These findings align with advances in stereotactic imaging and treatment planning, which enable high-precision targeting of appetite-regulating regions.[211] These studies agree on the therapeutic potential of targeting neural circuits implicated in anorexia pathophysiology as viable radiosurgical targets for refractory cases.

Substance Use Disorders/Addiction

Substance use disorders, also referred to as drug addictions, are conditions of repeated misuse of a substance to the detriment of health and function.[167] The prevalence of all substance use disorders is estimated to be up to 30%, led by alcohol use disorder at 20% and other drug use disorders at 10%.[212,213] Substance use disorder neurobiology reflects a complex pathophysiological process and results in the dysregulation of the reward pathway. First-line treatment options depend on the specific substance, but pharmacotherapy (if available) combined with psychosocial interventions is the mainstay. Relapse rates are also variable. Studies of patients with opioid use disorder commonly determine a 50% or greater relapse risk within 6 months, with similar rates for alcohol use disorder at follow-up periods of several years.[214-217] New therapeutic modalities are urgently needed to serve these patients better.

In recent decades, neuromodulation has been applied using multiple approaches, such as DBS and radiofrequency ablation.[218] However, the radiofrequency ablation studies were discontinued due to questionable efficacy and poor safety standards.[219-221] Non-invasive modalities, such as transcranial magnetic stimulation targeting the dorsolateral prefrontal cortex and recently low-intensity focused ultrasound targeting the nucleus accumbens, a key node in the reward pathway, are currently in the early stages of clinical trials.[218] Radiosurgery has recently been proposed as another alternative. In a preclinical study, a rat model of alcohol use disorder received SRS with 100 Gy to the nucleus accumbens and showed promising improvements in alcohol preference.[222] Future work in radiosurgery is likely to build on these studies.

Aggression

Aggression, behavior intended to harm others or oneself, can manifest in multiple conditions, including schizophrenia, BD, traumatic brain injury, and intellectual disability, requiring specialized intervention when severe.[223] Aggression is hypothesized to result from the loss of top-down inhibition of the prefrontal cortex over limbic structures, such as the amygdala.[224] Standard treatments combine antipsychotics

with cognitive-behavioral therapy.[225] Acute management typically employs antipsychotics and/or benzodiazepines in combination, though these agents show only small-to-moderate effect sizes for aggression reduction long-term.[226-229]

To date, most research studies on neuromodulation for aggression have focused on other brain stimulation techniques, such as DBS and radiofrequency ablation, for modulating activity in subcortical structures, including the amygdala and nucleus accumbens.[230,231] The capacity of these modalities to reduce unprovoked aggression and enhance impulse control underscores the therapeutic potential of a non-invasive and permanent method like radiosurgery. A study investigated SRS as a follow-up therapy after radiofrequency ablation in 3 patients with autism spectrum disorder with aggressive tendencies.[232] The amygdala was targeted with 24 Gy prescribed to the 50% isodose line, and the anterior cingulate cortex was treated with a maximum dose of 120 Gy. In all 3 patients, aggression scores decreased. These findings collectively suggest that while radiosurgical neuromodulation for aggression is still in its infancy, existing evidence from radiosurgical and other studies supports its further investigation as a next-generation intervention.

Anxiety

Anxiety disorders are a group of conditions characterized by disproportionate levels of fear, anxiety, or avoidance.[233] Together, they are estimated to have a lifetime prevalence of 34%, with higher rates in women than men, and are frequently comorbid with other medical and psychiatric conditions, such as OCD.[168] Multiple brain systems are implicated in anxiety pathophysiology, including the dysfunctional negative valence circuit, which promotes fear generalization via excessive reactivity of the amygdala and impaired top-down inhibition from the prefrontal cortex.[234] First-line therapies include monoamine reuptake inhibitors and cognitive behavioral therapy, but between 35% and 55% of patients do not respond, creating an opportunity for alternative treatments.[233,235]

Radiofrequency ablation capsulotomy has been studied as a treatment for patients with severe, life-limiting, and medically refractory anxiety disorders, with preliminary studies showing efficacy but also a high incidence of frontal lobe syndrome, which is marked by disinhibition, apathy, and impaired executive functioning.[236] However, radiation therapy has not received the same interest. One study involved 7 patients who underwent bilateral SRS capsulotomy with a dose of 120-160 Gy. Five of the 7 patients' anxiety scores improved to a satisfactory degree.[237] In a follow-up study of 11 patients, clinical efficacy criteria were not clearly defined, and the authors noted a high incidence of adverse effects.[238] As in the radiofrequency ablation study, frontal lobe syndrome was observed, and headaches were reported as well. An additional study of ten patients from a separate group treated patients who had multiple psychiatric disorders, but the study was criticized for its lack of rigor in methodology and data reporting.[239-241] As in psychiatric conditions in general, the challenges of treating anxiety disorders with a focal method like radiosurgery may be due to its complex pathophysiology.

Future Directions

Psychosurgery began on dubious grounds nearly a century ago, based on the physiological and anatomical knowledge and surgical techniques of the time. Subsequent decades of biomedical research have advanced our understanding of disease pathology and informed the development of safer, more effective therapies, with modern ethics emphasizing patient autonomy, informed consent, and equitable access to care. However, significant gaps remain for patients with intractable psychiatric disorders. SRS may offer an alternative treatment for some of these patients, pairing the advantages of a non-invasive procedure with stereotactic accuracy. Now guided by connectomics-based imaging approaches, the patient-specific target brain region can be deep within the brain, where the inputs of a neural circuit frequently converge onto a node. Modulation of these nodes can then alter the dynamics of the greater circuit and influence behavior. The dose may be tailored to suit the clinical context, as lower doses can be used for tuning neural activity and higher doses for ablation.[242] However, the limited sample sizes and preliminary nature of existing data underscore the need for larger, controlled studies to establish definitive efficacy and comprehensive safety profiles before clinical implementation can be recommended.

Conclusion

Radiation therapy, and SRS in particular, is a cornerstone in the management of numerous non-malignant central nervous system diseases. This review highlights its current use for treating patients with vestibular schwannomas, AVMs, TN, and ET. These indications are well-established. There is the potential of applying radiation therapy to treat patients with various psychiatric conditions, and even for those with AD. The advancement of these approaches will continue to be based on sound basic and clinical science, and work to date provides us with great optimism regarding these innovative uses of radiation therapy to benefit many patients around the world.

Data availability

No new data were used for the research described in the article.

