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

### 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

**Amygdala and Hypothalamus: Historical Overview With Focus on Aggression**

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. In the case of humans, the presence of complex emotions makes understanding the neurobiological mechanisms underlying human aggressive behavior a challenging task. 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 become a burden on the government as a result of their loss of productivity.

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. 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), postraumatic stress disorder (PTSD), and bipolar disorder. 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. The association between mental disorders and violent behavior is a common reason for patient institutionalization. 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. 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 lobe.
The hypothesized roles of the hypothalamus in relation to aggressive behavior are well recognized. The hypothalamus projects to the periaqueductal gray (PAG), which is involved in the regulation of pain and stress responses. The PAG also receives projections from the amygdala, which is a key brain region in mediating fear and aggression. The amygdala plays a crucial role in the processing of emotional stimuli and is involved in the regulation of autonomic responses, such as heart rate and blood pressure. The amygdala is also instrumental in the formation of emotional memories, which can influence aggressive behavior.

The amygdala is located in the temporal lobe and is divided into several subregions, each with distinct functions. One such subregion is the amygdala’s lateral nucleus, which is involved in the processing of fearful and threatening stimuli. The amygdala also receives input from the prefrontal cortex, which plays a role in top-down control and executive functions. Dysfunction in these connections can lead to abnormalities in the regulation of aggression.

The amygdala is also connected to the hypothalamus, which plays a critical role in the regulation of autonomic functions and the fight-or-flight response. The hypothalamus is involved in the regulation of the endocrine system and the release of hormones that affect mood and behavior. Dysfunction in these connections can lead to abnormalities in the regulation of aggression.

In conclusion, the amygdala and hypothalamus appear to be central regions in the neural circuitry underlying aggressive behavior. Dysfunction in these regions can lead to abnormalities in the regulation of aggression, which can manifest as impulsive and violent behavior. Understanding the role of these regions in aggression is critical for developing effective treatments and improving the quality of life for individuals affected by such disorders.
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 al144). 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    | Dopaminergic antagonists (mainly D2) | ID, DB, psychotic, schizophrenia, bipolar disorders                               | Extrapyramidal side effects when receptor occupancy exceeds 80%              |
| Atypical antipsychotics   | 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           | 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          | Alpha-2 adrenergic receptor agonists | ASD, DB                                                                           | Changes in blood pressure, decreased activity, sedation                      |
| Mood stabilizers (lithium)| Unknown. Possibly by interaction with glutamate receptors and/or with K⁺, Na⁺, Ca²⁺ channels | ID, DB, ADHD, bipolar aggressive patients, prison inmates                          | High risk for adverse drug reactions                                          |
| Psychostimulants (methylphenidate) | Dopamine and norepinephrine agonists | DB, ADHD, ODD                                                                      | Delay in weight gain and growth; cardiovascular risk                          |
| Anticonvulsants (divalproex sodium) | 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.5,10,17

