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Amygdala and Hypothalamus: Historical Overview With Focus on Aggression

Aggressiveness has a high prevalence in psychiatric patients and is a major health problem. Two brain areas involved in the neural network of aggressive behavior are the amygdala and the hypothalamus. While pharmacological treatments are effective in most patients, some do not properly respond to conventional therapies and are considered medically refractory. In this population, surgical procedures (ie, stereotactic lesions and deep brain stimulation) have been performed in an attempt to improve symptomatology and quality of life. Clinical results obtained after surgery are difficult to interpret, and the mechanisms responsible for postoperative reductions in aggressive behavior are unknown. We review the rationale and neurobiological characteristics that may help to explain why functional neurosurgery has been proposed to control aggressive behavior.

KEY WORDS: Aggression, Amygdala, Deep brain simulation, Hypothalamus, Stereotactic neurosurgery, Review

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Aggressive behavior is a primitive social conduct that is essential for individuals to compete for food, territory, and mating. In this regard, one may say that it is crucial for the maintenance of the species.[1] In the case of humans, the presence of complex emotions makes understanding the neurobiological mechanisms underlying human aggressive behavior a challenging task.[2,3] Violent crimes are often committed, and the costs required to address the consequences of these acts are high. Victims require physical and emotional care, and offenders are incarcerated and consequently became a burden on the government as a result of their loss of productivity.[4]

One strategy used to study human aggression is to simplify the behavior in a dichotomy model including premeditated (proactive or cold aggression) and impulsive (reactive or hot-headed aggression) aggression. Premeditated aggression involves a planned behavior that is intended to achieve a specific goal and is not accompanied by autonomic arousal or anger. Impulsive aggression is unrelated to a specific goal and usually involves frustration, provocation, or stress; this type of aggression is associated with high levels of autonomic arousal and impulsivity.[3] Impulsive aggression is the core symptom of intermittent explosive disorder and presents as a feature of several psychiatric disorders, including schizophrenia, personality disorders (in particular, borderline and antisocial personality disorders), autism spectrum disorder (ASD), posttraumatic stress disorder (PTSD), and bipolar disorder.[4-8] In addition, aggression in psychiatric patients is frequently associated with other comorbidities, such as anxiety, mood disorders, and sleep disturbances, as described in ASD patients.[6] The association between mental disorders and violent behavior is a common reason for patient institutionalization.[2]

Studies in humans and other mammals indicate that the amygdala is a key component of a broader neural circuit that modulates aggressive behavior and also includes the hypothalamus, hippocampus, orbitofrontal cortex, and periaqueductal gray (PAG) matter.[9,10] The amygdala presents reciprocal connections with the hypothalamus (mainly through the fornix and stria terminalis) and with the PAG (through the ventral amygdalofugal pathway), and receives massive projections from the prefrontal cortex through the uncinate

ABBREVIATIONS: 5-HT, serotonin; **ASD,** autism spectrum disorder; **DA,** dopamine; **DBS,** deep brain stimulation; **GABA,** gamma-aminobutyric acid; **HFS,** high-frequency stimulation; **MRI,** magnetic resonance imaging; **PAG,** periaqueductal gray; **PTSD,** posttraumatic stress disorder; **VMH,** ventromedial hypothalamic nucleus

fasciculus.[11-14] The hypothalamus projects to the PAG via the dorsal longitudinal fasciculus and receives projections from the prefrontal cortex through the medial forebrain bundle.[12,15,16] It is believed that impulsive forms of aggressive behavior occur when there is a hyperactivation of the limbic system, with insufficient top–down control from the prefrontal cortex.[3] Figure 1 shows a schematic representation of the main neurocircuitry underlying aggressive behavior.

The dysregulation of the serotonin (5-HT), dopamine (DA), and norepinephrine systems has been implicated in the overexpression of aggression. The impairment of receptor subunits and other neuronal elements, including the serotonin transporter (5-HT transporter), 5-HT1B receptor, gamma-aminobutyric acid A and B (GABA-A and GABA-B) receptors, glutamate (N-methyl D-aspartate) receptor, monoamine oxidase A, nitric oxide synthase, and neuroactive steroids, has been reported in aggressive subjects.[17-19] It is necessary to integrate and understand these complex neurochemical interactions to effectively treat an aggressive patient.[2]

The primary treatment for aggressive behavior involves the use of medications and/or nonpharmacological treatments.[20,21] Nonpharmacological treatments such as cognitive behavioral therapy and applied behavior analysis have an overall intervention effect that is considered low to medium and are sometimes ineffective.[21,22] Electroconvulsive therapy is more efficacious but is associated with side effects.[23,24]

As impulsive aggression is often a symptom of associated disorders, first-line treatments are initially chosen to address the primary underlying conditions.[25] As shown in Table 1, pharmacological treatment of aggressive behavior may involve the use of different classes of medications, such as typical and atypical antipsychotics, antidepressants, benzodiazepines, alpha 2 agonists, mood stabilizers, and anticonvulsants.[6,26-49]

Typical antipsychotics include dopaminergic antagonists and are effective in treating psychotic patients, children with conduct disorders, and cognitively impaired individuals.[27] Atypical antipsychotics, particularly risperidone and aripiprazole, act on multiple neurotransmitter systems (eg, antagonists of the DA and 5-HT2A receptors) and are effective in the patient populations described above.[27] Their effectiveness is particularly notable in ASD patients for which they are FDA approved.[6,29]

Antidepressants, primarily selective serotonin reuptake inhibitors, are effective in reducing irritability and aggressive behavior in patients with unipolar depression, Alzheimer's disease, autism, mental retardation, psychosis, PTSD, and personality disorders.[32] Mood stabilizers, such as lithium, have been shown to be effective in individuals with intellectual disabilities and physical handicaps, children with conduct-disordered and explosive behavior, and bipolar patients with excessive irritability and outbursts of rage.[31,50]

When patients fail to respond to an adequate dose and duration of a standard monotherapy, a high-dose monotherapy or a polypharmacy strategy may be used.[20,27] These include the use of typical antipsychotics (2 or more), atypical antipsychotics (2 or more), or a combination of both classes of drugs. However, this type of polypharmacy can increase the burden of side effects, including sedation, akathisia, and dystonia.[27]

Despite the variety of drugs and doses used to treat aggression, there is a subset of individuals who do not respond adequately to medical treatment and are considered to be treatment refractory.[29] For this limited population of nonresponsive impulsive aggressive patients, surgical interventions targeting the amygdala or hypothalamus have been proposed. We review the rationale behind and neurobiological mechanisms underlying these interventions and discuss some of the reported outcomes.

A review search was conducted in PubMed, Medline, and Scopus for original research articles. As this study aims to review a great number of published articles on the theme, there were no restrictions placed on the publication date for the search. Thus, we opted not to conduct a formal systematic review or meta-analysis. The studies were required to meet the terms "amygdalotomy," "amygdala," "hypothalamotomy," "hypothalamus," "lesion," "aggressive behavior," "aggression," "deep brain stimulation, " "DBS." The selection criteria included studies that (1) were performed in humans, (2) performed amygdalotomy or hypothalamotomy, (3) were focused on aggressive behavioral disorders. Only English language articles were considered. Studies of all sample sizes were included in the analysis. Studies were excluded if they (1) were reviews of the literature and (2) present repeated data from previous included studies. Figure 2 shows a PRISMA flow diagram describing the study selection performed in Tables 2 and 3. In order to evaluate the risk of bias/quality assessment of an individual study, the quality was assessed based on Cochrane risk-of-bias tool (see Table 4).[51]

AMYGDALA

The amygdala is an almond-shaped structure located bilaterally in the temporal lobes. Its average size in humans ranges from 1.24 to 1.63 cm^3.[52] The amygdala plays a critical role in processing threatening stimuli and mediating autonomic, neuroendocrine, and behavioral responses that enable an organism to adapt to social and environmental challenges.[14,52,53]

In 1923, J. B. Johnston introduced a fundamental description of the amygdala based on a detailed analysis of comparative vertebrate species.[54] He proposed subdividing the structure into a primitive group of nuclei associated with the olfactory system (the central, medial, and cortical nuclei and the nucleus of the lateral olfactory tract) and a phylogenetically newer group (the lateral and basal nuclei). More recently, a greater heterogeneity of regions within the amygdala has been unraveled, with one portion viewed as a ventromedial extension of the striatum, a second part comprising the caudal olfactory cortex, and a third region representing the ventromedial extension of the claustrum.[53,55] Furthermore, the amygdala has been subdivided based on its histological characteristics into 2 major areas (anterior amygdaloid area and corticoamygdaloid transition area), 6 nuclei (central, medial, cortical, accessory basal, basal, and lateral), and 1