Conflict of Interest

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CRediT authorship contribution statement

Felix Ehret: Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Investigation, Conceptualization. **Charles Leland Rogers:** Writing – review & editing, Writing – original draft. **James Fontanesi:** Writing – review & editing, Writing – original draft. **George D. Wilson:** Writing – review & editing, Writing – original draft. **Bhargava S. Chitti:** Writing – review & editing, Writing – original draft. **John Starner:** Writing – review & editing, Writing – original draft. **Baho Sidiqi:** Writing – review & editing, Writing – original draft. **Anuj Goenka:** Writing – review & editing, Writing – original draft. **Michael Schulder:** Writing – review & editing, Writing – original draft. **Anna M.E. Bruynzeel:** Writing – review & editing, Writing – original draft. **Joost J.C. Verhoeff:** Writing – review & editing, Writing – original draft. **Alexander C. MacDonagh:** Writing – review & editing, Writing – original draft. **Hannah I. Park:** Writing – review & editing, Writing – original draft. **Helen A. Shih:** Writing – review & editing, Writing – original draft. **Lawrence Kleinberg:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Conceptualization.

References

1. Carlson ML, Link MJ: Vestibular schwannomas. N Engl J Med 384 (14):1335-1348, 2021
2. Price M, Ballard C, Benedetti J, et al: CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2017-2021. Neuro Oncol 26(Supplement_6):vi1-vi85, 2024
3. Asthagiri AR, Parry DM, Butman JA, et al: Neurofibromatosis type 2. Lancet 373(9679):1974-1986, 2009
4. Evans DG, Moran A, King A, et al: Incidence of vestibular schwannoma and neurofibromatosis 2 in the North West of England over a 10-year period: higher incidence than previously thought. Otol Neurotol 26(1):93-97, 2005
5. Matthies C, Samii M: Management of 1000 vestibular schwannomas (acoustic neuromas): clinical presentation. Neurosurgery 40(1):1-9, 1997
6. Goldbrunner R, Weller M, Regis J, et al: EANO guideline on the diagnosis and treatment of vestibular schwannoma. Neuro Oncol 22 (1):31-45, 2020
7. Ehret F, Bhandarkar AR, Chisam M, et al: Stereotactic Radiosurgery for vestibular schwannoma—A case-based practice guide from the radiosurgery society. Pract Radiat Oncol 15:335-346, 2025
8. Tsao MN, Sahgal A, Xu W, et al: Stereotactic radiosurgery for vestibular schwannoma: international stereotactic radiosurgery society (ISRS) practice guideline. J Radiosurg SBRT 5(1):5-24, 2017
9. Balossier A, Sahgal A, Kotecha R, et al: Management of sporadic intracanalicular vestibular schwannomas: A critical review and International Stereotactic Radiosurgery Society (ISRS) practice guidelines. Neuro Oncol 26(3):429-443, 2024
10. Pikis S, Mantziaris G, Kormath Anand R, et al: Stereotactic radiosurgery for Koos grade IV vestibular schwannoma: A multi-institutional study. J Neurosurg 138(2):405-412, 2023
11. Tuleasca C, Kotecha R, Sahgal A, et al: Large vestibular schwannoma treated using a cranial nerve sparing approach with planned subtotal microsurgical resection and stereotactic radiosurgery: meta-analysis and International Stereotactic Radiosurgery Society (ISRS) practice guidelines. J Neurooncol 173:245-262, 2025
12. Santa Maria PL, Shi Y, Gurgel RK, et al: Long-term hearing outcomes following stereotactic radiosurgery in vestibular schwannoma patients—A retrospective cohort study. Neurosurgery 85(4):550-559, 2019
13. Meijer OW, Vandertop WP, Baayen JC, et al: Single-fraction vs. fractionated linac-based stereotactic radiosurgery for vestibular schwannoma: A single-institution study. Int J Radiat Oncol Biol Phys 56 (5):1390-1396, 2003
14. Williams JA: Fractionated stereotactic radiotherapy for acoustic neuromas. Int J Radiat Oncol Biol Phys 54(2):500-504, 2002
15. Marchetti M, Pinzi V, Gemma M, et al: Hypofractionated versus single-session radiosurgery to preserve hearing in patients affected by sporadic vestibular schwannoma: the ACOUNEU randomized clinical trial. Int J Radiat Oncol Biol Phys 123:107-117, 2025
16. Tosi U, Guadix S, An A, et al: Efficacy and comorbidities of hypofractionated and single-dose radiosurgery for vestibular schwannomas: A systematic review and meta-analysis. Neurooncol Pract 8(4):391-404, 2021
17. Sharma M, Papisetty S, Dhawan S, et al: Comparison of stereotactic radiosurgery and hypofractionated radiosurgery for vestibular schwannomas: A meta-analysis of available literature. World Neurosurg 182: e742-e754, 2024
18. Johnson S, Kano H, Faramand A, et al: Long term results of primary radiosurgery for vestibular schwannomas. J Neurooncol 145(2):247-255, 2019
19. Pollock BE, Link MJ, Stafford SL, et al: The risk of radiation-induced tumors or malignant transformation after single-fraction intracranial radiosurgery: results based on a 25-year experience. Int J Radiat Oncol Biol Phys 97(5):919-923, 2017
20. Hasegawa T, Kato T, Ishikawa T, et al: Incidence of rare malignant transformation in vestibular schwannomas treated with stereotactic radiosurgery: A single-institution analysis of 1,061 cases. J Neurooncol 173(3):695-705, 2025
21. Balossier A, Olteanu M, Delsanti C, et al: Dynamics of tumor evolution after Gamma Knife radiosurgery for sporadic vestibular schwannoma: defining volumetric patterns characterizing individual trajectory. Neuro Oncol 27(2):545-556, 2025
22. Régis J, Delsanti C, Roche PH: Editorial: vestibular schwannoma radiosurgery: progression or pseudoprogression? J Neurosurg 127(2):374-379, 2017
23. Pollock BE: Management of vestibular schwannomas that enlarge after stereotactic radiosurgery: treatment recommendations based on a 15 year experience. Neurosurgery 58(2):241-248, 2006
24. Rueß D, Schütz B, Celik E, et al: Pseudoprogression of vestibular schwannoma after stereotactic radiosurgery with Cyberknife(®): proposal for new response criteria. Cancers (5):15, 2023
25. Hayhurst C, Zadeh G: Tumor pseudoprogression following radiosurgery for vestibular schwannoma. Neuro Oncol 14(1):87-92, 2012
26. Windisch PY, Tonn JC, Fürweger C, et al: Clinical results after single-fraction radiosurgery for 1,002 vestibular schwannomas. Cureus 11 (12):e6390, 2019
27. Dhayalan D, Tveiten Ø V, Finnkirk M, et al: Upfront radiosurgery vs a wait-and-scan approach for small- or medium-sized vestibular schwannoma: the V-REX randomized clinical trial. JAMA 330(5):421-431, 2023
28. Bin-Alamer O, Abou-Al-Shaar H, Peker S, et al: Vestibular Schwannoma International Study of active surveillance versus stereotactic radiosurgery: the VISAS Study. Int J Radiat Oncol Biol Phys 120 (2):454-464, 2024
29. Bin-Alamer O, Abou-Al-Shaar H, Peker S, et al: Vestibular Schwannoma Koos Grade I international study of active surveillance versus