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, Klüver and Bucy62,63 demonstrated that bilateral temporal lesions in rhesus monkeys markedly reduced aggressive behavior. Thereafter, Rosvold and colleagues64 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.
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, cingulotomy, hypothalamotomy, thalamotomy, fornixotomy, hippocampotomy, fornixotomy, 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 | 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 |
| 67/2012       | 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 + iodized oil (surgical wax) | No other surgery | 100% Clinical observations | No side effects reported | 3-15 |
| 68/2017       | 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 |
| 69/1966       | N: 40 | Follow-up of patients from previous paper (01/1963) | | | | | | | | | |
| 67/1968       | N: 44 M: 32 F: 12 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 |
| 69/1969       | 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 |
| 68/1970       | 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) |
|---------------|-----|--------|-----|------------|----------------------|-------------------------------|-----------------|---------------------------------|-----------------|------------------|-----------------------------|-------------|----------------|----------------|
| 1970          | N:12| All female | 23-69 yr | ID; PD; schizophrenia; In. patients | Aggressive and destructive behavior with or without seizures; self-mutilation | Amygdala and hypothalamus tractotomy (5) | PEG/PCV | DR of the amygdala | Thermal coagulation (55°C, 45 s) | Previous frontal lobotomy | 75% Psychological tests | No side effects reported | Up to 36 |
| 1973          | N:18| M: 13 F: 5 | 8-43 yr | ID; PD; AuD | Behavioral disturbances with seizures; abnormal aggressive behavior | Amygdala and hypothalamus tractotomy (5) | Angiograph | DR en route and at target | Thermal coagulation (3 x 1.8 mm probe) | Previous unilateral amygdalotomy | 55% | Several questionnaires | 11% Hemplegia with disability in one arm | 22% Deficit in face recognition | Up to 60 |
| 1966          | N:18| M: 14 F: 4 | 13-37 yr | ID; PD; schizophrenia | Aggressive and destructive behavior; refractory to ECT, drug therapy, and psychotherapy | Amygdala and hypothalamus tractotomy (5) | EEG; DR of the amygdala with electric stimulation | Thermal coagulation (60–65°C, 30 s) | Cryoprobe (–70°C, 3 min/–120°C, 3 min) | Previous leucotomy | 39%-50% | Several questionnaires | 22% | Convulsions | 5.5% | Persistent mild hemiparesis | 12-72 |
| 1966          | 235 | N/G N/A | 10-20 yr | C; schizophrenia | Aggression, violent and destructive behavior; low rage threshold; self-mutilation | Amygdala and hypothalamus tractotomy (5) | EEG; DR of the amygdala with electric stimulation | Thermal coagulation; mechanical methods; surgical wax | Simultaneous thalamotomy | Subsequent hypothalamotomy | 75% | Grading scale developed by the authors | 2.5% | Transient hemplegia | 1% Permanent hemplegia | 1% Temporary ballistic movement | 4% Mortality | Up to 108 |
| 1974          | N:10| M: 8 F: 2 | 10-20 yr | IH | Aggressive, assaultive and destructive behavior; low rage threshold; refractory to drug therapy | Amygdala and hypothalamus tractotomy (5) | EEG; DR of the amygdala with electric stimulation | Thermal coagulation; mechanical methods; surgical wax | Simultaneous thalamotomy | 100% | Grading scale developed by the authors | No side effects reported | 24-108 |
| 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 and hypothalamus tractotomy (5) | Head X-rays | EEG; DR of the amygdala with electric and olfactory stimulations (ether) | Thermal coagulation (70–80°C, 90°C, 60 s. Mono and bipolar) | Previous temporal lobectomy | 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 |
| 1975          | N:58 M:39 F:19 | 8-61 yr | C; In. patients | Aggressive and destructive behavior with or without seizures; refractory to therapies | Antero-medial amygdala and hypothalamus tractotomy (5) | PCV | Cryolesion | Previous frontal lobotomies | 30%-40% Structured psychiatric interviews; neuropsychological tests | Permanent hemiparesis | 2% | Transient hypersexuality | 5% | Temporary visual field defects | 9% Memory loss | 12% Others mild | 2.5% Behavior | 12-132 |

