Stereotactic amygdalotomy in the management of severe aggressive behavioral disorders

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Object. Stereotactic amygdalotomy has been utilized as a surgical treatment for severe aggressive behavioral disorders. Several clinical studies have been reported since the first description of the procedure. In the current study, the authors reviewed the literature and evaluated the surgical results, neuropsychological outcome, and complication rate in patients who had undergone stereotactic amygdalotomy for severe aggressive behavioral disorders.

Methods. The PubMed database was searched using the following terms: "amygdalotomy," "amygdalectomy," "amygdaloidectomy," "psychosurgery," "aggressive disorder," and "behavioral disorder." Clinical series with more than 5 patients undergoing stereotactic amygdalotomy for aggressive or other behavioral disorders were included in this review. The surgical technique, anatomical target, improvement in psychiatric symptomatology, postoperative employment and social rehabilitation, postoperative neurocognitive function, procedure-related complications, and long-term follow-up were evaluated.

Results. Thirteen clinical studies met our inclusion criteria. Reported postoperative improvement in aggressive behavior varied between 33 and 100%. Procedure-related complication rates ranged from 0 to 42%, whereas the mortality rate was as high as 3.8%. In the majority of the reviewed clinical series, the performance of stereotactic amygdalotomy did not compromise a patient's learning, language, and intellectual capabilities. The long-term follow-up, although very limited, revealed that initially observed improvement was maintained in most cases.

Conclusions. Stereotactic amygdalotomy can be considered a valid surgical treatment option for carefully selected patients with medically refractory aggressive behavioral disorders. Recent advances in imaging and stereotactic navigation can further improve outcome and minimize the complication rate associated with this psychosurgical procedure. (DOI: 10.3171/FOC/2008/25/7/E6)

KEY WORDS • aggressive behavioral disorder • amygdalotomy • complication • outcome • stereotaxy

THE hippocampus and medial temporal structures have been considered major components of the limbic lobe since its original description by Broca in 1878.⁶ From the beginning it was postulated that structures of the limbic lobe were not exclusively or even primarily olfactory in function but instead were implicated in the formation of emotions and behavior.²³ Friedrich Goltz¹¹ first reported in 1892 that the removal of the temporal lobe in dogs made them calmer and more tame. Later, Klüver and Bucy,¹⁹ Thomson and Walker,⁴² and Schreiner and Kling^{35–37} also demonstrated in monkeys and cats that a temporal lobectomy and amygdalectomy had a taming effect. Terzian and Ore⁴¹ confirmed these findings by showing the same taming effect in humans following temporal cortical structure and amygdala removal.

Over the next decades, there was increasing evidence that the amygdaloid nucleus was a dominant component of

the basolateral limbic circuit and actively involved in the development of aggressive behavior.²³ Ursin⁴³ demonstrated in experimental animal studies that electrical stimulation of the amygdala could provoke organized affective reactions. Based on these observations, Narabayashi et al.³² described a clinical series of 60 patients who had undergone stereotactic amygdalotomy for severe aggressive behavior. Since that initial report, there have been > 500 reported cases of stereotactic amygdalotomy for various behavioral disturbances and epilepsy, with varying results.^{10,12,13,15,18,20,21,26,27,30,31,39} Different surgical approaches have involved various stereotactic devices and modalities for amygdaloid nucleus destruction, such as the injection of alcohol, oil, kaolin, or wax; cryoprobe lesioning; mechanical destruction; diathermy loop; and radiofrequency lesioning.^{1,9,12,14,16,20,25,38} During the past 3 decades, however, advances in neuropharmacology along with the practical banning of psychosurgery have led to a significant decrease in the number of amygdalotomies performed around the world.

Abbreviations used in this paper: EEG = electroencephalography; PEG = pneumoencephalography.

In the current study, we reviewed the pertinent literature while focusing on the role of stereotactic amygdalotomy in the management of aggressive behavioral disorders, the surgical technique of stereotactic amygdalotomy, procedure-related complications, and clinical and neuropsychological outcomes.

Methods

An extensive search of the PubMed medical database was performed using the terms “amygdalotomy,” “amygdalectomy,” “amygdalectomy,” “psychosurgery,” “aggressive disorder,” and “behavioral disorder.” Retrieved articles were carefully screened for series of patients undergoing stereotactic amygdalotomy for either a behavioral disorder alone or behavioral and epilepsy disorders combined. Clinical series with > 5 patients undergoing stereotactic amygdalotomy for aggressive or other behavioral disorders were included in our review, whereas miniseries (4 patients) and case reports were excluded. Clinical series of patients undergoing stereotactic amygdalotomy exclusively for epilepsy without concomitant behavioral symptomatology were also excluded from our study. We attempted to identify the repetition of clinical series reported in different journals; only the original clinical series were included in our study. Note, however, that this task was not easy, and the reader must be aware of potential redundancies in the reported data.