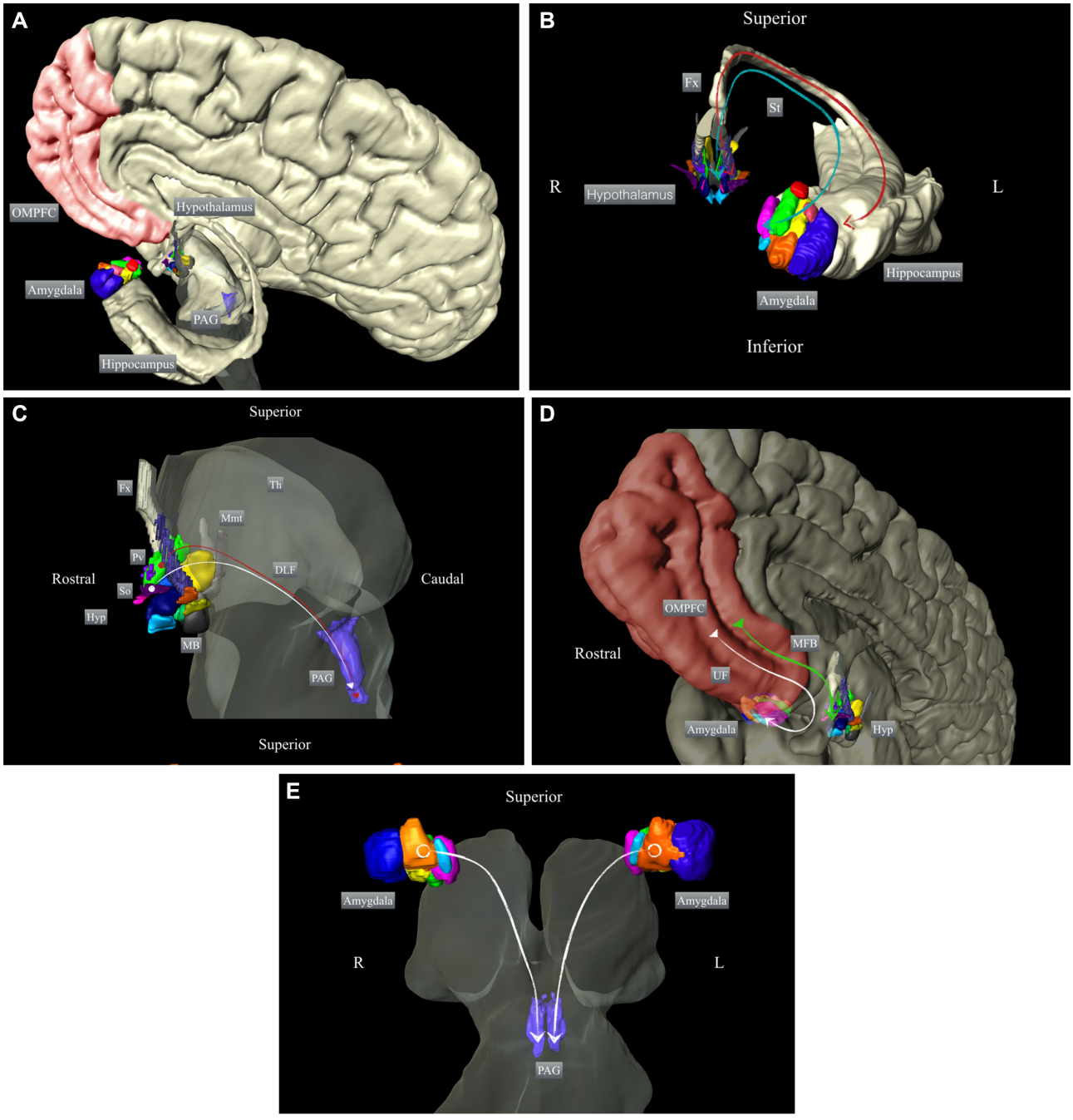

FIGURE 1. *Schematic representation of the participation of the amygdala and hypothalamus in the neurocircuitry underlying aggressive behavior. Overview of* **A**, *the main structures implicated in the control of aggressive behavior and* **B**, *the main connections between the hypothalamus and amygdala;* **C**, *between the hypothalamus and PAG;* **D**, *among the amygdala, hypothalamus, and frontal cortex; and* **E**, *between the amygdala and PAG. The 3-dimensional reconstructions are based on histological segmentations of the depicted structures (methods described in Alho et al[144]). OMPFC: orbitomedial prefrontal cortex; PAG: periaqueductal gray; Fx: fornix; St: stria terminalis; Hyp: hypothalamus; So: supraoptic nucleus; Pv: paraventricular hypothalamic nucleus; MB: mammillary body; Mmt: mammillothalamic tract; Th: thalamus; DLF: dorsal longitudinal fasciculus; MFB: medial forebrain bundle; UF: uncinate fasciculus.*

TABLE 1. Pharmacological Treatment of Aggressive Behavior

Drug	Neurotransmitters involved	Target population	Observations
Typical antipsychotics[26-28]	Dopaminergic antagonists (mainly D2)	ID, DB, psychotic, schizophrenia, bipolar disorders	Extrapyramidal side effects when receptor occupancy exceeds 80%
Atypical antipsychotics[6,29-31]	Multiple: dopaminergic and serotonergic antagonists	ID, DB, ASD, dementia; psychotic	Risperidone and aripiprazole are FDA approved in ASD patients. Clozapine use is related to lower mortality in schizophrenia
Antidepressants[32-35]	Selective serotonin reuptake inhibitors	ASD, ID, PTSD, unipolar depression, Alzheimer's disease, psychosis	The use of this class of drugs has been limited due to the side effects that occur at higher doses
Alpha 2 agonists[36-38]	Alpha-2 adrenergic receptor agonists	ASD, DB	Changes in blood pressure, decreased activity, sedation
Mood stabilizers (lithium)[39-42]	Unknown. Possibly by interaction with glutamate receptors and/or with K^+, Na^+, Ca^{2+} channels	ID, DB, ADHD, bipolar aggressive patients, prison inmates	High risk for adverse drug reactions
Psychostimulants (methylphenidate)[43-46]	Dopamine and norepinephrine agonists	DB, ADHD, ODD	Delay in weight gain and growth; cardiovascular risk
Anticonvulsants (divalproex sodium)[47-49]	Increases GABA concentration and/or inhibition of voltage-sensitive sodium channels	ADHD, ODD, DB, schizophrenia	Low-quality evidence to support the use of this drug

ADHD = attention deficit/hyperactivity disorder; ASD = autism spectrum disorder; DB = disruptive behavior; ID = intellectual disability; ODD = oppositional defiant disorder; PTSD = posttraumatic stress disorder.

intercalated cell group. As the subdivision of the human amygdala proposed by Sims and Williams presents good homology with experimental animals, it will be used in this review.[56]

The lateral nucleus is viewed as the gatekeeper because it receives inputs from sensory systems (ie, visual, auditory, somatosensory, pain, olfactory, and taste) and enables the concurrent processing of multiple types of information.[53,55] The central nucleus is considered a prominent output region for the expression of innate emotional responses and their associated physiological processes, projecting mainly to hypothalamic and brainstem regions.[53] Another important set of output projections from the amygdala arises from the basal nucleus, which directly innervates the central nucleus and striatal areas involved in the control of instrumental behaviors, such as avoidance and escape.[53,57] A schematic representation of the main projections, inputs, and outputs from the central, basolateral, basomedial, and medial amygdala nuclei is provided in Figure 3.

Since the beginning of the last century, several studies have been performed with the aim of understanding the role of the amygdala in social and emotional functions. As a result, the amygdala has been considered a key structure in a wide range of conditions from mood disorders to autism and schizophrenia.[58,59] Likewise, the amygdala is a component of the neural network that regulates aggressive behavior and also includes the hypothalamus, hippocampus, orbitofrontal cortex, and PAG.[3,10,17]

Studies performed in dogs have shown that the bilateral removal of the temporal lobes has a taming effect.[60] Similarly, bilateral lesions damaging the temporal lobe in nonhuman primates can produce dramatic changes in social and emotional behaviors, including aggressiveness.[61-64] In a milestone article, Kluver and Bucy[62,63] demonstrated that bilateral temporal lesions in rhesus monkeys markedly reduced aggressive behavior.