AMYGDALA AND HYPOTHALAMUS IN AGGRESSION
| 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) |
|---------------|----------------|------------|----------------------|-------------------------------|-----------------|---------------------------------|-------------------|-------------------|---------------------------------|-------------|---------------|
| 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 |
| 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 hippocampectomy (29) | 75-84% Clinical observations | No side effects reported | 24-156 |
| 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 |
| 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 |
| 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 | thermal coagulation 2 lesions in each nucleus (3 mm apart) | Thermal coagulation; surgical wax | Previous bifrontal tractotomy (100) | 100% Clinical observations | Disorders of facial recognition; social behavior; elements of Kluver and Bucy syndrome | 120 |
| 1988          | N:48I N/G <15 yr | ID; C; 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 hypothalamicotomy (47) Subsequent hypothalamo- or septal reductions (123) | 70% Clinical observations. Psychological assessments in 60 patients | 6% Transient hemiplegia | 36 |
| 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 fornix section (3) Temporal lobectomy (1) | 45-5% Clinical observations | No side effects reported | Up to 120 |
| 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) |
|--------------|----------------|------------|----------------------|-----------------------------|-----------------|-------------------------------|-----------------|--------------------|---------------------------------|-------------|----------------|
| 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 observation | Right hemiparesis and swallowing difficulty (surgical accident 1 patient) | 12-72 |
| 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 (180˚, 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 |
| 1992         | N: 2 N/G N/A | NR             | Medically intractable aggressive behavior | Amygdala nucleus not specified; All bilateral | PCV            | Thermal coagulation           | Simultaneous Subcaudate Tractotomy | 100% Several questionnaires | No side effects reported | 84 |
| 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; surgical 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 |
| 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 2/0 μs; 130 Hz 2-6.5 V | No other surgery | 100% Father rating scale; clinical observation; questionnaires | No side effects reported | 24 |
| 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) |
|--------------|------------|----------------|----------------------|-------------------------------|----------------|-------------------------------|------------------|------------------|-------------------------------|-------------|---------------|
| [NR/2007](#) | [1] Female 19 yr | ID | Refractory aggressive behavior | Whole amygdala Bilateral | Brain MR; stereotactic MR; 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 | N: 1217 | ID: 12 | Refractory: 14 | Lateral n: 2 | 1960s: PEG; PCV; CT | DR en route: 2 | Surgical wax: 6 | No other surgery: 12 | Total: 69.5% | No side effects: 12 | NR: 1 |
| | M: 268 | IN: 4 | With seizures: 13 | Medial n: 3 | 1970s: PEG; PCV; CT | DR local: 13 | Cryolesion: 3 | Previous: 8 | Permanent: 9 | 0-12: 2 | 10-24: 4 |
| | F: 139 | CT: 20 | | Posterior: 1 | 1980s: PEG; PCV; CT | Olfactory stimulation: 4 | Thermal: 15 | Simultaneous: 7 | 13-24: 4 | 25-36: 4 | 37-17 |
| | N/G: 810 | PTPD: 1 | | Centre: 1 | 1990s: MR; Stereotactic CT | Electric stimulation: 10 | DBS: 1 | Subsequent: 4 | | | |
| | 0-69 yr | OCD: 1 | | Anteromedial: 3 | 2000: MRI, Stereotactic CT, Corticography: 1 | Other stimulation: 1 | DBS: 1 | | | | |
| | | PD: 4 | | Whole: 4 | | | | | | | |
| | | AuD: 1 | | NR: 12 | | | | | | | |
| | | IH: 1 | | Bilateral: 907 | | | | | | | |
| | | SMPD: 1 | | Unilateral: 227 | | | | | | | |
| | | Hyperactivity: 4 | | | | | | | | | |
| | | Psychopath: 5 | | | | | | | | | |
| | | Schizophrenia: 6 | | | | | | | | | |
| | | Suicidal: 1 | | | | | | | | | |
| | | Depression: 1 | | | | | | | | | |
| | | Autism: 1 | | | | | | | | | |
| | | In.patients: 6 | | | | | | | | | |
| | | NR: 2 | | | | | | | | | |

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.
| 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) |
|---------------|----------------|------------|----------------------|-----------------------------|----------------|---------------------------|----------------|----------------|---------------------------------|-------------|---------------|
| 1972          | N: 11 M: 0 F: 0 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 |
| 1976          | N: 49 M: 0 F: 0 N/G N/A | CI; schizophrenia | Aggression, violent and destructive behavior; low rage threshold; self-mutation | 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 |
| 1988          | N: 122 M: 0 F: 0 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 |
| 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 | 79% Clinical observations | No side effects reported | Up to 300 |
| 2008          | 1 Male 18yr | 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       | 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; ventriculography > 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 |
| 2008          | 1 Male 22yr | ID | Drug-resistant aggressiveness | Posteromedial hypothalamus Bilateral | Brain MRI; ventriculography | Scalp EEG; DR, and electrical stimulation of the target | DBS | No other surgery | 100% ICAP | No surgical complications, worsening of unilateral headaches | 18 |
| 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) |
|--------------|----------------|------------|---------------------|-----------------------------|----------------|-------------------|-----------------|-----------------|-----------------------------------------------|--------------|
| 1972/2010    | 1 Female 22 yr | CI; ID     | Drug-resistant self-mutilating behavior | Posterior hypothalamus Bilateral | Not reported | Not reported | DBS Initial parameters: 15 V, 90 μs, 130 Hz | No other surgery | 100% Clinical observations | No surgical complications, no side effects of stimulation | 4            |
| 1972/2013    | 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"/71 min "off" | No other surgery | 100% Clinical observations | No surgical complications, no side effects of stimulation | 24           |
| 1973/2013    | 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 the 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 |
| 1975/2015    | N: 6 M: 4 F: 2 17-48 yr | CI; ID     | Uncontrollable refractory aggressiveness | Posteroomeral hypothalamus Laterality not reported | Brain MRI; stereotactic head CT scan; BrainLAB workstation. | 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, ITN | 83% ICAP | No surgical complications, worsening of unilateral headaches in 1 patient | Up to 82 |
| 1978/1988    | N: 5 M: 4 F: 1 16-33 yr | ID         | Intractable aggressive behavior | Posteroomeral 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 IED: 1