We evaluated preoperative imaging and surgical planning, the use or exclusion of additional intraoperative electrophysiological monitoring, the surgical technique, the exact anatomical target, observed procedure-related complications, the reported response of preoperative psychiatric symptomatology, postoperative employment and social rehabilitation, postoperative neurocognitive function, and long-term follow-up data whenever available.

Results

Eighteen clinical series met our inclusion criteria; however, only 13 were finally included in our review, because the remaining 5 studies consisted of presenting cases that had been included in a previous series. The number of patients, indication for undergoing stereotactic amygdalotomy, surgical technique, observed complications, and immediate and long-term outcome rates are summarized in Table 1.

In their original clinical series consisting of 60 patients with marked behavior disturbances (such as hyperexcitability, assaultive behavior, or violent aggressiveness) treated with bilateral stereotactic amygdalotomy, Narabayashi and colleagues³² reported that 51 (85%) of 60 patients demonstrated a marked reduction in emotional excitability and normalization of social behavior and adaptation postoperatively. These authors routinely performed the surgical procedures in patients in a state of general endotracheal anesthesia. Pneumoencephalography was used for anatomical target localization, whereas intraoperative depth EEG and olfactory stimulation were utilized for physiological confirmation of the target. A stereotactic apparatus devised by the authors was used in all of their cases. The lateral group of amygdaloid nuclei was routinely targeted in their series,

and a lesion 8–10 mm in diameter was created by injecting 0.6–0.8 ml of a mixture of lipiodol, oil, and wax. In a follow-up study,³³ the authors reported that follow-up data were available for only 40 patients from the original series. They found that 27 of these patients (67.5%) continued to have marked and relatively satisfactory improvement in behavior, maintaining the calming and taming effect of bilateral stereotactic amygdalotomy ~ 3 years afterward. They also found that younger patients (between 5 and 13 years of age) had better long-term outcomes than older patients. In a later follow-up study, Narabayashi³⁰ reported that among patients undergoing bilateral stereotactic amygdalotomy, those who most benefited from treatment of their behavioral and emotional disturbances also experienced improvement in any coexistent epileptic traits.

During this same period, in 1966, Chitanondh⁷ described a stereotactic amygdalotomy involving a slightly different technique. The procedure was performed after applying a local anesthetic. A bur hole was placed 3 cm lateral to the midline and 1 cm anterior to the interaural line. Target localization was performed with contrast ventriculography. The target was placed in the medial half of the amygdaloid nuclear complex. Verification of the anatomical target was achieved by performing EEG and amygdalography via a stereotactically inserted needle. Chitanondh reported on a series of 7 patients: 3 with olfactory seizures, 2 with schizophrenia including olfactory hallucinations, 1 with post-traumatic personality disorder with olfactory hallucinations, and 1 with an obsessive-compulsive habit of smelling. Interestingly, he reported significant postoperative behavioral improvement and resolution of preoperative EEG abnormalities in all of the patients. Lesions were formed by injecting 1 ml of a mixture of olive oil, white bee wax, and strong iodized oil, and these stereotactic lesions served as a means of mechanical blocking.

Also in 1966, Heimbürger and associates¹³ described a series of 25 patients undergoing stereotactic amygdalotomy for behavioral abnormalities, epilepsy, and major depression. Procedures were performed after applying a local anesthetic while carefully tracking the emotional and neurological responses of the patient throughout the procedure. This study differed from others in that the operative technique was slightly different and target localization was solely anatomical. The use of PEG or ventriculography with positive contrast medium allowed for target localization, whereas a cryoprobe was used to create lesions. The cryoprobe was stereotactically introduced through a 3-mm twist drill skull opening into the amygdaloid nucleus complex. The anatomical target averaged 2.0 cm lateral to the midline, 1.0 cm below the intercommissural line, and 45% posterior to the anterior commissure along the intercommissural line. The center of the lesion was placed in the anteromedial part of the amygdala. The tip of the cryoprobe was gradually cooled over 5 minutes to (120°C, and this temperature was maintained for 3 minutes. A second lesion was usually produced using the same technique. Later, however, this method was abandoned, and the cryoprobe-created lesions were replaced with mechanical lesions, which were more precise from an anatomical standpoint and had a smaller volume.³⁹ Heimbürger and colleagues¹³ reported that 35% of their patients became free of any behavioral abnormalities and that 45% of them had significant improvement.