stereotactic radiosurgery: the VISAS-K1 study. Neurosurgery 96(1):41-49, 2025
30. Bin-Alamer O, Abou-Al-Shaar H, Peker S, et al: Vestibular Schwannoma Koos Grade II international study of active surveillance versus stereotactic radiosurgery: the VISAS-K2 study. Neurosurgery 96 (1):50-58, 2025
31. Bin-Alamer O, Trifiletti DM, Sheehan JP: Neurologic outcomes in vestibular schwannoma management: comparative analysis of the VISAS and V-REX studies: early treatment likely proves more beneficial. Int J Radiat Oncol Biol Phys 121(2):481-483, 2025
32. Hollosi N-A, Reimers JL, Santacroce A, et al: Reirradiation with stereotactic radiosurgery for vestibular schwannomas - a systematic review and meta-analysis. Clin Transl Radiat Oncol 54, 2025
33. Leksell L: The stereotaxic method and radiosurgery of the brain. Acta Chir Scand 102(4):316-319, 1951
34. Steiner L, Leksell L, Greitz T, et al: Stereotaxic radiosurgery for cerebral arteriovenous malformations. Report of a case. Acta Chir Scand 138 (5):459-464, 1972
35. Schneider BF, Eberhard DA, Steiner LE: Histopathology of arteriovenous malformations after gamma knife radiosurgery. J Neurosurg 87 (3):352-357, 1997
36. Kashba SR, Patel NJ, Grace M, et al: Angiographic, hemodynamic, and histological changes in an animal model of brain arteriovenous malformations treated with Gamma Knife radiosurgery. J Neurosurg 123 (4):954-960, 2015
37. Szeifert GT, Levivier M, Lorenzoni J, et al: Morphological observations in brain arteriovenous malformations after gamma knife radiosurgery. Prog Neurol Surg 27:119-129, 2013
38. Johnson MD, Staarmann B, Zuccarello M: A rational approach to the management of cerebral arteriovenous malformations. World Neurosurg 159:338-347, 2022
39. Solomon RA, Connolly E.S. Jr.: Arteriovenous malformations of the brain. N Engl J Med 376(19):1859-1866, 2017
40. Ondra SL, Troupp H, George ED, et al: The natural history of symptomatic arteriovenous malformations of the brain: A 24-year follow-up assessment. J Neurosurg 73(3):387-391, 1990
41. Brown R.D. Jr, Wiebers DO, Forbes G, et al: The natural history of unruptured intracranial arteriovenous malformations. J Neurosurg 68 (3):352-357, 1988
42. Stapf C, Mast H, Sciacca RR, et al: Predictors of hemorrhage in patients with untreated brain arteriovenous malformation. Neurology 66 (9):1350-1355, 2006
43. Zhu S, Brodin NP, Garg MK, et al: Systematic review and meta-analysis of the dose-response and risk factors for obliteration of arteriovenous malformations following radiosurgery: an update based on the last 20 years of published clinical evidence. Neurosurg Pract 2(1): okab004, 2021
44. Engenhart R, Wowra B, Debus J, et al: The role of high-dose, single-fraction irradiation in small and large intracranial arteriovenous malformations. Int J Radiat Oncol Biol Phys 30(3):521-529, 1994
45. Flickinger JC, Kondziolka D, Maitz AH, et al: An analysis of the dose-response for arteriovenous malformation radiosurgery and other factors affecting obliteration. Radiother Oncol 63(3):347-354, 2002
46. Milano MT, Grimm J, Niemierko A, et al: Single- and multifraction stereotactic radiosurgery dose/volume tolerances of the brain. Int J Radiat Oncol Biol Phys 110(1):68-86, 2021
47. Flickinger JC, Kondziolka D, Lunsford LD, et al: Development of a model to predict permanent symptomatic postradiosurgery injury for arteriovenous malformation patients. Arteriovenous malformation radiosurgery study group. Int J Radiat Oncol Biol Phys 46(5):1143-1148, 2000
48. Shaaban A, Tos SM, Mantziaris G, et al: Repeat single-session stereotactic radiosurgery for cerebral arteriovenous malformations: A systematic review, meta-analysis, and international stereotactic radiosurgery society practice guidelines. Neurosurgery 96(1):29-40, 2025
49. Awad AJ, Walcott BP, Stapleton CJ, et al: Repeat radiosurgery for cerebral arteriovenous malformations. J Clin Neurosci 22(6):945-950, 2015
50. Maesawa S, Flickinger JC, Kondziolka D, et al: Repeated radiosurgery for incompletely obliterated arteriovenous malformations. J Neurosurg 92(6):961-970, 2000
51. Mantziaris G, Pikis S, Dumot C, et al: Outcome evaluation of repeat stereotactic radiosurgery for cerebral arteriovenous malformations. Stroke 54(8):1974-1984, 2023
52. Seymour ZA, Sneed PK, Gupta N, et al: Volume-staged radiosurgery for large arteriovenous malformations: An evolving paradigm. J Neurosurg 124(1):163-174, 2016
53. Pollock BE, Link MJ, Stafford SL, et al: Volume-staged stereotactic radiosurgery for intracranial arteriovenous malformations: outcomes based on an 18-year experience. Neurosurgery 80(4):543-550, 2017
54. Kano H, Kondziolka D, Flickinger JC, et al: Stereotactic radiosurgery for arteriovenous malformations, part 6: multistaged volumetric management of large arteriovenous malformations. J Neurosurg 116 (1):54-65, 2012
55. Marciscano AE, Huang J, Tamargo RJ, et al: Long-term outcomes with planned multistage reduced dose repeat stereotactic radiosurgery for treatment of inoperable high-grade arteriovenous malformations: an observational retrospective cohort study. Neurosurgery 81(1):136-146, 2017
56. Jaikumar V, Rho K, Nobrega N, et al: Hypofractionated radiosurgery for intracranial arteriovenous malformations: A systematic review and meta-analysis. J Neurosurg 143:678-689, 2025
57. Mohr JP, Parides MK, Stapf C, et al: Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): A multicentre, non-blinded, randomised trial. Lancet 383(9917):614-621, 2014
58. Mohr JP, Overbey JR, Hartmann A, et al: Medical management with interventional therapy versus medical management alone for unruptured brain arteriovenous malformations (ARUBA): final follow-up of a multicentre, non-blinded, randomised controlled trial. Lancet Neurol 19(7):573-581, 2020
59. Snyder MH, Chen CJ, Farzad F, et al: Interventional outcomes for patients eligible for entry into the ARUBA clinical trial: A systematic review and meta-analysis. J Neurosurg 137(1):108-120, 2022
60. Bambakidis NC, Cockroft KM, Hirsch JA, et al: The case against a randomized trial of unruptured brain arteriovenous malformations: misinterpretation of a flawed study. Stroke 45(9):2808-2810, 2014
61. Gajjar AA, Goyal AD, Custozzo A, et al: Too late to save: the national surge in ruptured arteriovenous malformations and the decline in endovascular utilization from 2016 to 2022. Interv Neuroradiol 2025:15910199251347794
62. Spetzler RF, Martin NA: A proposed grading system for arteriovenous malformations. J Neurosurg 65(4):476-483, 1986
63. Chen CJ, Ding D, Wang TR, et al: Microsurgery versus stereotactic radiosurgery for brain arteriovenous malformations: A matched cohort study. Neurosurgery 84(3):696-708, 2019
64. Tos SM, Osama M, Mantziaris G, et al: Spetzler-martin grade IV cerebral arteriovenous malformations in adult patients: A propensity-score matched analysis of resection and stereotactic radiosurgery. Neurosurg Rev 48(1):337, 2025
65. Tos SM, Osama M, Mantziaris G, et al: Spetzler-Martin grade I and II cerebral arteriovenous malformations: A propensity-score matched analysis of resection and stereotactic radiosurgery in adult patients. Neurosurg Rev 48(1):276, 2025
66. Tos SM, Hajikarimloo B, Osama M, et al: A comparative analysis of microsurgical resection versus stereotactic radiosurgery for Spetzler-Martin grade III arteriovenous malformations: A multicenter propensity score matched study. Clin Neurol Neurosurg 249, 2025:108669
67. Zhou S, Wang G, Zhou X, et al: A comprehensive meta-analysis on the efficacy of stereotactic radiosurgery versus surgical resection for cerebral arteriovenous malformations. World Neurosurg 191:190-196, 2024
68. Starke RM, Yen CP, Ding D, et al: A practical grading scale for predicting outcome after radiosurgery for arteriovenous malformations: Analysis of 1012 treated patients. J Neurosurg 119(4):981-987, 2013
69. Katusic S, Beard CM, Bergstralh E, et al: Incidence and clinical features of trigeminal neuralgia, Rochester, Minnesota, 1945-1984. Ann Neurol 27(1):89-95, 1990