Thereafter, Rosvold and colleagues[64] designed a study to evaluate changes in the social behavior of rhesus monkeys following damage to the amygdala. The researchers established artificial social groups of male rhesus monkeys and identified the dominant animal. A common finding after bilateral lesions of the amygdala was a decrease in social dominance, with the lesioned animals assuming a subordinate position within the group.[64] It is well established that the stimulation or ablation of various amygdalar nuclei in animals produces not only reductions in aggressive behavior but also changes in autonomic functions, such as the heart rate, respiration, and skin conductance.[65-69]

In humans, amygdala stimulation increases aggression.[70] Neuroimaging studies using functional magnetic resonance imaging (MRI) in humans have revealed pronounced amygdala activation when subjects are shown angry or fearful facial expressions.[71,72] Similar results have been described in patients with antisocial behavior, intermittent explosive disorder, and other psychopathologies, revealing that the amygdala is a core structure

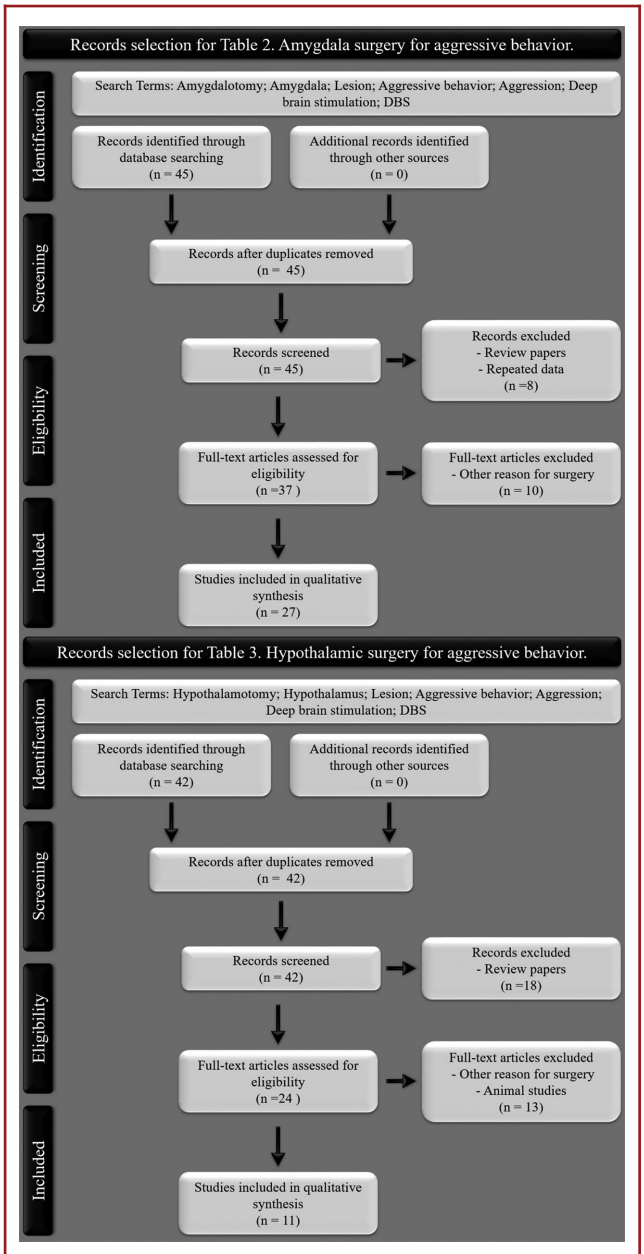

FIGURE 2. *PRISMA flow diagram describing study selection in Tables 2 and 3.*

involved in the processing of aggressive information, regardless of an individual's psychiatric status.[2,73] In addition, recent reports have shown that subjective experiences may influence amygdala volume and connectivity. Veterans with aggressive behavior disorders have a more intense brain response to external stimuli, including the amygdala, and have lower connectivity between the amygdala and prefrontal cortex.[74,75] Similarly, adolescents exposed to family aggression show larger amygdala volume and altered patterns of connections with cortical regions.[74,76]

In contrast, other studies have reported that the level of amygdala activation is lower in criminal psychopaths during processing of negative affective stimuli, fear conditioning paradigms, and emotional moral decision making.[77-79] These apparently opposite effects could be explained by differences in data processing methods. Some studies have investigated the nucleus as a single compact structure, while others have subdivided it into a few regions. Ablating or stimulating distinct regions within the amygdala may cause different or opposing effects on aggressiveness in both animals and humans.[80,81]

Taken together, these results suggest a relationship between aggressive behavior and amygdala hyperactivity and that the removal of the amygdala may be sufficient to reduce aggressiveness. Although the exact mechanism responsible for the marked reduction in aggressive behavior observed after amygdala lesion remains unknown, it has been suggested that this effect is related to an increase in tolerance to provocation and a decline in the level of autonomic arousal.[82,83] Taking this into account, investigators proposed the use of amygdalotomy in humans to control extreme aggressive behavior. Table 2 summarizes the published literature on the use of amygdalotomy in humans.

Over the last 60 yr, more than 1000 such surgeries have been reported. Their results have indicated that beneficial effects can be achieved, including reductions in the severity and frequency of aggressive behaviors.[68-73,84-105] As shown in Table 2, nearly 70% of patients treated with amygdalotomy show good or excellent improvement in behavioral disorders. In patients with concomitant epilepsy, improvements in seizure frequency and intensity have also been reported. There were 6 case reports of only one patient and most studies comprised case series, summing up a total of 1217 patients included in the studies pooled in our review. Although many studies do not reported details of patient psychiatric status, the ones that present this information mostly reports cerebral insults, severe intellectual disabilities, or schizophrenia as cause for the behavioral disturbance. Moreover, several patients had other ablation surgeries performed previously, during or after the amygdalotomy (eg, frontal lobotomy, leucotomy, subcaudate tractotomy, cingulectomy, hypothalamotomy, thalamotomy, fornicotomy, hippocampotomy, fornicotomy, or hypothalamotomy). Thus, a conclusion based on intervention by diagnosis is not possible in those cases.

We note, however, that patients treated with amygdalotomy were often cognitively impaired and nonverbal prior to surgery. Tests to assess other emotional and cognitive aspects (ie, threat processing, avoidance, and approach)[103,104] were usually not performed. Nevertheless, in most cases, authors reported transient or no postoperative side effects and no impairment in overall measures of intelligence and global memory. However, permanent side effects and worsened behavioral problems have been reported, including movement disorders, depression, and cognitive disturbances involving memory, language, and nonverbal visual stimuli.

TABLE 2. Surgery Targeting the Amygdala for Aggressive Behavior

Ref. and year	No. Gender Age	Population	Behavior disturbance	Surgical target and laterality	Imaging guidance	Electro physiological recordings	Surgical technique	Associated surgery	Improvement and form of evaluation	Side effects	Follow-up (mo)
[66]/1963	N: 60 M: 38 F: 22 5-35 yr	ID; IN; CI; hyperactivity; psychopath	Disruptive behavior with or without seizures; assaultive behavior; violent aggressiveness	Lateral nucleus of the amygdala Bilateral: 21 Unilateral: 39	PEG; head X-rays	DR en route and at target with olfactory stimulation (ether-inhalation)	Oil-wax-lipiodol (surgical wax)	No other surgery	85% Clinical observations	1.5% Transient capsular palsy 1.5% Transient hypersexuality	Up to 24
[101]/2012	N: 7 M: 5 F: 9 <53 yr	Schizophrenia PTPD; OCD; IN	Olfactory seizures and psychiatric disorders with olfactory hallucination	Medial amygdala Bilateral: 1 Unilateral: 6	PCV; head X-rays	EEG; DR of the amygdala with different stimuli (electric, olfactory, reading, calculation, anticonvulsant)	Olive oil + white bee wax + lodized oil (surgical wax)	No other surgery	100% Clinical observations	No side effects reported	3-15
[102]/2017	N: 25 M: 14 F: 11 7-61 yr	ID; IN; hyperactivity; In.patients	Hostile, aggressive, and destructive behavior; epilepsy and depression; refractory to drug therapy	Posterior half of the amygdala Bilateral: 8 Unilateral: 16	PEG; PCV	NR	Cryolesion (–120°C, 5 min cooling and 3 min place) 2 lesions in each nucleus	Subsequent temporal lobectomy (1)	80% Grading scale developed by the authors	4% Worse behavior after surgery	12-36
[84]/1966	N: 40	Follow-up of patients from previous paper (01/1963)							67,5% Interview with authors and patient doctor; Family questionnaire	2.5% Worse behavior after surgery 1% Transient partial Kluver and Bucy syndrome	36-72
[67]/1968	N: 44 N/G 0-40 yr	CI; schizophrenia	Violent and destructive acts; pyromania; episodic attacks of behavior disorders	Amygdala nucleus not specified Bilateral: 39 Unilateral: 5	PCV	DR of the amygdala with and without olfactory and electric stimulations	Thermal coagulation; mechanic methods	No other surgery	62% Grading scale developed by the authors	12% Worse behavior after surgery or died	12-48
[68]/1969	1 Male 33 yr	IN; CI	Violent aggressive behavior with seizures; verbal and physical aggression	Lateral amygdala Bilateral	Head X-rays	EEG; DR of the amygdala with electric stimulation (implanted electrodes for 6 mo)	Thermal coagulation (insulated multi-lead deep electrodes)	No other surgery	100% Clinical observation; psychological tests	No side effects or discomfort reported	12
[69]/1970	N: 100 M: 82 F: 18 0-50 yr	CI; schizophrenia; hyperactivity	Assaultive, destructive and self-destructive behavior; pyromania; hyper-oral	Whole amygdala Bilateral: 87 Unilateral: 13	PEG; PCV	DR of the amygdala with electric stimulation	Thermal coagulation; mechanic methods; oil-wax-lipiodol (surgical wax)	No other surgery	75% Grading scale developed by the authors	9% mortality	24-72