TABLE 1
Literature review of clinical series on stereotactic amygdalotomy.*

Authors & Year	No. of Patients	Reason for Surgery	Preop Imaging	Intraop Electrophysiological Study	Surgical Procedure	Exact Anatomical Target	Complications	% Immediate Improvement	Long-Term Outcome
Chitanondh, 1966	85	aggressive behavioral disorders	contrast ventriculography	EEG recording & stimulation study	lesioning by injecting mixture of oil, wax, & iodized oil	medial amygdala	none	100	NA
Heimburger et al., 1966	20	aggressive behavioral disorders	air or contrast ventriculography	no monitoring	lesioning by cryoprobe	anteromedial amygdala	none	75	NA
Narabayashi & Uno, 1966	98	aggressive behavior w/ or w/o epilepsy	PEG	EEG recording & stimulation study	Narabayashi stereotactic device, lesioning by injecting mixture of oil, wax, & lipiodol	lat amygdala	1 case Kliver-Bucy syndrome	85	3-yr data in 40 patients: 67.5% maintained improvement
Vaernet, 1972	45	psychomotor epilepsy & aggressive behavioral disorders	PEG	EEG recording & stimulation study	Leksell stereotactic device, lesioning by electrocoagulation	NA	none	100, in preop behavioral symptoms	NA
Hitchcock & Cairns, 1973	18	aggressive behavioral disorders	NA	EEG recording & stimulation study	lesioning by thermocoagulation	medial amygdala	none	33, in preop behavioral symptoms	NA
West, 1973	7	psychomotor epilepsy & aggressive behavioral disorders	PEG	EEG recording & stimulation study	Leksell stereotactic device, lesioning by electrocoagulation	NA	increased libido in 42.8% cases, increased body weight in 14.2%, recent memory deficit in 14.2%	71.4, in preop behavioral symptoms	NA
Balasubramaniam & Kanaka, 1975 ¹	10	infantile hemiplegia, seizures, & severe aggressive behavioral disorders	contrast ventriculography	EEG recording & stimulation study	Leksell stereotactic device, lesioning by thermocoagulation, wax-oil mixture injection, or leucotome	central amygdala	none	100	2-9 yrs: all patients maintained initial improvement
Balasubramaniam & Kanaka, 1975 ²	235	aggressive behavioral disorders	contrast ventriculography	EEG recording & stimulation study	Leksell stereotactic device, lesioning by thermocoagulation, wax-oil mixture injection, or leucotome	central amygdala	3.8% mortality rate	75.7, in preop behavioral symptoms	NA
Sonnen et al., 1976	7	aggressive behavioral disorders	NA	EEG recording & stimulation study	van Hoytema & van Manen stereotactic device, lesioning by thermocoagulation	central amygdala	transient changes in respiration, mouth movements, & mumbling	71.4, in preop behavioral symptoms	NA
Small et al., 1977	58	aggressive behavior w/ or w/o epilepsy	air or contrast ventriculography	no monitoring	lesioning by cryoprobe	anteromedial amygdala	transient polydipsia	33, in preop behavioral symptoms	NA
Mempel et al., 1980	70	aggressive behavioral disorders	NA	EEG recording & stimulation study	medial amygdalotomy, other information NA	medial amygdala	none	75.7, in anger attacks; 83.4, in aggression; 42.9, in obsession	NA
Ramamurthi, 1988	481	aggressive behavioral disorders	contrast ventriculography	electrical stimulation study	Leksell stereotactic device, lesioning by thermocoagulation or wax-oil mixture injection	central amygdala	immediate or slightly delayed hemiplegia in 6% of cases	76, in preop behavioral symptoms	55% of patients maintained improvement
van Manen & van Veelen, 1988	7	aggressive behavioral disorders	CT	electrical stimulation study	van Hoytema & van Manen stereotactic device	central amygdala	none	43, in preop behavioral symptoms	postop yr NA

* NA = not available.