Refactory: 6 With seizures: 4

Posteroomeral: 3

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

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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; ITN = 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 = posteroomedial 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 |
|---------------|----------------------------|------------------------|----------------------------------------|-------------------------|--------------------------|
| 66/1963       | High                       | High                   | High                                   | High                    | High                     |
| 69/2012       | High                       | High                   | High                                   | High                    | High                     |
| 60/2017       | High                       | High                   | High                                   | High                    | High                     |
| 59/1966       | High                       | High                   | High                                   | High                    | High                     |
| 67/1968       | High                       | High                   | High                                   | High                    | High                     |
| 68/1969       | High                       | High                   | High                                   | High                    | High                     |
| 70/1970       | High                       | High                   | High                                   | High                    | High                     |
| 70/1970       | High                       | High                   | High                                   | High                    | High                     |
| 83/1966       | High                       | High                   | High                                   | High                    | High                     |
| 82/1969       | High                       | High                   | High                                   | High                    | High                     |
| 65/1966       | High                       | High                   | High                                   | High                    | High                     |
| 87/1974       | High                       | High                   | High                                   | High                    | High                     |
| 85/1975       | High                       | High                   | High                                   | High                    | High                     |
| 65/1975       | High                       | High                   | High                                   | High                    | High                     |
| 86/1978       | High                       | High                   | High                                   | High                    | High                     |
| 87/1976       | High                       | High                   | High                                   | High                    | High                     |
| 87/1977       | High                       | High                   | High                                   | High                    | High                     |
| 87/1980       | High                       | High                   | High                                   | High                    | High                     |
| 85/1981       | High                       | High                   | High                                   | Low                     | Low                      |
| 83/1982       | High                       | High                   | High                                   | High                    | High                     |
| 85/1983       | High                       | High                   | High                                   | High                    | High                     |
| 86/1986       | High                       | High                   | High                                   | High                    | High                     |
| 86/1988       | High                       | High                   | High                                   | Low                     | Low                      |
| 87/1992       | High                       | High                   | High                                   | Low                     | Low                      |
| 89/1998       | High                       | High                   | High                                   | Low                     | Low                      |
| 74/2002       | High                       | High                   | High                                   | Low                     | Low                      |
| 98/2007       | 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%                      |

#### Amygdalotomy studies

| Ref. and year | Random sequence generation | Allocation concealment | Blinding participants and investigators | Incomplete outcome data | Selective reporting bias |
|---------------|----------------------------|------------------------|----------------------------------------|-------------------------|--------------------------|
| 127/1972      | High                       | High                   | High                                   | High                    | High                     |
| 85/1966       | High                       | High                   | High                                   | High                    | High                     |
| 85/1966       | High                       | High                   | High                                   | High                    | High                     |
| 87/1988       | High                       | High                   | High                                   | High                    | High                     |
| 105/2008      | High                       | High                   | High                                   | High                    | High                     |
| 106/2008      | High                       | High                   | High                                   | High                    | High                     |
| 107/2008      | High                       | High                   | High                                   | Low                     | Low                      |
| 129/2010      | High                       | High                   | High                                   | High                    | High                     |
| 129/2013      | High                       | High                   | High                                   | High                    | High                     |
| 130/2013      | High                       | High                   | High                                   | Low                     | Low                      |
| 132/2015      | High                       | High                   | High                                   | Low                     | Low                      |
| 134/1988      | 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%                    |