70. Koopman JS, Dieleman JP, Huygen FJ, et al: Incidence of facial pain in the general population. Pain 147(1−3):122-127, 2009
71. Campbell FG, Graham JG, Zilkha KJ: Clinical trial of carbazepine (tegretol) in trigeminal neuralgia. J Neurol Neurosurg Psychiatry 29 (3):265-267, 1966
72. Zakrzewska JM, Linskey ME: Trigeminal neuralgia. BMJ: Br Med J 348: g474, 2014
73. Maarbjerg S, Di Stefano G, Bendtsen L, et al: Trigeminal neuralgia—diagnosis and treatment. Cephalalgia 37(7):648-657, 2017
74. Lopez BC, Hamlyn PJ, Zakrzewska JM: Systematic review of ablative neurosurgical techniques for the treatment of trigeminal neuralgia. Neurosurgery 54(4):973-983, 2004
75. Kondziolka D, Lunsford LD, Flickinger JC, et al: Stereotactic radiosurgery for trigeminal neuralgia: A multiinstitutional study using the gamma unit. J Neurosurg 84(6):940-945, 1996
76. Romanelli P, Conti A, Bianchi L, et al: Image-guided robotic radiosurgery for trigeminal neuralgia. Neurosurgery 83(5):1023-1030, 2018
77. Dandy WE: Concerning the cause of trigeminal neuralgia. Am J Surg 24(2):447-455, 1934
78. Jannetta PJ: Vascular compression is the cause of trigeminal neuralgia. Am Phys Soc J 2(4):217-227, 1993
79. Spiegel EA, Wycis HT, Marks M, et al: Stereotaxic apparatus for operations on the Human brain. Science 106(2754):349-350, 1947
80. Lindquist C, Kihlström L, Hellstrand E: Functional neurosurgery—A future for the Gamma knife? Stereot Funct Neurosurg 57(1−2):72-81, 1992
81. Régis J, Tuleasca C, Resseguier N, et al: Long-term safety and efficacy of Gamma Knife surgery in classical trigeminal neuralgia: A 497-patient historical cohort study. J Neurosurg JNS 124(4):1079-1087, 2016
82. Romanelli P, Heit G, Chang SD, et al: Cyberknife radiosurgery for trigeminal neuralgia. Stereotact Funct Neurosurg 81(1−4):105-109, 2003
83. Mistry AM, Niesner KJ, Lake WB, et al: Neurovascular compression at the root entry zone correlates with trigeminal neuralgia and early microvascular decompression outcome. World Neurosurg 95:208-213, 2016
84. Hodaie M, Chen DQ, Quan J, et al: Tractography delineates microstructural changes in the trigeminal nerve after focal radiosurgery for trigeminal neuralgia. PLoS One 7, 2012(3):e32745
85. Barker FG, Jannetta PJ, Bissonette DJ, et al: The long-term outcome of microvascular decompression for trigeminal neuralgia. N Eng J Med 334(17):1077-1084, 1996
86. Sheehan J, Pan H-C, Stroila M, et al: Gamma knife surgery for trigeminal neuralgia: outcomes and prognostic factors. J Neurosurg 102 (3):434-441, 2005
87. Romanelli P, Morris D, Jr J, et al: Image-guided robotic radiosurgery. Youmans Neurological Surgery; 2641-2643, 2011
88. Rogers CL, Shetter AG, Fiedler JA, et al: Gamma knife radiosurgery for trigeminal neuralgia: the initial experience of The Barrow Neurological Institute. Int J Radiat Oncol Biol Phys 47(4):1013-1019, 2000
89. Helis CA, Lucas J.T. Jr, Bourland JD, et al: Repeat radiosurgery for trigeminal neuralgia. Neurosurgery 77(5):755-761, 2015
90. Helis CA, McTyre E, Munley MT, et al: Gamma knife radiosurgery for bilateral trigeminal neuralgia. Int J Radiat Oncol Biol Phys 102(3): e433, 2018
91. Ravikumar VK, Parker JJ, Hornbeck TS, et al: Cost-effectiveness of focused ultrasound, radiosurgery, and DBS for essential tremor. Mov Disord 32(8):1165-1173, 2017
92. Fraioli MF, Strigari L, Fraioli C, et al: Preliminary results of 45 patients with trigeminal neuralgia treated with radiosurgery compared to hypofractionated stereotactic radiotherapy, using a dedicated linear accelerator. J Clin Neurosci 19(10):1401-1403, 2012
93. Louis ED, Ottman R: How many people in the USA have essential tremor? Deriving a population estimate based on epidemiological data. Tremor Other Hyperkinet Mov (NY) 4:259, 2014
94. Louis ED, McCreary M: How common is Essential tremor? Update on the worldwide prevalence of essential tremor. Tremor Other Hyperkinet Mov (NY) 11:28, 2021