TABLE 2. Continued

Ref. and year	No. Gender Age	Population	Behavior disturbance	Surgical target and laterality	Imaging guidance	Electro physiological recordings	Surgical technique	Associated surgery	Improvement and form of evaluation	Side effects	Follow-up (mo)
[70]/1970	N: 12 All female 23-69 yr	ID; PD; schizophrenia; In.patients	Aggressive and destructive behavior with or without seizures; self-mutilation	Amygdala nucleus not specified All bilateral	PEG; PCV	DR of the amygdala	Thermal coagulation (65°C, 45 s) 2 lesions in each nucleus	Previous frontal lobotomy (5) Cingulectomy (2) Subsequent basofrontal tractotomy (3)	75% Psychological tests	No side effects reported	Up to 36
[82]/1973	N: 18 M: 13 F: 5 8-43 yr	ID; PD; AuD	Behavioral disturbances with seizures; abnormal aggressive behavior	Medial amygdala Bilateral: 17 Unilateral: 1	Angiograph Cerebral isotope scan.	DR en route and at target	Thermal coagulation 3 × 1.8 mm probe	Previous unilateral amygdalotomy (1)	55% Several questionnaires	11% Hemiplegia with disability in one arm 22% Deficit in face recognition	Up to 60
[85]/1966	N: 18 M: 14 F: 4 13-37 yr	ID; PD; schizophrenia	Aggressive and self-mutilation behavior; refractory to ECT, drug therapy, and psychotherapy	Amygdala nucleus not specified Bilateral: 15 Unilateral: 3	PEG; PCV	EEG; DR of the amygdala with electric stimulation	Thermal coagulation (60-65°C, 30 s) Cryoprobe (–70°C, 3 min/–120°, 3 min)	Previous leucotomy (1) Subsequent bimedial leucotomy (1)	39%-50% Several questionnaires	22% Convulsions 5.5% Persistent mild hemiparesis	12-72
[86]/1966	235 N/G N/A	CI; schizophrenia	Aggression, violent and destructive behavior; low rage threshold; self-mutilation	Amygdala nucleus not specified Bilateral: 207 Unilateral: 28	NR	EEG; DR of the amygdala with electric stimulation	Thermal coagulation; mechanic methods; surgical wax	Subsequent hypothalam-otomy (33)	75% Grading scale developed by the authors	2.5% Transient hemiplegia 1% Permanent hemiplegia 1% Temporary ballistic movement 4% Mortality	Up to 108
[87]/1974	N: 10 M: 8 F: 2 10-20 yr	IH	Aggressive, assaultive and destructive behavior; low rage threshold; refractory to drug therapy	Amygdala nucleus not specified All unilateral	PEG; PCV	DR of the amygdala with electric stimulation	Thermal coagulation; mechanic methods; surgical wax	Simultaneous thalamotomy (2)	100% Grading scale developed by the authors	No side effects reported	24-108
[88]/1975	N: 8 M: 6 F: 2 12-26 yr	ID; psychotic; In.patients	Aggressive and impulsive behavior with seizures; dangerous outbursts of rage	Centre of the amygdala Bilateral: 6 Unilateral: 2	Head X-rays	EEG; DR of the amygdala with electric and olfactory stimulations (ether)	Thermal coagulation (70°, 80°, 90°C, 60 s. Mono and bipolar) 1 lesion at target and 1 above it (12 mm range)	Previous temporal lobectomy (1) Simultaneous fornicotomy (3)	62.5% Observation scale and annotations of the staff members	12.5% Behavior worse than before 25% Transient hemiparesis 50% Rise in temperature 12.5% Rise in blood pressure	NR
[89]/1975	N: 58 M:39 F: 19 8-61 yr	CI; In.patients	Aggressive and destructive behavior with or without seizures; refractory to therapies	Antero-medial of the amygdala Bilateral: 28 Unilateral: 30	PCV	NR	Cryolesion; mechanical methods	Previous frontal lobotomies (11)	30%-40% Structured psychiatric interviews; neuropsycho-logical tests	2% Permanent hemiparesis 2% Transient hyper sexuality 5% Temporary visual field defects 9% Memory loss 12% Others mild 2.5% Behavior	12-132 Mean: 72

TABLE 2. Continued

Ref. and year	No. Gender Age	Population	Behavior disturbance	Surgical target and laterality	Imaging guidance	Electro physiological recordings	Surgical technique	Associated surgery	Improvement and form of evaluation	Side effects	Follow-up (mo)
[65]/1978	N: 44 N/G 8-61 yr	ID; In.patients	Aggressive behavior with or without seizures	Anteromedial amygdala Bilateral: 14 Unilateral: 30	PCV	NR	NR	No other surgery	30%-50% Grading scale developed by the authors	12% Decrease in recent memory 9% Temporary loss of peripheral vision 5% Transient increase in sex drive 2% Permanent hemiparesis 2% Permanent speech difficulties	12-132
[90]/1976	N: 70 M: 39 F: 31 N/A	Schizophrenia; suicidal tendencies; depression	Attacks of anger; verbal or physical aggression, with epilepsy; refractory to drug therapy	Medial nucleus of the amygdala Bilateral: 33 Unilateral: 34	NR	EEG; DR of the amygdala and hippocampus with electrical stimulation	NR	Previous temporal lobectomy (10) Simultaneous anterior hippocam-potomy (29)	75-84% Clinical observations	No side effects reported	24-156
[91]/1977	1 Female 34 yr	ID; In.patients	Uncontrollable aggressive; refractory to ECT and drug therapy	Amygdala nucleus not specified Bilateral	NR	NR	NR	No other surgery	100% Clinical observations	No side effects reported	12
[92]/1980	N: 4 All male 17-57 yr	NR	Aggressive behavior with epilepsy	Amygdala nucleus not specified. All unilateral	NR	SEG	NR	No other surgery	50% Clinical observations	25% Occasional depression	36-72
[93]/1981	1 Female 37 yr	PD; normal to superior IQ	Self-mutilation, depression and overdose; refractory to ECT, drug therapy, and psychotherapy	Amygdala nucleus not specified Bilateral	PEG	NR	Thermal coagulation 2 lesions in each nucleus (3 mm apart)	Previous bifrontal tractotomy	100% Clinical observations	Disorders of facial recognition; social behavior; elements of Kluver and Bucy syndrome	120
[83]/1988	N: 481 N/G <15 yr	ID; CI; hyperactivity	Aggressive, destructive, and self-destructive behavior; refractory to drug therapy	Amygdala nucleus not specified Bilateral: 402 (at 1-stage surgery) Unilateral: NR	PCV	DR of the amygdala with electric stimulation	Thermal coagulation; surgical wax	Previous hypothalam-otomy (47) Subsequent hypothalamotomy (73)	70% Clinical observations. Psychological assessments in 60 patients	6% Transient hemiplegia	36
[94]/1983	N: 11 N/G N/A	ID	Automutilation and aggressive behavior with seizures	Medially in the amygdala. Bilateral: 7 Unilateral: 4	PEG; CT head scan	NR	NR	Simultaneous Unilateral fornicotomy (3) Temporal lobectomy (1)	45.5% Clinical observations	No side effects reported	Up to 120

TABLE 2. Continued

Ref. and year	No. Gender Age	Population	Behavior disturbance	Surgical target and laterality	Imaging guidance	Electro physiological recordings	Surgical technique	Associated surgery	Improvement and form of evaluation	Side effects	Follow-up (mo)
[95]/1986	2 Male 30 and 35 yr	CI; psychotic	Rage and aggression with seizures; refractory to drug therapy	Amygdala nucleus not specified All unilateral	NR	Corticography	NR	Simultaneous Lesion in Hippocampus and Uncus	100% Clinical observations	Right hemiparesis and swallowing difficulty (surgical accident 1 patient)	12-72
[96]/1988	2 Male 19 and 21 yr	CI; psychotic	Medically intractable aggressive behavior	Whole amygdala All bilateral	Brain MRI; stereotactic X-rays	NR	Thermal coagulation (80°, 90°C, 60 s. 2.1 × 5 mm uninsulated tip) 3 lesions in each nucleus (4 mm apart)	No other surgery	50% Clinical observations.	No side effects reported	96
[97]/1992	N: 2 N/G N/A	NR	Medically intractable aggressive behavior	Amygdala nucleus not specified All bilateral	PCV	NR	Thermal coagulation	Simultaneous Subcaudate Tractotomy	100% Several questionnaires	No side effects reported	84
[98]/1998	1 Female 38 yr	SMPD	Aggressive behavior and self-inflicted injuries; refractory to drug and behavioral therapies	Whole amygdala Bilateral	Brain MRI; head CT scan; surgiplan workstation; fluoroscopy	NR	Thermal coagulation (90°C, 60 s. 2 × 4 mm, monopolar) 3 lesions in each nucleus	No other surgery	100% Clinical observations	No side effects reported	18
[99]/2002	1 Male 13 yr	Severe Kanner's autism	Life-threatening self-injurious behavior; refractory to drug therapy	Basolateral nucleus of amygdala Bilateral	Brain MRI; stereotactic head CT scan; human brain atlas	NR	DBS 2 quadripolar non-insulated electrodes 120 μs; 130 Hz; 2-6.5 V	No other surgery	100% Father rating scale; clinical observation; questionnaires	No side effects reported	24