#### Hypothalamotomy studies

The risk of bias is the percentage of bias items reported considering all included studies.
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 (e.g., 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. 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; i.e., 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. In patients with movement disorders, similar outcomes have been observed with the use of
these 2 approaches. 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. In a recent study, DBS was successfully used to treat an autistic teenager with life-threatening self-injurious behavior refractory to medications.

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. It is composed of several distinct nuclei with widespread connections throughout the nervous system. The hypothalamus is largely known for its role in controlling homeostasis and motivated behaviors.

Based on nuclear landmarks, the hypothalamus can be divided into 3 areas along its rostro-caudal axis: anterior, medial, and posterior. 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. 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. 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. 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. 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.

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.” Notwithstanding these promoting 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.
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. 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.

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 investigative 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. 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 stereotactic approaches can now be applied with great precision. Should improvements in targeting translate to be used to ensure optimal targeting.

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.

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REFERENCES

1. Batrinos ML. Testosterone and aggressive behavior in man. Int J Androloc Metab. 2012;10(3):563-568.
2. Comai S, Taur M, Gobbi G. The psychopharmacology of aggressive behavior. J Clin Psychopharmacol. 2012;32(1):83-94.
3. Siewer LJ. Neurobiology of aggression and violence. Am J Psychiatry. 2008;165(4):349-442.
4. Dorfman HM, Meyer-Lindenberg A, Buckholz JW. Neurobiological Mechanisms for Impulsive-Aggression: The Role of MAOA. In: Miczek K, Meyer-Lindenberg A. (eds). Neuroscience of Aggression. Current Topics in Behavioral Neurosciences, Vol. 17. Springer, Berlin, Heidelberg: 2013. doi:10.1007/978-54_2013_272.
5. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Vol. 64, Arlington, VA, American Psychiatric Association; 2013. doi:10.1176/appi.books.9780890425596.
6. Brentani H, de Paula CS, Bordini D, et al. Autism spectrum disorders: an overview on diagnosis and treatment. Rev Bras Psiquiatr. 2013;35(suppl 1):S62-S72.
7. Comai S, Taur M, Pavlovic Z, Gobbi G. The psychopharmacology of aggressive behavior. J Clin Psychopharmacol. 2012;32(2):237-260.
8. Arseneault L, Moffit TE, Caspi A, Taylor PJ, Silva PA. Mental disorders and violence in a total birth cohort. Arch Gen Psychiatry. 2000;57(10):979.
9. Blair R. The neurobiology of impulsive aggression. J Child Adolesc Psychopharmacol. 2016;26(1):4-9.
10. Rosell DR, Siewer LJ. The neurobiology of aggression and violence. CNS Spectr. 2015;20(5):254-279.
11. Rizvi TA, Ennis M, Belshehani MM, Shipley MT. Connections between the central nucleus of the amygdala and the midbrain periaqueductal gray: topography and reciprocity. J Comp Neurol. 1991;303(1):121-131.
12. Reppucci CJ, Petrovic GD. Organization of connections between the amygdala, medial prefrontal cortex, and lateral hypothalamus: a single and double retrograde tracing study in rats. Brain Struct Funct. 2016;221(6):2957-2962.
13. Swanson LW. What is the brain? Trends Neurosci. 2000;23(11):519-527.
14. LeDoux J. The amygdala. Curr Biol. 2007;17(20):R868-R874.
15. Swanson LW. The hypothalamus. In: Bjorklund A, Hokfelt T, Swanson L, eds. Handbook of Chemical Neuroanatomy, Vol. 5: Integrated Systems off the CNS. Part F, Amsterdam: Elsevier Sciences; 1987:1-124.
16. Buijs RM, Van Eden CG. The integration of stress by the hypothalamus, amygdala and prefrontal cortex: balance between the autonomic nervous system and the neuroendocrine system. Prog Brain Res. 2000;126:117-132. doi:10.1016/S0079-6123(00)26011-1.
17. Miczek KA, de Almeida RMM, Kravitz EA, Risman EF, de Boer SF, Raine A. Neurobiology of escalated aggression and violence. J Neurosci. 2007;27(44):11803-11806.
18. Nelson RJ, Trainor BC, Chiavegatto S, Demas GE. Phloretin contributions of nitric oxide to aggressive behavior. Neurosci Biobehav Rev. 2006;30(3):346-355.
19. Godar SC, Fite PJ, McFarlin KM, Borotallo M. The role of monooamine oxidase A in aggression: current translational developments and future challenges. Prog Neuropsychopharmacol Biol Psychiatry. 2016;60:99-100.
20. Citrome L, Volavka J. The psychopharmacology of violence: making sensible decisions. CNS Spectr. 2014;19(5):411-418.
21. Hassiotis A, Robertam D, Canagasabey A, Marston L, Thomas B, King M. Brief report: Impact of applied behaviour analysis (ABA) on carer burden and
28. Correll CU, Yu X, Xiang Y, Kane JM, Masand P. Biological treatment of acute aggression in pediatric patients with attention deficit hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2014;24(5):497-502.