95. Zesiewicz TA, Elble RJ, Louis ED, et al: Evidence-based guideline update: treatment of essential tremor: report of the Quality Standards subcommittee of the American Academy of Neurology. Neurology 77 (19):1752-1755, 2011
96. Kumar R, Lozano AM, Sime E, et al: Long-term follow-up of thalamic deep brain stimulation for essential and parkinsonian tremor. Neurology 61(11):1601-1604, 2003
97. BUCY PC, CASE TJ: Tremor: physiologic mechanism and abolition by surgical means. Arch Neurol Psychiatry 41(4):721-746, 1939
98. Elias WJ, Huss D, Voss T, et al: A pilot study of focused ultrasound thalamotomy for essential tremor. N Eng J Med 369(7):640-648, 2013
99. Elias WJ, Lipsman N, Ondo WG, et al: A randomized trial of focused ultrasound thalamotomy for essential tremor. N Eng J Med 375 (8):730-739, 2016
100. Duma CM, Jacques DB, Kopyov OV, et al: Gamma knife radiosurgery for thalamotomy in parkinsonian tremor: A five-year experience. J Neurosurg 88(6):1044-1049, 1998
101. Hassler R, Riechert T: Indications and localization of stereotactic brain operations]. Nervenarzt 25(11):441-447, 1954
102. Velasco FC, Molina-Negro P, Bertrand C, et al: Further definition of the subthalamic target for arrest of tremor. J Neurosurg 36(2):184-191, 1972
103. Frighetto L, De Salles A, Wallace R, et al: Linear accelerator thalamotomy. Surg Neurol 62(2):106-113, 2004
104. Fang W, Chen H, Wang H, et al: Essential tremor is associated with disruption of functional connectivity in the ventral intermediate Nucleus—Motor Cortex—Cerebellum circuit. Hu Brain Map 37 (1):165-178, 2016
105. Tuleasca C, Najdenovska E, Régis J, et al: Clinical response to Vim's thalamic stereotactic radiosurgery for essential tremor is associated with distinctive functional connectivity patterns. Acta Neurochirurgica 160(3):611-624, 2018
106. Schreglmann SR, Krauss JK, Chang JW, et al: Functional lesional neurosurgery for tremor: A systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 89(7):717-726, 2018
107. Lim S-Y, Hodaie M, Fallis M, et al: Gamma knife thalamotomy for disabling tremor: A blinded evaluation. Arch Neurol 67(5):584-588, 2010
108. Kondziolka D, Ong JG, Lee JYK, et al: Gamma Knife thalamotomy for essential tremor. J Neurosurg 108(1):111-117, 2008
109. Friedman DP, Goldman HW, Flanders AE, et al: Stereotactic radiosurgical pallidotomy and thalamotomy with the Gamma knife: MR imaging findings with clinical correlation—preliminary experience. Radiology 212(1):143-150, 1999
110. Young RF, Jacques S, Mark R, et al: Gamma knife thalamotomy for treatment of tremor: long-term results. J Neurosurg 93(supplement_3):128-135, 2000
111. Kooshkabadi A, Lunsford LD, Tonetti D, et al: Gamma Knife thalamotomy for tremor in the magnetic resonance imaging era: clinical article. J Neurosurg 118(4):713-718, 2013
112. Cho KR, Kim HR, Im YS, et al: Outcome of gamma knife thalamotomy in patients with an intractable tremor. J Korean Neurosurg Soc 57 (3):192-196, 2015
113. Witjas T, Carron R, Krack P, et al: A prospective single-blind study of Gamma Knife thalamotomy for tremor. Neurology 85(18):1562-1568, 2015
114. Niranjan A, Raju SS, Kooshkabadi A, et al: Stereotactic radiosurgery for essential tremor: retrospective analysis of a 19-year experience. Mov Disord 32(5):769-777, 2017
115. Thomas EM, Walker H, Middlebrooks EH, et al: Frameless MLC-based radiosurgical thalamotomies on the Modern Linear Accelerator Platform - prospective phase I/II clinical trial results. Int J Radiat Oncol Biol Phys 111(3):S100, 2021
116. Khattab MH, Cmelak AJ, Sherry AD, et al: Noninvasive thalamotomy for refractory tremor by frameless radiosurgery. Int J Radiat Oncol Biol Phys 112(1):121-130, 2022
117. Ankrah NK, Thomas EM, Bredel M, et al: Frameless LINAC-based stereotactic radiosurgery is safe and effective for essential and parkinsonian tremor. Int J Radiat Oncol Biol Phys 117(Supplement_2):S173, 2023