TABLE 2. Continued

Ref. and year	No. Gender Age	Population	Behavior disturbance	Surgical target and laterality	Imaging guidance	Electro physiological recordings	Surgical technique	Associated surgery	Improvement and form of evaluation	Side effects	Follow-up (mo)
[100]/2007	1 Female 19 yr	ID	Refractory aggressive behavior	Whole amygdala Bilateral	Brain MRI; stereotactic MRI; surgiplan workstation	NR	Thermal coagulation (75°C, 60 s) Multiple lesions	Simultaneous Bilateral Anterior Capsulotomy	100% Several questionnaires Psychological tests	No side effects reported	36
Summary Total: 27	N: 1217 M: 268 F: 139 N/G: 810 0-69 yr	ID: 12 IN: 4 CI: 20 PTPD: 1 OCD: 1 PD: 4 AuD: 1 IH: 1 SMPD: 1 Hyperactivity: 4 Psychopath: 5 Schizophrenia: 6 Suicidal: 1 Depression: 1 Autism: 1 In.patients: 6 NR: 2	Refractory: 14 With seizures: 13	Lateral n: 2 Medial n: 3 Posterior: 1 Centre: 1 Anteromedial: 3 Whole: 4 NR: 12 Bilateral: 907 Unilateral: 227	1960s: PEG; PCV; X-rays 1970s: PEG; PCV; ACIS 1980s: PEG; PCV; CT 1990s: MRI; stereotactic X-rays >2000: MRI; stereotactic CT; surgiplan workstation; brain atlas	DR en route: 2 DR local: 13 Olfactory stimulation: 4 Electric stimulation: 10 Other stimulation: 1 EEG: 6 SEG: 1 Corticography: 1 NR: 10	Surgical wax: 6 Cryolesion: 3 Mechanic: 5 Thermal: 15 DBS:1 NR: 6	No other surgery: 12 Previous: 8 Simultaneous: 7 Subsequent: 4	Total: 69.5%	No side effects: 12 Transient: 10 Permanent: 9 Worse behavior: 5	NR: 1 0-12: 2 13-24: 4 25-36: 4 37: 17

ACIS = angiograph cerebral isotope scan; AuD = alcohol use disorder; CI = cerebral insults; CT = computed tomography; DBS = deep brain stimulation. DR = depth recording; ECT = electro-convulsive therapy; EEG = electroencephalogram; F = female; ID = intellectual disabilities; IH = infantile hemiplegia; IN = intellectual normal; In. patients. = institutionalized patients; M = male; MRI = magnetic resonance imaging; N/A = no age specified in the article; N/G = no gender specified in the article; NR = not reported; OCD = obsessive compulsive disorder; PCV = positive contrast ventriculography; PD = personality disorder; PEG = pneumoencephalography; PTPD: posttraumatic personality disorder; SEG = stereoelectroencephalography; SMPD = self-mutilation psychiatric disorder.

TABLE 3. Hypothalamic Surgery for Aggressive Behavior

Ref. and year	No. Gender Age	Population	Behavior disturbance	Surgical target and laterality	Imaging guidance	Electro physiological recordings	Surgical technique	Associated surgery	Improvement and form of evaluation	Side effects	Follow-up (mo)
[121]/1972	N: 11 N/G N/A	CI; ID; psychopathic personality; schizophrenia	Hetero and auto-aggressiveness, violent and destructive behavior	Posteromedial hypothalamus Bilateral: 10 Unilateral: 1	PEG	Electrical stimulation of the target	Thermal coagulation	Not reported	90% Clinical observations	18% Transient hypersomnia 9% Transient tachycardia	Up to 48
[86]/1966	N: 49 N/G N/A	CI; schizophrenia	Aggression, violent and destructive behavior; low rage threshold; self-mutilation	Hypothalamus nucleus not specified Bilateral: 21 Unilateral: 28	Not reported	DR and electrical stimulation of the target	Thermal coagulation; surgical wax	Previous amygdalotomy (33)	75% Grading scale developed by the authors	4% Transient diabetes insipidus 2% Ballistic movement 4.1% Mortality	Up to 108
[83]/1988	N: 122 N/G N/A	CI, ID	Refractory physical aggression, hyperkinesis, wandering tendency, destructive and self-destructive tendencies	Posteromedial hypothalamus Laterality not reported	PCV	Electrical stimulation of the target	Thermal coagulation	Amygdalotomy	60% Clinical observations	No side effects reported	Up to 36
[125]/2008	N: 60 M: 44 F: 16 N/A	CI; ID	Refractory aggressive behavior, rage attacks, restless behavior	Posteromedial hypothalamus Laterality not reported	Ventriculo-graphy	EEG; electrical stimulation of the target	Thermal coagulation	Not reported	78% Clinical observations	No side effects reported	Up to 300
[126]/2008	1 Male 18 yr	Hypothalamic hamartoma	Refractory aggressive behavior	Hypothalamus: hamartoma Unilateral	Brain MRI; stereotactic head CT scan; Schaltenbrand digital brain atlas	EEG; DR en route and at target; electrical stimulation of target	Thermal coagulation	No other surgery	100% Clinical observations	No surgical complications, no side effects reported	24
Summary Lesions Total: 5	N: 243 M:45 F: 16 N/G:182 N/A	CI: 5 ID: 3 Psychopathic personality: 1 Schizophrenia: 2	Refractory: 5 With seizures:5	Posteromedial hypothalamus Bilateral: 31 Unilateral: 30	<2000: PEG; PCV; ventricu-lography >2000: brain MRI; stereotactic head CT scan; brain atlas	DR en route: 1 DR target: 1 Electrical stimulation of target: 5	Thermal coagulation: 5 Surgical wax: 1	No other surgery: 3 Associated surgery: 2	Total: 80.6%	No side effects: 3 Transient: 2 Permanent: 1	0-24: 1 25-36: 1 55-48: 1 >49: 2
[127]/2008	1 Male 22 yr	ID	Drug-resistant aggressiveness	Posteromedial hypothalamus Bilateral	Brain MRI; ventriculog-raphy	Scalp EEG; DR, and electrical stimulation of the target	DBS Initial parameters: left 0.4 V, right 0.1 V, 450 μs, 15 Hz	No other surgery	100% ICAP	No surgical complications, worsening of unilateral headaches	18

TABLE 3. Continued

Ref. and year	No. Gender Age	Population	Behavior disturbance	Surgical target and laterality	Imaging guidance	Electro physiological recordings	Surgical technique	Associated surgery	Improvement and form of evaluation	Side effects	Follow-up (mo)
[128]/2010	1 Female 22 yr	CI; ID	Drug-resistant self-mutilating behavior	Posterior hypothalamus Bilateral	Not reported	Not reported	DBS Initial parameters: 1.5 V, 90 μs, 130 Hz	No other surgery	100% Clinical observations	No surgical complications, no side effects of stimulation	4
[129]/2013	1 Female 19 yr	IED; ID	Severe violent attacks against family	Orbitofrontal projections to the hypothalamus Unilateral	Brain MRI; stereotactic head CT scan; Schaltenbrand-Wahren atlas	Not reported	DBS Initial parameters: 2.5 V, 360 μs,40 Hz, 1 min "on"/1 min "off"	No other surgery	100% Clinical observations	No surgical complications, no side effects of stimulation	24
[130]/2013	N: 7 M: 6 F: 1 20-68 yr	CI; ID	Refractory aggressive behavior	Posterior hypothalamus All bilateral	Brain MRI; stereotactic head CT scan Framelink 4 software	Scalp EEG; DR en route and at target; electrical stimulation of target	DBS Initial parameters: 1-3 V, 60-90 μs, 185 Hz	No other surgery	85% OAS	No surgical complications, no side effects of stimulation	Up to 118
[131]/2015	N: 6 M:4 F: 2 17-488 yr	CI; ID	Uncontrollable refractory aggressiveness	Posteromedial hypothalamus Laterality not reported	Brain MRI; stereotactic head CT scan; BrainLAB wokstation.	Scalp EEG; DR and electrical stimulation of the target	DBS Initial parameters: 0.1-0.9 V, 15-60 Hz, 180-450 μs	1 patient lesion ST, AC, IC PMH, DmTN, IITN	83% ICAP	No surgical complications, worsening of unilateral headaches in 1 patient	Up to 82
[124]/1988	N: 5 M: 4 F: 1 16-33 yr	ID	Intractable aggressive behavior	Posteromedial hypothalamus All bilateral	Brain MRI; stereotactic head CT scan; Praezis 3.1 workstation	DR en route and at target	DBS Initial parameters: 2.4-3 V, 185 Hz, 90 μs 1 min "on"/5 min "off"	No other surgery	80% OAS	No surgical complications	Up to 48
Summary DBS Total: 6	N: 21 M:15 F: 6 16-68 yr	CI: 3 ID: 6 IED: 1	Refractory: 6 With seizures: 4	Posteromedial: 3 Posterior: 2 Other: 1 Bilateral: 31 Unilateral: 30	Brain MRI; stereotactic head CT scan; surgical planning workstations; brain atlas	EEG: 3 DR en route: 2 DR target: 4 Electrical stimulation of target: 4	DBS Parameters: 0.1-3 V, 60-450 μs, 15-185 Hz	No other surgery: 5 Associated surgery: 1	Total: 91.3%	No side effects: 4 Permanent: 2	0-24: 3 25-48: 1 >49: 2