29. Adler BA, Wink LK, Early M, et al. Drug-refractory aggression, self-injurious behavior, and severe tantrums in autism spectrum disorders: a chart review study. *Aust J Clin Psychiatry*. 2015;19(1):102-106.

30. Yu X, Correll CU, Xiang Y, et al. Efficacy of atypical antipsychotics in the management of acute agitation and aggression in hospitalized patients with schizophrenia or bipolar disorder: results from a systematic review. *Shanghai Arch Psychiatry*. 2016;28(5):241-252.

31. Taskiran PS, Coffey DBJ. Untremitting impulsive aggression in a child with childhood onset schizophrenia and pervasive development disorder—not otherwise specified: the role of stimulants, atypical antipsychotics and mood stabilizers. *J Child Adolesc Psychopharmacol*. 2013;23(5):363-366.

32. Fava M. Psychopharmacologic treatment of pathologic aggression. *Psychiatr Clin North Am*. 1997;20(2):427-451.

33. Baribeau DA, Anagnostou E. The update on medication management of behav-

34. Fava M. Psychopharmacologic treatment of pathologic aggression. *Psychiatr Clin North Am*. 1997;20(2):427-451.

35. Adler BA, Wink LK, Early M, et al. Drug-refractory aggression, self-injurious

36. Yu X, Correll CU, Xiang Y, et al. Efficacy of atypical antipsychotics in the management of acute agitation and aggression in hospitalized patients with schizophrenia or bipolar disorder: results from a systematic review. *Shanghai Arch Psychiatry*. 2016;28(5):241-252.

37. Willner P. The neurobiology of aggression: Implications for the pharmacotherapy of aggressive challenging behaviour by people with intellectual disabilities. *J Intelllect Disabil Res*. 2015;59(1):82-92.

38. Farmer CA, Arnold LE, Bukstein OG, et al. The treatment of severe child
treatment for sustaining resolution of severe aggression in a major neurocognitive disorder. *BMJ Case Rep*. 2018;2017:bcr-2017-222100.

39. van den Berg JF, Kruihoff HC, Kok RM, Verwijk E, Spans H-P. Electroconvul-

40. Malone RP, Delaney MA, Luebbert JF, Cater J, Campbell M. A double-blind placebo-controlled study of lithium in hospitalized aggressive children and adolescents with conduct disorder. *Arch Gen Psychiatry*. 2000;57(7):649.

41. List BA, Barzman DH. Evidence-based recommendations for the treatment of aggression in pediatric patients with attention deficit hyperactivity disorder. *Psychiatry Q*. 2011;82(1):33-42.

42. Hayes JF, Pitman A, Marston L, et al. Self-harm, unintentional injury, and suicide in bipolar disorder during maintenance mood stabilizer treatment. *JAMA Psychiatry*. 2016;73(6):630-637.