118. Horisawa S, Hayashi M, Tamura N, et al: Gamma knife thalamotomy for essential tremor: A retrospective analysis. World Neurosurg 175: e90-e96, 2023
119. Larcipretti ALL, Gomes FC, Udoma-Udofa OC, et al: Radiosurgical thalamotomy for the management of tremors: A systematic review and meta-analysis. Neurol Sci 46(1):79-88, 2025
120. Kondapavulur S, Silva AB, Molinaro AM, et al: A systematic review comparing focused ultrasound surgery with radiosurgery for essential tremor. Neurosurgery 93(3):524-538, 2023
121. Niranjan A, Raju SS, Monaco EA, et al: Is staged bilateral thalamic radiosurgery an option for otherwise surgically ineligible patients with medically refractory bilateral tremor? J Neurosurg 128(2):617-626, 2018
122. Alzheimer A: Uber eine eigenartige erkankung der hirnrinde. Allgemeine Zeitschrift fur Psychiatric Psychisch-Gerichtliche Medizin 64:146-148, 1907
123. Alzheimer's Association, Alzheimer's Disease facts and figures. Available at: https://www.alz.org/alzheimers-dementia/facts-figures, 2025, Accessed July 7, 2025.
124. Brookmeyer R, Corrada MM, Curriero FC, et al: Survival following a diagnosis of Alzheimer disease. Arch Neurol 59(11):1764-1767, 2002
125. Nandi A, Counts N, Broker J, et al: Cost of care for Alzheimer's disease and related dementias in the United States: 2016 to 2060. NPJ Aging 10(1):13, 2024
126. Budd Haeberlein S, Aisen PS, Barkhof F, et al: Two randomized phase 3 studies of Aducanumab in early Alzheimer's disease. J Prev Alzheimers Dis 9(2):197-210, 2022
127. van Dyck CH, Swanson CJ, Aisen P, et al: Lecanemab in early Alzheimer's Disease. N Engl J Med 388(1):9-21, 2023
128. Sims JR, Zimmer JA, Evans CD, et al: Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. JAMA 330(6):512-527, 2023
129. Avgerinos KI, Manolopoulos A, Ferrucci L, et al: Critical assessment of anti-amyloid-beta monoclonal antibodies effects in Alzheimer's disease: A systematic review and meta-analysis highlighting target engagement and clinical meaningfulness. Sci Rep 14, 2024(1):25741
130. Cao W, Zhu B, Liu Z, et al: Comparison of the efficacy of updated drugs for the treatment on the improvement of cognitive function in patients with Alzheimer 's disease: A systematic review and network meta-analysis. Neuroscience 565:29-39, 2025
131. Wu W, Ji Y, Wang Z, et al: The FDA-approved anti-amyloid-beta monoclonal antibodies for the treatment of Alzheimer's disease: A systematic review and meta-analysis of randomized controlled trials. Eur J Med Res 28(1):544, 2023
132. Fortea J, Zaman SH, Hartley S, et al: Alzheimer's disease associated with Down syndrome: A genetic form of dementia. Lancet Neurol 20 (11):930-942, 2021
133. Marples B, McGee M, Callan S, et al: Cranial irradiation significantly reduces beta amyloid plaques in the brain and improves cognition in a murine model of Alzheimer's Disease (AD). Radiother Oncol 118 (1):43-51, 2016
134. Wilson GD, Wilson TG, Hanna A, et al: Low dose brain irradiation reduces amyloid-beta and tau in 3xTg-AD mice. J Alzheimers Dis 75 (1):15-21, 2020
135. Ochs J, Mulhern R: Long-term sequelae of therapy for childhood acute lymphoblastic leukaemia. Baillieres Clin Haematol 7(2):365-376, 1994
136. Rogers CL, Lageman SK, Fontanesi J, et al: Low-dose whole brain radiation therapy for Alzheimer's dementia: results from a pilot trial in humans. Int J Radiat Oncol Biol Phys 117(1):87-95, 2023
137. Ceyzeriat K, Tournier BB, Millet P, et al: Low-dose radiation therapy reduces amyloid load in young 3xTg-AD mice. J Alzheimers Dis 86 (2):641-653, 2022
138. Ceyzeriat K, Zilli T, Fall AB, et al: Treatment by low-dose brain radiation therapy improves memory performances without changes of the amyloid load in the TgF344-AD rat model. Neurobiol Aging 103:117-127, 2021
139. Ceyzeriat K, Zilli T, Millet P, et al: Low-dose brain irradiation normalizes TSPO and CLUSTERIN levels and promotes the non-amyloidogenic pathway in pre-symptomatic TgF344-AD rats. J Neuroinflammation 19(1):311, 2022
140. Garibotto V, Frisoni GB, Zilli T: Re: cranial irradiation significantly reduces beta amyloid plaques in the brain and improves cognition in a murine model of Alzheimer's Disease (AD). Radiother Oncol 118 (3):577-578, 2016
141. Iacono D, Murphy EK, Avantsa SS, et al: Reduction of pTau and APP levels in mammalian brain after low-dose radiation. Sci Rep 11 (1):2215, 2021
142. Kim S, Chung H, Ngoc Mai H, et al: Low-dose ionizing radiation modulates microglia phenotypes in the models of Alzheimer's disease. Int J Mol Sci 21, 2020(12)
143. Kim S, Nam Y, Kim C, et al: Neuroprotective and anti-inflammatory effects of low-moderate dose ionizing radiation in models of Alzheimer's disease. Int J Mol Sci 21, 2020(10)
144. Yang EJ, Kim H, Choi Y, et al: Modulation of neuroinflammation by low-dose radiation therapy in an animal model of Alzheimer's disease. Int J Radiat Oncol Biol Phys 111(3):658-670, 2021
145. Ceyzeriat K, Tournier BB, Millet P, et al: Low-dose radiation therapy: A new treatment strategy for Alzheimer's disease? J Alzheimers Dis 74 (2):411-419, 2020
146. Chung M, Rhee HY, Chung WK: Clinical approach of low-dose whole-brain ionizing radiation treatment in Alzheimer's disease dementia patients. J Alzheimers Dis 80(3):941-947, 2021
147. Kaul D, Ehret F, Roohani S, et al: Radiation therapy in Alzheimer's Disease: A systematic review. Int J Radiat Oncol Biol Phys 119(1):23-41, 2024
148. Wilson GD, Rogers CL, Mehta MP, et al: The rationale for radiation therapy in Alzheimer's disease. Radiat Res 199(5):506-516, 2023
149. Kim DY, Kim JS, Seo YS, et al: Evaluation of efficacy and safety using low dose radiation therapy with Alzheimer's disease: A protocol for multicenter Phase II clinical trial. J Alzheimers Dis 95(3):1263-1272, 2023
150. Bloch S (ed). Foundations of clinical psychiatry (4th ed.): Melbourne, Australia: Melbourne University Publishing Ltd; 2017.
151. Fornaro M, Clementi N, Fornaro P: Medicine and psychiatry in Western culture: ancient Greek myths and modern prejudices. Ann Gen Psychiatry 8:21, 2009
152. Coffey RJ, Caroff SN: Neurosurgery for mental conditions and pain: an historical perspective on the limits of biological determinism. Surg Neurol Int 15:479, 2024
153. Galante J, Schulder M: The proud history of psychosurgery in the USA. Acta Neurochir Suppl 128:161-167, 2021
154. Mahoney DE, Green AL: Psychosurgery: history of the neurosurgical management of psychiatric disorders. World Neurosurg 137:327-334, 2020
155. Feldman RP, Goodrich JT: Psychosurgery: A historical overview. Neurosurgery 48(3):647-657, 2001
156. Lichterman BL, Schulder M, Liu B, et al: A comparative history of psychosurgery. Prog Brain Res 270(1):1-31, 2022
157. Leiphart JW, Valone F.H. 3rd: Stereotactic lesions for the treatment of psychiatric disorders. J Neurosurg 113(6):1204-1211, 2010
158. Neurosurgical treatment in psychiatry, pain, and epilepsy. In: Proceedings of the Fourth World Congress of Psychiatric Surgery. Baltimore: University Park Press, 1975.
159. Siddiqi SH, Schaper F, Horn A, et al: Brain stimulation and brain lesions converge on common causal circuits in neuropsychiatric disease. Nat Hum Behav 5(12):1707-1716, 2021
160. Chandler JA, Cabrera LY, Doshi P, et al: International legal approaches to neurosurgery for psychiatric disorders. Front Hum Neurosci 14, 2020:588458
161. Mayles P, Nahum A, Rosenwald JC: Handbook of radiotherapy physics. Taylor & Francis Group, 2007.
162. Ranjan M, Mahoney J.J. 3rd, Rezai AR: Neurosurgical neuromodulation therapy for psychiatric disorders. Neurotherapeutics 21, 2024(3): e00366
163. Müller S, van Oosterhout A, Bervoets C, et al: Concerns about psychiatric neurosurgery and how they can Be overcome: recommendations for responsible research. Neuroethics 15(1):6, 2022
164. Grant JE: Clinical practice: obsessive-compulsive disorder. N Engl J Med 371(7):646-653, 2014