AC = anterior cingulum, CI = cerebral Insults; CT = computed tomography; DBS = deep brain stimulation; DmTN = dorsomedial thalamic nuclei, DR = depth recording; EEG = electroencephalogram; F = female; IC = internal capsule; ICAP = Inventory for Client and Agency Planning; ID = intellectual disabilities; IED = intermittent explosive disorder; IITN = intralaminar thalamic nuclei; M = male; MRI = magnetic resonance imaging; N/A = no age specified in the article; N/G = no gender specified in the article; OAS = Overt Aggression Scale; PCV = positive contrast ventriculography; PEG = pneumoencephalography; PMH = postermedial hypothalamus; ST = stria terminalis.

TABLE 4. Risk of Bias According to the Cochrane Risk-of-Bias Tool

Ref. and year	Random sequence generation	Allocation concealment	Blinding participants and investigators	Incomplete outcome data	Selective reporting bias
Amygdalotomy studies					
[66]/1963	High	High	High	High	High
[101]/2012	High	High	High	High	High
[102]/2017	High	High	High	High	High
[84]/1966	High	High	High	High	High
[67]/1968	High	High	High	High	High
[68]/1969	High	High	High	High	High
[69]/1970	High	High	High	High	High
[70]/1970	High	High	High	High	High
[82]/1973	High	High	High	High	High
[85]/1966	High	High	High	High	High
[86]/1966	High	High	High	High	High
[87]/1974	High	High	High	High	High
[88]/1975	High	High	High	High	High
[89]/1975	High	High	High	High	High
[65]/1978	High	High	High	High	High
[90]/1976	High	High	High	High	High
[91]/1977	High	High	High	High	High
[92]/1980	High	High	High	High	High
[93]/1981	High	High	High	Low	Low
[83]/1988	High	High	High	High	High
[94]/1983	High	High	High	High	High
[95]/1986	High	High	High	High	High
[96]/1988	High	High	High	Low	Low
[97]/1992	High	High	High	Low	Low
[98]/1998	High	High	High	Low	Low
[99]/2002	High	High	High	Low	Low
[100]/2007	High	High	High	Low	Low
Low	0%	0%	0%	22.2%	22.2%
Unclear	0%	0%	0%	0%	0%
High	100%	100%	100%	77.8%	77.%%
Hypothalamotomy studies					
[121]/1972	High	High	High	High	High
[86]/1966	High	High	High	High	High
[83]/1988	High	High	High	High	High
[125]/2008	High	High	High	High	High
[126]/2008	High	High	High	High	High
[127]/2008	High	High	High	Low	Low
[128]/2010	High	High	High	High	High
[129]/2013	High	High	High	High	High
[130]/2013	High	High	High	Low	Low
[131]/2015	High	High	High	Low	Low
[124]/1988	High	High	High	Low	Low
Low	0%	0%	0%	36.7%	36.7%
Unclear	0%	0%	0%	0%	0%
High	100%	100%	100%	63.3%	63.3%

The risk of bias is the percentage of bias items reported considering all included studies.