43. Hannestad J, Gallezot J-D, Planet-Wilson B, et al. Clinically relevant doses of methylphenidate significantly occupy norepinephrine transporters in humans in vivo. *Biol Psychiatry*. 2010;68(9):854-860.
96. van Manen J, van Veelen CW. Experiences in psycho-surgery in The Nether-lands: the Acta Neurochirurgica Scientiarum. 1988;44:167-169.

97. Sachdev P, Smith JS, Matheson J, Last P, Blumbergs P. Amygdalo-hippocampectomy for pathological aggression. Aust N Z J Psychiatry. 1992;26(4):671-676.

98. Lee GP, Bechara A, Adolphs R, et al. Clinical and physiological effects of stereotactic bilateral amygdalotomy for intractable aggression. J Neuropsychiatry Clin Neurosci. 1998;10(4):413-420.

99. Kim M-C, Lee T-K, Choi C-R. Review of long-term results of stereotactic psychosurgery. Neurol Med Choi (Tokyo). 2002;42(9):365-371.

100. Fountas KN, Smith JR, Lee GP. Bilateral stereotactic amygdalotomy for self-mutilation disorder. Stereotact Funct Neurosurg. 2007;85(2-3):121-128.

101. Sturm V, Fricke O, Bührlé C, et al. DBS in the basolateral amygdala improves symptoms of autism and related self-injurious behavior: a case report and hypothesis on the pathogenesis of the disorder. Front Hum Neurosci. 2012;6:341.

102. Zhang S, Zhou P, Jiang S, Li P, Wang W. Bilateral anterior capsulotomy and amygdalotomy for mental retardation with psychiatric symptoms and aggression. Medicine. 2017;96(1):10-13.

103. Harrison LA, Hurlemann R, Adolphs R. An enhanced default approach bias following amygdala lesions in humans. Psychol Sci. 2015;26(10):1543-1555.

104. Hortensius R, Terburg D, Morgan B, Stein DJ, van Honk J, de Gelder B. The dynamic consequences of amygdala damage on threat processing in Urbach–Wiethe Disease. A commentary on Puthmanaz et al. (2016). Cereb. 2017;88:192-197.

105. Greenberg BD, Askland KD, Carpenter LL. The evolution of deep brain stimulation for neuropsychiatric disorders. Front Biosci. 2008;13(13):6438-6448.

106. Hamani C, Hodaie M, Lozano AM. Present and future of deep brain stimulation for refractory epilepsy. Acta Neurochir (Wien). 2005;147(3):227-229.

107. Awan NR, Lozano A, Hamani C. Deep brain stimulation: current and future perspectives. NeuroFocus. 2009;27(1):E2.

108. Hamani C, Temel Y. Deep brain stimulation for psychiatric disease: contributions and validity of animal models. Sci Transl Med. 2012;4(142):142rv8-142rv8.

109. Hamani C, Florence G, Heinzen H, et al. Subthalamic nucleus deep brain stimulation: basic concepts and novel perspectives. eNeuro. 2017;4(5). doi:10.1523/ENEURO.0140-17.2017.

110. Reznikov R, Binko M, Nobrega JN, Hamani C. Deep brain stimulation in animal models of fear, anxiety and posttraumatic stress disorder. Neuropsychopharmacol. 2016;41(12):2810-2817.

111. Hitchcock E, Cairns V. Amygdalotomy. J Neurol Neurosurg Psychiatry. 1970;33(6):858-863.

112. Putman P, Herman E, Van Honk J. Emotional stroop performance for masked angry faces: it’s BAS, not BIS. Emotion. 2004;4(3):305-311.

113. da Cunha-Bang S, Fisher PM, Hjordt L V., Holst K, Knudsen GM. Amygdala reactivity to fearful faces correlates positively with impulsive aggression. Soc Neurosci. 2018;11-1. doi: 10.1084/j17470919.2017.1421262.

114. Schneider F, Habel U, Kessler C, Posse S, Grodd W, Müller-Gärtner HW. Functional imaging of conditioned aversive emotional responses in antipsychotic personality disorder. Neuropsychobiology. 2000;42(4):192-201.