Similarly, Balasubramaniam and Ramamurthi⁴ reported on a large clinical series of 100 patients who had undergone bilateral stereotactic amygdalotomy for assaultive, hyperkinetic, destructive, self-destructive, or pyromaniac behavior. The surgical procedure was routinely performed after inducing a state of general endotracheal anesthesia.^{3,5} The researchers used PEG or contrast ventriculography to preoperatively define the anatomical target, whereas intraoperative EEG with or without olfactory stimulation was performed in the majority of cases. They used the Leksell stereotactic system with a slight modification consisting of a central hole in the original carrier to facilitate the entrance of the lesioning device. The center of the amygdaloid nucleus was always targeted in their patients, and 9 adjacent lesions were placed using either a diathermy 8-mm electrode for thermal lesioning or a Bertrand loop for mechanical destruction of the amygdala. Results showed that 6% of the patients studied had marked behavior improvement with no episodes of violence even without medication, whereas another 33% demonstrated significant improvement while remaining on their preoperative medications and exhibiting only occasional violent outbursts. Another 36% of the patients experienced some improvement in their symptoms.⁴ Unfortunately, there was no report on the duration of the follow-up period in their study. The authors did find that patients with behavioral disorders associated with epilepsy had better outcomes than those with disorders linked to encephalitis.

In 1973 Hitchcock and Cairns¹⁴ reported on 18 patients with hyperactive, destructive, and rebellious behavioral disorders. Most patients in their study also had a history of epilepsy. The authors performed bilateral stereotactic amygdalotomies after applying a local anesthetic or inducing general anesthesia, depending on the patient's willingness to cooperate during the procedure. They preferred a transtemporal approach instead of the previously described transfrontal method, because they believed that a direct transtemporal route might be both shorter and safer. They obtained physiological confirmation of the anatomical target via electrical stimulation in cases treated after applying a local anesthetic. A 3 × 1.8-mm depth electrode (Radio-nics) was stereotactically introduced, and electrical stimulation was applied to verify the target. The stimulation parameters were as follows: voltage 1–10 V, frequency 5–100 Hz, and pulse width 1 msec. The target was centered on the medial group of the amygdaloid nucleus complex, although the intention was to destroy the whole amygdala. Postoperative improvement in violent and destructive behavior in 27.7% of patients was reported.

Similarly, Small et al.³⁹ described a series of 58 patients, of whom 12 had solely behavior disorders and 46 had seizure and behavior disorders for which they underwent bilateral stereotactic amygdalotomy. Procedures were performed in all 58 patients after the application of a local anesthetic. The surgical technique was the same as that described by Heimburger et al.,¹³ whereas the anatomical target was centered in the anteromedial part of the amygdaloid nucleus.³⁹ Intraoperative EEG monitoring was available in most cases. Approximately one-third of the patients who had undergone the operation primarily for behavioral disorders experienced behavioral improvement (mean follow-up time 6 years), whereas 40% in the combined disorder group had behavioral improvement. The authors also

noted a trend among patients with psychomotor attacks: those who were younger fared slightly better than older patients. Similarly, Mempel et al.²⁷ reported clinical improvement in behavior disturbances in 60–70% of 70 patients with epilepsy and behavioral disturbances.

Discussion

Since Narabayashi's 1961 introduction of stereotactic amygdalotomy for the treatment of severe aggressive behavior, numerous outcome studies have been published.^{1–5,7,12–15,24,26,32–34,39,40,45,46} It must be emphasized that a comparison of the results of these series is meaningless given the nonhomogenous populations studied, the differences in the surgical technique applied, and the significantly varying outcome criteria. It has been demonstrated that the amygdala in humans consists of 23 distinct subnuclei, which have been identified.^{14,17} In the literature focused on this subject, there has been some discussion about the optimal anatomical target in cases of stereotactic amygdalotomy. In initial descriptions of the procedure,^{8,32} the lateral group of amygdaloid nuclei, which is better developed than the medial group, was targeted. In contrast, other clinical investigators^{7,13,14,27,39} have targeted the anteromedial group of amygdaloid nuclei, and the central region of the amygdaloid nucleus has been targeted in only a limited number of clinical series.^{1,2,34,40,45}

Physiological confirmation of the anatomical target, by using intraoperative EEG monitoring alone or EEG monitoring together with olfactory stimulation by ether, has been performed in the majority of published clinical series.^{1,2,7,14,27,33,34,40,44–46} However, Heimburger et al.¹³ and Small et al.³⁹ performed their procedures without electrophysiological monitoring. Recent advances in neuroanesthesia may allow intraoperative electrical stimulation studies in awake patients undergoing stereotactic amygdalotomy not only to confirm the accuracy of the anatomical target, but also to define the exact part of the amygdaloid nuclei complex that must be lesioned. Careful observation of a patient's response to intraoperative electrical stimulation may well guide the surgeon in selecting the most appropriate amygdaloid nuclei subgroup as a target.