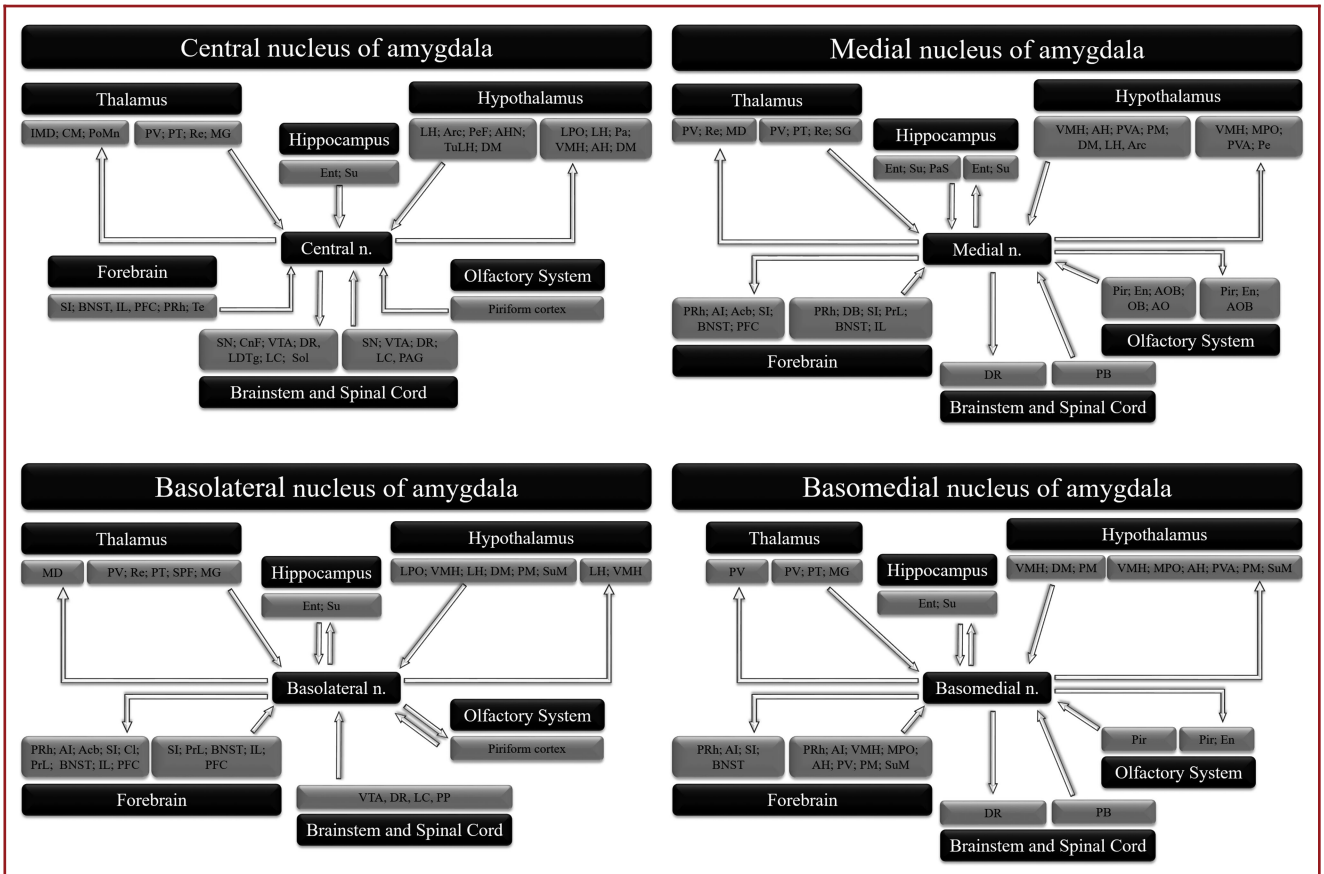

FIGURE 3. *Schematic representation of the main connections of the central, medial, basolateral, and basomedial amygdala nuclei. Acb: nucleus accumbens; AH: anterior hypothalamic area; AHN: anterior hypothalamic nucleus; AI: agranular insular cortex; AO: anterior olfactory nucleus; AOB: accessory olfactory bulb; Arc: arcuate nucleus of the hypothalamus; BNST: bed nucleus of the stria terminalis; Cl: claustrum; CM: central medial thalamic nucleus; CnF: cuneiform nucleus; DB: nucleus of the diagonal band; DM: dorsomedial hypothalamic nucleus; DR: dorsal raphe nucleus; En: endopiriform nucleus; Ent: entorhinal cortex; GP: globus pallidus; IL: infralimbic cortex; IMD: intermediodorsal thalamic nucleus; LC: locus coeruleus; LDTg: laterodorsal tegmental nucleus; LH: lateral hypothalamic area; LPO: lateral preoptic area; MD: mediodorsal thalamic nucleus; MG: medial geniculate nucleus; MPO: medial preoptic area; OB: olfactory bulb; Pa: paraventricular hypothalamic nucleus; PAG: periaqueductal gray; PaS: parasubiculum; PB: parabrachial nucleus; Pe: periventricular hypothalamic nucleus; PeF: perifornical nucleus; PFC: prefrontal cortex; Pir: piriform cortex; PM: premammillary nucleus; PoMn: posteromedial thalamic nucleus; PP: peripeduncular nucleus; PRh: perirhinal cortex; PrL: prelimbic cortex; PT: paratenial thalamic nucleus; PV: paraventricular nucleus of the thalamus; PVA: paraventricular nucleus of the hypothalamus; Re: reuniens thalamic nucleus; SG: supragenicular thalamic nucleus; SI: substantia innominate; SN: substantia nigra; Sol: nucleus of the solitary tract; SPF: subparafascicular thalamic nucleus; Su: subiculum; SuM: supramammillary nucleus; Te: temporal cortex; TuLH: tuberal region of lateral hypothalamus; VMH: ventromedial hypothalamic nucleus; VTA: ventral tegmental area.*

It is also worth noting that studies published to date have numerous confounders, including differences in age, pathologies underlying the behavioral disturbances, heterogeneity of the behaviors, and most importantly, the use of different surgical ablation procedures before, after, or concomitant to the amygdalotomy. In addition, the methods used to lesion the amygdala, the lateralization of the lesion, and the precise targets that were lesioned varied among surgical centers. Some of the techniques used are now considered obsolete, and modern imaging guidance (eg, high-resolution computed tomography, multiplanar 1.5- and 3-Tesla magnetic resonance imaging, and neuronavigational devices) was not available when most of the studies were conducted.

In recent decades, deep brain stimulation (DBS) has emerged as an attractive alternative for treating neurological and psychiatric disorders.[105-108] This technique involves the insertion of electrodes into specific brain targets and the subsequent local delivery of an electrical current, commonly at high frequencies (HFS; ie, 130-185 Hz). Though DBS and lesions are 2 different therapeutic modalities, common mechanisms of HFS include axonal depolarization and the inhibition of cell bodies in the vicinity of the electrodes.[108-111] In patients with movement disorders, similar outcomes have been observed with the use of

these 2 approaches.[112] The fact that stimulation-induced effects are reversible and adjustable (ie, the current can be reduced or the systems turned off upon the occurrence of side effects) has helped to rekindle interest in the notion that psychiatric diseases can be treated with surgery.[105,106] In a recent study, DBS was successfully used to treat an autistic teenager with life-threatening self-injurious behavior refractory to medications.[101]

Notwithstanding these promising results of lesions and DBS studies, the vast majority consist of open-label trials in which subjective measures of behavior were used, resulting in a low level of evidence and a high risk of bias, as presented in Table 4. Ideal surgical targets, the optimal localization within respective nuclei, and the extension/size of the lesions remain to be established. In addition, no detailed information has been provided on postoperative changes in personality and emotions, an issue that will need to be addressed by multidisciplinary teams. Further research is certainly necessary to evaluate the safety of chronic temporal lobe stimulation and to improve our understanding of the mechanisms underlying amygdala DBS.

HYPOTHALAMUS

The hypothalamus is a small diencephalic structure located under the thalamus. It lies on the wall and floor of the third ventricle, extends a few millimeters laterally, and is positioned above the optic chiasm anteriorly and adjacent to the mammillary bodies posteriorly.[113] It is composed of several distinct nuclei with widespread connections throughout the nervous system.[114] The hypothalamus is largely known for its role in controlling homeostasis and motivated behaviors.[114]

Based on nuclear landmarks, the hypothalamus can be divided into 3 areas along its rostro-caudal axis: anterior, medial, and posterior.[15] Alternatively, based on the anatomical localization of cells projecting to the pituitary gland, it can be subdivided along its medial-lateral axis into periventricular, medial, and lateral areas.[15,113,114] The anterior region is primarily responsible for producing oxytocin and vasopressin and for controlling the circadian cycle; the medial region is associated with producing hypothalamic-releasing hormones and controlling numerous motivated behaviors; and the posterior region is involved in thermoregulation, memory, and emotions.[114,115] Figure 4 shows the main hypothalamic connections based on functions.

Studies performed in animals indicate the presence of specific hypothalamic areas (eg, the ventromedial nucleus of the hypothalamus [VMH] and lateral hypothalamus) that, when electrically stimulated, result in the expression of aggressive behavior.[116,117] The VMH projects to the anteromedial hypothalamus and the dorsolateral aspect of the PAG. The neurons in the latter region project to other brainstem areas and the spinal cord, and induce autonomic and motor responses when excited. In terms of afferents, the VMH receives massive inputs from the lateral hypothalamus as well as the cortical and basolateral amygdala, which modulate the expression and duration of aggressive behaviors.[118,119] Similarly, the lateral hypothalamus projects to the midbrain tegmentum, trigeminal motor nucleus, and locus coeruleus, and has reciprocal connections with the PAG. While the latter connections are important for controlling the duration of aggressive episodes, projections from the central, lateral, and basal nuclei of the amygdala facilitate aggressive attacks.[116,119]

In humans, studies suggest that there is a hypothalamic area related to the control of aggressive behavior located in the posteromedial region, an area that includes the midpoint of the anterior commissure/posterior commissure line, the anterior border of the mammillary bodies and the beginning of the aqueduct, and that forms a triangular zone, now called the "Triangle of Sano."[83,88,120,121] Likewise, neuroimaging studies show that the hypothalamus is more activated in individuals with aggressive features and that domestic violence offenders present lower metabolism in this region.[122,123]

Although these results seem conflicting, they reaffirm that the hypothalamus is a component of the neurocircuitry involved in human aggressive behaviors and corroborate the idea that different regions of the hypothalamus are associated with the expression or suppression of these behaviors.[116,119] Furthermore subthalamic DBS induced acute transient aggressiveness when regions near the hypothalamus were stimulated,[120] suggesting that it may be possible to modulate aggressive behavior by electrically stimulating the hypothalamic region in humans.

In the past century, extremely aggressive patients have been treated with hypothalamic lesions with encouraging results.[83,88,121,124-130,131] Table 3 presents the studies using hypothalamic surgery to control aggressive behavior in humans.

When making a hypothalamic lesion, the choice of target is of major importance due to the potential for surgical complications, such as seizures, hyponatremia, cardiovascular changes (including hypertension and tachycardia), disturbances in food and water intake, and thermoregulatory disruption.[132-134] Transient and permanent side effects have been observed after hypothalamic lesions, with one study reporting a 4% mortality rate.[88,121] It is important to note that some patients had previous amygdalotomy surgery and patient psychiatric status is not carefully detailed, but overall is similar to that observed in the amygdalotomy studies (eg, severe intellectual disabilities, cerebral insults, and schizophrenia). Nevertheless, in the 243 published cases, the average rate of improvement in aggressive behavior is approximately 80%. This suggests that the hypothalamus may be a very attractive target for modulating aggressive behavior in humans.