165. Ruscio AM, Stein DJ, Chiu WT, et al: The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. Mol Psychiatry 15(1):53-63, 2010
166. Kalra SK, Swedo SE: Children with obsessive-compulsive disorder: Are they just "little adults"? J Clin Invest 119(4):737-746, 2009
167. Association AP: Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). American Psychiatric Association, 2013.
168. Goodman WK, Grice DE, Lapidus KA, et al: Obsessive-compulsive disorder. Psychiatr Clin North Am 37(3):257-267, 2014
169. Goodman WK, Storch EA, Sheth SA: Harmonizing the neurobiology and treatment of Obsessive-compulsive disorder. Am J Psychiatry 178 (1):17-29, 2021
170. Pittenger C, Bloch MH: Pharmacological treatment of obsessive-compulsive disorder. Psychiatr Clin North Am 37(3):375-391, 2014
171. Fineberg NA, Hollander E, Pallanti S, et al: Clinical advances in obsessive-compulsive disorder: A position statement by the International College of Obsessive-Compulsive Spectrum Disorders. Int Clin Psychopharmacol 35(4):173-193, 2020
172. Miguel EC, Lopes AC, McLaughlin NCR, et al: Evolution of gamma knife capsulotomy for intractable obsessive-compulsive disorder. Mol Psychiatry 24(2):218-240, 2019
173. Gupta R, Chen JW, Hughes NC, et al: Benefits of stereotactic radiosurgical anterior capsulotomy for obsessive-compulsive disorder: A meta-analysis. J Neurosurg 141(2):394-405, 2024
174. Paiva RR, Batistuzzo MC, McLaughlin NC, et al: Personality measures after gamma ventral capsulotomy in intractable OCD. Prog Neuropsychopharmacol Biol Psychiatry 81:161-168, 2018
175. Brown LT, Mikell CB, Youngerman BE, et al: Dorsal anterior cingulotomy and anterior capsulotomy for severe, refractory obsessive-compulsive disorder: A systematic review of observational studies. J Neurosurg 124(1):77-89, 2016
176. McLaughlin NCR, Magnotti JF, Banks GP, et al: Gamma knife capsulotomy for intractable OCD: neuroimage analysis of lesion size, location, and clinical response. Transl Psychiatry 13(1):134, 2023
177. Sadashiva N, Tripathi M, De Salles A: Contemporary role of stereotactic radiosurgery for psychiatric disorders. Neurol India 71(Supplement):S31-s38, 2023
178. Rück C, Larsson JK, Mataix-Cols D, et al: A register-based 13-year to 43-year follow-up of 70 patients with obsessive-compulsive disorder treated with capsulotomy. BMJ Open 7, 2017(5):e013133
179. Pepper J, Hariz M, Zrinzo L: Deep brain stimulation versus anterior capsulotomy for obsessive-compulsive disorder: A review of the literature. J Neurosurg 122(5):1028-1037, 2015
180. Merikangas KR, Jin R, He JP, et al: Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch Gen Psychiatry 68(3):241-251, 2011
181. Carvalho AF, Firth J, Vieta E: N Engl J Med 383(1):58-66, 2020
182. Magioncalda P, Martino M: A unified model of the pathophysiology of bipolar disorder. Mol Psychiatry 27(1):202-211, 2022
183. Vieta E, Berk M, Schulze TG, et al: Bipolar disorders. Nat Rev Dis Primers 4, 2018:18008
184. Fountoulakis KN: Refractoriness in bipolar disorder: definitions and evidence-based treatment. CNS Neurosci Ther 18(3):227-237, 2012
185. Solvason HB, Marianayagam NJ, Soltys SG, et al: Treatment of refractory bipolar depression with stereotactic radiosurgery targeting the subgenual cingulate cortex. Cureus 16, 2024(4):e57904
186. Tseng VWS, Tharp JA, Reiter JE, et al: Identifying a stable and generalizable factor structure of major depressive disorder across three large longitudinal cohorts. Psychiatry Res 333, 2024:115702
187. Brody DJ, Pratt LA, Hughes JP: Prevalence of depression among adults aged 20 and over: united States, 2013-2016. NCHS Data Brief (303):1-8, 2018
188. Hasin DS, Sarvet AL, Meyers JL, et al: Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. JAMA Psychiatry 75(4):336-346, 2018
189. Kessler RC: The costs of depression. Psychiatr Clin North Am 35(1):1-14, 2012
190. Fries GR, Saldana VA, Finnstein J, et al: Molecular pathways of major depressive disorder converge on the synapse. Mol Psychiatry 28 (1):284-297, 2023
191. Tassone VK, Demchenko I, Salvo J, et al: Contrasting the amygdala activity and functional connectivity profile between antidepressant-free participants with major depressive disorder and healthy controls: A systematic review of comparative fMRI studies. Psychiatry Res Neuroimaging 325, 2022:111517
192. Ho TC, Gutman B, Pozzi E, et al: Subcortical shape alterations in major depressive disorder: findings from the ENIGMA major depressive disorder working group. Hum Brain Mapp 43(1):341-351, 2022
193. Winter NR, Leenings R, Ernsting J, et al: Quantifying deviations of brain structure and function in major depressive disorder across neuroimaging modalities. JAMA Psychiatry 79(9):879-888, 2022
194. Brown SSG, Rutland JW, Verma G, et al: Structural MRI at 7T reveals amygdala nuclei and hippocampal subfield volumetric association with Major Depressive Disorder symptom severity. Sci Rep 9, 2019 (1):10166
195. Sacher J, Neumann J, Fünfstück T, et al: Mapping the depressed brain: A meta-analysis of structural and functional alterations in major depressive disorder. J Affect Disord 140(2):142-148, 2012
196. Simon GE, Moise N, Mohr DC: Management of depression in adults: A review. JAMA 332(2):141-152, 2024
197. Zhdanava M, Pilon D, Ghelerter I, et al: The prevalence and national burden of treatment-resistant depression and major depressive disorder in the United States. J Clin Psychiatry 82, 2021(2)
198. Khattab MH, Sherry AD, Devan SP, et al: Noninvasive capsulotomy for refractory depression by frameless stereotactic radiosurgery. Int J Radiat Oncol Biol Phys 113(5):960-966, 2022
199. Martínez-Álvarez R, Torres-Diaz C: Modern Gamma Knife radiosurgery for management of psychiatric disorders. Prog Brain Res 270 (1):171-183, 2022
200. Park SC, Lee JK, Kim CH, et al: Gamma-knife subcaudate tractotomy for treatment-resistant depression and target characteristics: A case report and review. Acta Neurochir 159(1):113-120, 2017
201. Crone C, Fochtmann LJ, Attia E, et al: The American Psychiatric Association Practice guideline for the treatment of patients with eating disorders. Am J Psychiatry 180(2):167-171, 2023
202. Qian J, Wu Y, Liu F, et al: An update on the prevalence of eating disorders in the general population: A systematic review and meta-analysis. Eat Weight Disord 27(2):415-428, 2022
203. Skowron K, Kurnik-Łucka M, Dadaski E, et al: Backstage of eating disorder-about the biological mechanisms behind the symptoms of anorexia Nervosa. Nutrients 12, 2020(9)
204. Frank GKW, Shott ME, Stoddard J, et al: Association of brain reward response with body mass index and ventral striatal-hypothalamic circuitry among young women with eating disorders. JAMA Psychiatry 78(10):1123-1133, 2021
205. Himmerich H, Lewis YD, Conti C, et al: World Federation of Societies of Biological Psychiatry (WFSBP) guidelines update 2023 on the pharmacological treatment of eating disorders. World J Biol Psychiatry 1-64, 2023
206. Bryson C, Douglas D, Schmidt U: Established and emerging treatments for eating disorders. Trends Mol Med 30(4):392-402, 2024
207. Guerrero Alzola F, Casas Rivero J, Martínez-Álvarez R: Stereotactic surgery on a female patient with severe chronic anorexia nervosa: 10-year follow-up. Eat Weight Disord 25(6):1827-1831, 2020
208. Wang F, Liu W, Paerhati H, et al: Weight restoration in patients with anorexia nervosa after stereotactic surgery and brain morphometric insights. BMC Psychiatry 25(1):474, 2025
209. Liu W, Li D, Sun F, et al: Long-term follow-up study of MRI-guided bilateral anterior capsulotomy in patients with refractory anorexia nervosa. Neurosurgery 83(1):86-92, 2018
210. Coquery N, Adam JF, Nemoz C, et al: Locomotion and eating behavior changes in Yucatan minipigs after unilateral radio-induced ablation of the caudate nucleus. Sci Rep 9, 2019(1):17082
211. Gorgulho AA, Pereira JL, Krahl S, et al: Neuromodulation for eating disorders: obesity and anorexia. Neurosurg Clin N Am 25(1):147-157, 2014
212. Mojtabai R: Estimating the prevalence of substance use disorders in the US using the benchmark multiplier method. JAMA Psychiatry 79 (11):1074-1080, 2022