In regard to the observed mortality rate associated with stereotactic amygdalotomy, only a study by Balasubramaniam and Kanaka² revealed a 3.8% mortality rate. The occurrence of procedure-related complications has varied significantly among published clinical series.^{1–5,7,12–15,24,27,32–34,39,40,44–46} Hitchcock and Cairns¹⁴ reported no procedure-related complications and no postoperative impairment in the intellectual functioning of their patients. Similarly, Balasubramaniam and Ramamurthi⁴ reported no postoperative cases of Klüver–Bucy syndrome, memory deficits, or hypersexuality. In another clinical series of 50 patients, Balasubramaniam et al.⁵ reported 1 case of transient ptosis, 10 cases of transient hemiplegia (which was attributed to the proximity of the crus to the created lesion), and 1 case of prolonged postoperative unconsciousness, irregular temperature, and convulsions in a patient with postencephalitic aggressive behavioral disturbance. In their original series Narabayashi and colleagues³² encountered no cases of postoperative Klüver–Bucy syndrome; in their expanded series,³³ however, 1 patient (1.0%) had partial Klüver–Bucy

syndrome 1 week after surgery, with symptoms consisting of unsteadiness, oral tendency, hypersexuality, and relative hypermetamorphosis. This patient's symptoms lasted for ~ 2 months but were finally controlled with high doses of chlorpromazine.

Numerous animal electrophysiological studies in monkeys have shown that visual discrimination learning is increasingly impaired after combined amygdala-hippocampal lesioning compared with that following destruction of the hippocampus alone.^{22,28,49} Furthermore, it has been demonstrated that monkeys with combined amygdala-hippocampal ablations are severely impaired in both tactile and visual versions of a memory task, whereas monkeys that undergo hippocampectomy alone show no learning deficits in either modality.^{22,29} Young and associates^{47,48} have described a case of face-processing impairment following a partial bilateral amygdalotomy; however, Lee et al.²² have reported a patient whose attention and memory were preserved after undergoing bilateral stereotactic amygdalotomy. Lee and colleagues concluded that bilateral amygdalotomy does not impair a patient's ability to associate an object from one sensory modality to another. Furthermore, Luczywek and Mempel²⁴ reported that in a series of 46 patients with epilepsy who had undergone bilateral mediodorsal amygdalotomy, the majority had significant IQ improvement postoperatively. This improvement was even more prominent among patients with preoperative IQs > 90. Their findings further support the impression that amygdalotomy does not compromise learning, language, and intellectual capabilities of patients.^{21,22}

Advances in neuropharmacology during the last 3 decades, along with the skepticism regarding the surgical treatment of psychiatric disorders, have led to the abandonment of stereotactic amygdalotomy in treating patients with severe aggression or self-mutilation disorders. Note, however, that certain cases of violent behavioral disorders that do not respond to any other treatment modality might benefit from stereotactic amygdalotomy. Medically refractory cases of aggressive, assaultive behavior or of self-mutilation resistant to appropriate pharmacological or behavioral treatment may improve with stereotactic amygdalotomy. The introduction of high-field MR imaging units in routine clinical practice, in which the amygdaloid nuclei can be nicely identified, and the development of frameless neuronavigational systems of high accuracy can make stereotactic amygdalotomy an appealing treatment option in these patients. A team of experienced psychiatrists and a functional neurosurgeon very familiar with psychosurgical procedures should select appropriate surgical candidates. It cannot be overemphasized that this procedure should be considered only in extreme cases after exhausting all other therapeutic options and only when the patient and his or her family are fully aware of the potential outcome and risks of the procedure.

Conclusions

Since its introduction by Narabayashi, stereotactic amygdalotomy has evolved into a more accurate and precise stereotactic procedure. However, the development of psychopharmacology and the growing skepticism of the international medical community regarding psychosurgery

have resulted in the minimal utilization and almost total disregard for the procedure as well as many other psychosurgical procedures. Nonetheless, continuing improvement in neuroimaging along with the evolution of neuronavigational and stereotactic systems may well increase the application of stereotactic amygdalotomy in treating carefully selected patients suffering from severe, medically refractory aggressive behavioral disorders.

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