Based on these data, DBS hypothalamic surgery has been performed to control aggressive behavior in a few centers around the world. Surgeries have been performed with the aid of modern imaging and surgical planning workstations that merge MRI and stereotactic computed tomography with brain atlases for optimal target localization. DBS studies include patients who suffered cerebral insults, with severe intellectual disabilities, or diagnosed with intermittent explosive disorder, and the average improvement in aggressive behavior after hypothalamic DBS is 91%. Side effects were observed in only a few cases and mainly

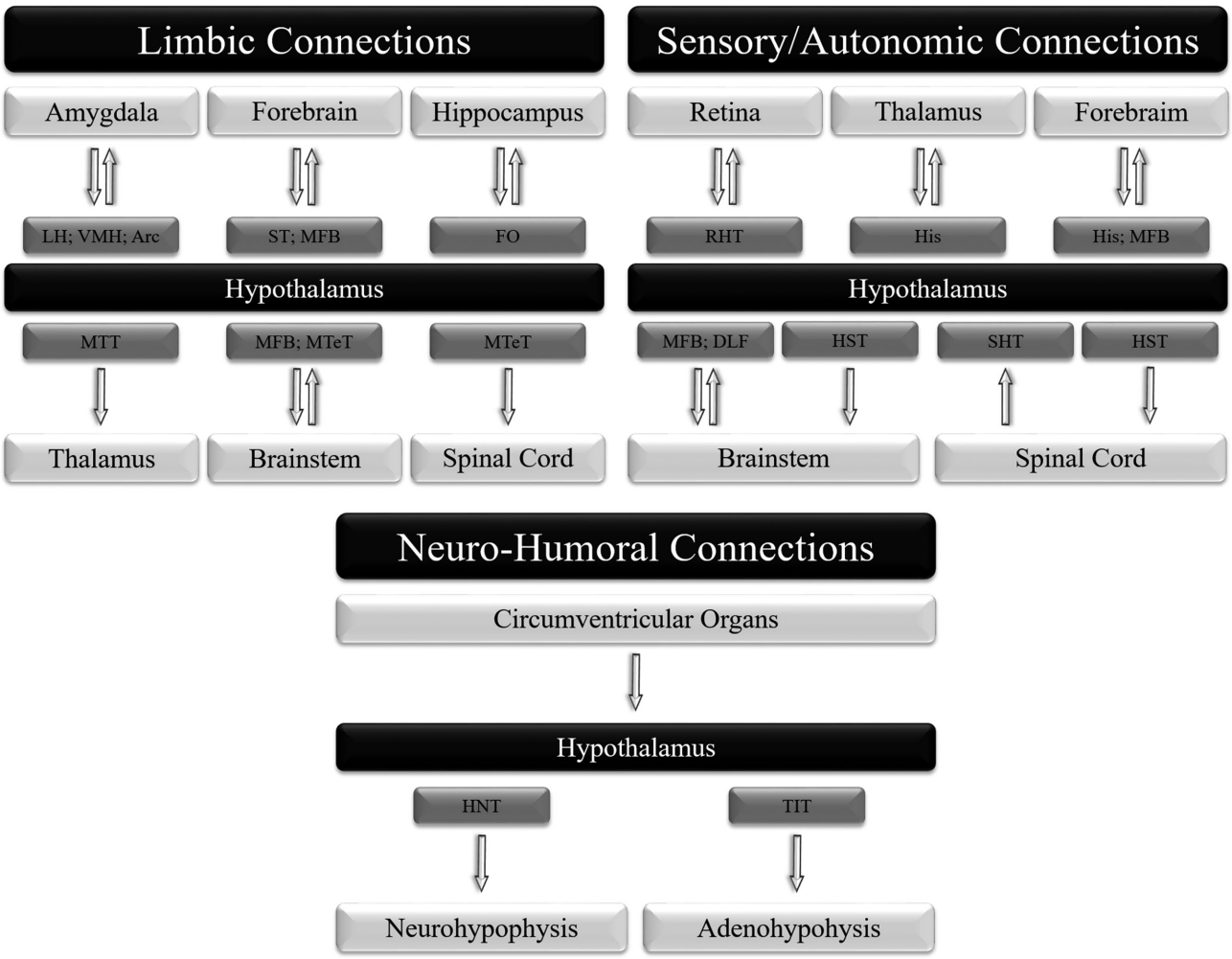

FIGURE 4. *Main hypothalamic connections based on functions. Arc: arcuate nucleus of the hypothalamus; DLF: dorsal longitudinal fasciculus; FO: fornix; His: histamine projection; HNT: hypothalamo-neurohypophyseal tract; HST: hypothalamo-spinal tract; LH: lateral hypothalamic area; MFB: medial forebrain bundle; MTeT: mammillo-tegmental tract; MTT: mammillo-thalamic tract; RHT: retino-hypothalamic tract; SHT: spino-hypothalamic tract; ST: stria terminalis; TIT: tubero-infundibular tract; VMH: ventromedial hypothalamic nucleus.*

included headaches that could be easily treated with medication. The most adequate hypothalamic target remains to be determined, as different studies have reported good results following the application of DBS to the posteromedial hypothalamus or the projections from the orbital frontal cortex to the hypothalamus.[100,135]

Even though there are few published reports on this technique, the results so far indicate that long-lasting reductions in violent outbursts, improved control over emotions, and higher quality of life can be achieved following surgery, with minor side effects. Despite these promising results, when viewed from a modern perspective, some studies lacked specific endpoints, specific measuring instruments, and multidisciplinary evaluation.[136] Moreover, the bias analysis shows a high risk of bias for those studies (see Table 4) and a low level of evidence; thus, it is not possible to present any formal treatment recommendation. However, this literature undoubtedly has merit and needs to be analyzed according to the time and conditions in which it was published.

SURGICAL PERSPECTIVE

After a promising start, surgery for psychiatric indications was indiscriminately used with poor patient selection and a high incidence of serious side effects, which led to public disbelief.[137-139] In the 1950s, new pharmacological and nonpharmacological treatments became available, limiting the need for

surgical interventions even more. Since its peak, the use of ablative stereotactic surgery for psychiatric disorders has stagnated at a low level and is currently only conducted in a few centers around the world.[140] The reasons for this decrease are multifactorial and include the development of psychopharmacology and the growing skepticism of the international community regarding the benefits of these surgical interventions.[140]

Several questions need to be addressed before considering surgery, including indications, patient selection, and criteria for treatment refractoriness. In addition, treating physicians and organizations need to follow regional/federal rules and mandates for conducting psychiatric surgery. If investigational procedures are to be conducted, these should be performed carefully and in a well-documented manner following approval by a research ethics board. The use of psychosurgery should be restricted to extremely severe cases that do not respond to standard/available treatment when no other means of relieving patient suffering is available.[137-139,141] To manage the patients, the center is required to have an experienced multidisciplinary team that may provide optimal clinical care and follow-up support. Additionally, such surgeries should be considered as part of a clinical trial in which outcome measures are objective and reproducible. Modern neuroimaging and refined functional neurosurgery techniques are to be used to ensure optimal targeting.

Technically, stereotactic surgery has become widely available, and frameless stereotaxic approaches can now be applied with great precision.[142] Should improvements in targeting translate into ameliorations in surgical outcomes, one may expect a revival of interest in psychiatric surgery, including surgeries used to treat certain cases of medically refractory aggressive behavior. Indeed, ablation in other targets have been previous reported for the control of aggressive behavior (eg, frontal lobotomy, leucotomy, subcaudate tractotomy, cingulectomy, thalamotomy, fornicotomy, hippocampotomy, anterior cingulotomy, anterior capsulotomy) and more recently, nucleus accumbens DBS was performed, with good results.[143] Moreover, patient self-aggressive characteristic and cognitive performance can be a determinant factor when deciding the best surgical technique (ablative/neuromodulatory). More severe patients or those who present aggressive behavior toward face/head may not be eligible for DBS due to a greater risk of complications such as infection, skin erosion, and lead fracture. Thus, future research is certainly necessary for the determination of optimal target and technique.

CONCLUSION

Aggressive behavior is generally managed with medication and/or behavioral approaches. In a small number of well-selected refractory cases, surgery has been proposed with promising results. Due to the potential for side effects, the use of hypothalamotomy and amygdalotomy has been fairly restricted. The reversibility of DBS makes it an attractive alternative for treating these disorders. For all applications of the technique, however, we stress the need for multidisciplinary teams who are experienced in managing aggressive patients. In addition, the treatments must be performed with high ethical standards and in accordance with local legislation.

Disclosures

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COMMENT

Does free will exist? Do humans have the ability to choose between what we consider good and evil, between moral and immoral behavior? The great majority of people in the world believe this to be the case. But until not very long ago we believed that infections were a divine punishment and that epilepsy was a sign of demonic possession. Are we on the cusp of viewing criminal or just plain nasty behavior as being biologically determined?

We have lesioning or DBS for movement disorders, well-established. We don't understand exactly how it works but we more or less know the targets. Brain surgery for pain? Doesn't work as well but what else do we have to offer some patients? Psychiatric surgery? Now you're getting controversial…but ok, it seems to work for OCD and it's worth working on for patients who are suicidally depressed. But surgery for aggression? This is the third rail of stereotactic and functional neurosurgery. Mind control, turning rambunctious free-thinkers into zombies, political repression…surely neurosurgeons aren't going to go near any of **that** again!

Read this paper, and open your minds. Consider the patients who are referred for this surgery. Amygdalotomy and hypothalamotomy, or DBS in those regions, are not for the jerk who takes your parking spot. These procedures are reserved for very rare patients, who cannot be managed anywhere without deep sedation, who have lost any quality of life by any reasonable measure, and whose families suffer tremendously. The authors bring together case reports and small, single center studies. As they point out, these all provide a "weak level of evidence", but one that is tantalizing nonetheless. Surgery for severe and medically refractory aggression should be studied and perfected in a small number of centers where there are proper multidisciplinary teams who can be trusted to select the rare patient candidates, and who will advance our knowledge in this area by carefully designed and ethically proper trials.

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