213. Grant BF, Goldstein RB, Saha TD, et al: Epidemiology of DSM-5 Alcohol use disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions III. JAMA Psychiatry 72(8):757-766, 2015
214. Rudolph KE, Williams NT, Goodwin ATS, et al: Buprenorphine & methadone dosing strategies to reduce risk of relapse in the treatment of opioid use disorder. Drug Alcohol Depend 239, 2022:109609
215. Lee JD, Nunes E.V. Jr, Novo P, et al: Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): A multicentre, open-label, randomised controlled trial. Lancet 391(10118):309-318, 2018
216. Timko C, Schultz NR, Cucciare MA, et al: Retention in medication-assisted treatment for opiate dependence: A systematic review. J Addict Dis 35(1):22-35, 2016
217. Fleury MJ, Djouini A, Huỳnh C, et al: Remission from substance use disorders: A systematic review and meta-analysis. Drug Alcohol Depend 168:293-306, 2016
218. Mehta DD, Praecht A, Ward HB, et al: A systematic review and meta-analysis of neuromodulation therapies for substance use disorders. Neuropsychopharmacology 49(4):649-680, 2024
219. Gao G, Wang X, He S, et al: Clinical study for alleviating opiate drug psychological dependence by a method of ablating the nucleus accumbens with stereotactic surgery. Stereotact Funct Neurosurg 81(1−4):96-104, 2003
220. Fang J, Gu JW, Yang WT, et al: Clinical observation of physiological and psychological reactions to electric stimulation of the amygdaloid nucleus and the nucleus accumbens in heroin addicts after detoxification. Chin Med J 125(1):63-66, 2012
221. Ma S, Zhang C, Yuan TF, et al: Neurosurgical treatment for addiction: lessons from an untold story in China and a path forward. Natl Sci Rev 7(3):702-712, 2020
222. Sozer A, Sahin MC, Sozer B, et al: Radioneuromodulation of nucleus accumbens for addiction: the first animal study. World Neurosurg 191:e779-e791, 2024
223. Lane SD, Kjome KL, Moeller FG: Neuropsychiatry of aggression. Neurol Clin 29(1):49-64, 2011. vii
224. Siever LJ: Neurobiology of aggression and violence. Am J Psychiatry 165(4):429-442, 2008
225. Lee AH, DiGiuseppe R: Anger and aggression treatments: A review of meta-analyses. Curr Opin Psychol 19:65-74, 2018
226. Bak M, Weltens I, Bervoets C, et al: The pharmacological management of agitated and aggressive behaviour: A systematic review and meta-analysis. Eur Psychiatry 57:78-100, 2019
227. Hirsch S, Steinert T: The use of rapid tranquilization in aggressive behavior. Dtsch Arztebl Int 116(26):445-452, 2019
228. Correll CU, Yu X, Xiang Y, et al: Biological treatment of acute agitation or aggression with schizophrenia or bipolar disorder in the inpatient setting. Ann Clin Psychiatry 29(2):92-107, 2017
229. van Schalkwyk GI, Beyer C, Johnson J, et al: Antipsychotics for aggression in adults: A meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry 81:452-458, 2018
230. Hoppe S, Harat M, Martin CR, Preedy VR, Patel VB: Martin CR, Preedy VR, Patel VB, editors. Treating aggression, in handbook of anger, aggression, and violence 1901-1923, 2023. Editors.
231. Gouveia FV, Germann J, Devenyi GA, et al: Bilateral amygdala radiofrequency ablation for refractory aggressive behavior alters local cortical thickness to a pattern found in non-refractory patients. Front Hum Neurosci 15, 2021:653631
232. Torres CV, Martínez N, Ríos-Lago M, et al: Surgery and radiosurgery in autism: A retrospective study in 10 patients. Stereotact Funct Neurosurg 99(6):474-483, 2021
233. Szuhany KL, Simon NM: Anxiety disorders: A review. JAMA 328(24):2431-2445, 2022
234. Akiki TJ, Jubeir J, Bertrand C, et al: Neural circuit basis of pathological anxiety. Nat Rev Neurosci 26(1):5-22, 2025
235. Bystritsky A: Treatment-resistant anxiety disorders. Mol Psychiatry 11(9):805-814, 2006
236. Rück C, Andréewitch S, Flyckt K, et al: Capsulotomy for refractory anxiety disorders: long-term follow-up of 26 patients. Am J Psychiatry 160(3):513-521, 2003
237. Mindus P, Bergström K, Levander SE, et al: Magnetic resonance images related to clinical outcome after psychosurgical intervention in severe anxiety disorder. J Neurol Neurosurg Psychiatry 50(10):1288-1293, 1987
238. Kihlström L, Guo WY, Lindquist C, et al: Radiobiology of radiosurgery for refractory anxiety disorders. Neurosurgery 36(2):294-302, 1995
239. Valle Rd, Anda Sd, Garnica R, et al: Radiocirugía Psiquiátrica con Gamma Knife. Salud Mental 29, 2006(1)
240. Lévêque M, Carron R, Régis J: Radiosurgery for the treatment of psychiatric disorders: A review. World Neurosurg 80(3−4):S32.e1-S32.e9, 2013
241. Kwinta R, Kopcik K, Koberling A: Gamma knife radiosurgery in psychiatry: A review. Eur J Transl Clin Med 7(1):87-96, 2024
242. Schneider MB, Walcott B, Adler J.R. Jr: Neuromodulation via focal radiation: Radiomodulation update. Cureus 13, 2021(4):e14700