115. Heesink T, Gladwin TE, Vink M, van Honk J, Kleber R, Geuze E. Neural activity during the viewing of emotional pictures in veterans with pathological anger and aggression. Eur Psychiatry. 2018;47:1-8.

116. Varkevisser T, Gladwin TE, Heesink L, van Honk J, Geuze E. Resting-state functional connectivity in combat veterans suffering from impulsive aggression. Soc Cogn Affect Neurosci. 2017;12(12):1881-1889.

117. Saxbe D, Lyden H, Gimbel SI, et al. Longitudinal associations between family aggression, externalizing behavior, and the structure and function of the amygdala. J Res Adolesc. 2018;28(1):134-149.

118. Birbaumer N, Veit R, Lotze M, et al. Deficient fear conditioning in psychopathy. Arch Gen Psychiatry. 2005;62(7):799.

119. Kiehl KA, Smith AM, Hare RD, et al. Limbic abnormalities in affective processing by criminal psychopaths as revealed by functional magnetic resonance imaging. Biol Psychiatry. 2001;50(9):677-684.

120. Glenn AL, Raine A, Schug RA. The neural correlates of moral decision-making in psychopathy. Med Psychiatry. 2009;14(3):5-6.

121. Heath R, Monroe R, Mickle W. Stimulation of the amygdaloid nucleus in a patient with basilar skull fracture and intracerebral haemorrhage. Acta Neurochir Suppl. 1980;30:161-167.

122. Tyree SM, de Lecea L. Lateral hypothalamic control of the ventral tegmental area: reward evaluation and the driving of motivated behavior. Front Syst Neurosci. 2017;11:50. doi:10.3389/fnsys.2017.00050.

123. Siegel A, Brutus M. Neural substrates of aggression and rage in the cat. In: Epstein AN, Morrison AR. (eds). The hypothalamus and behavior disorders. New York, NY, Academic Press; 1990:135-233.

124. van Manen J, van Veelen CW. Intractable aggression, externalizing behavior disorders. Acta Neurochirurgica Scientiarum. 1988;44:167-169.

125. Sachdev P, Smith JS, Matheson J, Last P, Blumbergs P. Amygdalotomy: a clinical and scientific study. Stereotact Funct Neurosurg. 1998;75(1):193-201.

126. Balasubramaniam V, Kanaka TS. Why hemispherectomy? J Neurol Neurosurg Psychiatry. 1989;52(5-6):367-373.

127. Vaermert K, Madsen A. Stereotactic amygdalotomy and basalfrontal tractotomy in psychotics with aggressive behaviour. J Neurol Neurosurg Psychiatry. 1970;33(6):858-863.

128. Bernassoni SA, Lynch ME, Holsot C. Bilateral stereotactic amygdalotomy. Nurs Times. 1981;77(43):1928-1930.

129. Hood T, Siegfried J, Wieser HG. The role of stereotactic amygdalotomy in the treatment of temporal lobe epilepsy associated with behavioral disorders. Appl Neurophysiol. 1983;6(1-4):19-25.

130. Jacobson R. Disorders of facial recognition, social-behavior and affect after combined bilateral amygdalotomy and subcortical tractotomy—a clinical and experimental-study. Psychol Med. 1986;16(2):439-450.

131. Hitchcock E, Cairns V. Amygdalotomy. J Neurol Neurosurg Psychiatry. 1970;33(6):858-863.
and reduced relationships between cortical/subcortical brain structures in position emission tomography. *Psychiatry Res.* 2004;130(1):11-25.

123. Van den Stock J, Hoertensius R, Sinke C, Goebel R, de Gelder B. Personality traits predict brain activation and connectivity when witnessing a violent conflict. *Sci Rep.* 2015;5(1):13779.

124. Sano K, Mayanagi Y. Posteromedial hypothalamotomy in the treatment of violent, aggressive behaviour. *Acta Neurochir Suppl (Wien).* 1988;44:145-151.

125. De Almeida AN, Fonoff ET, Ballester G, Teixeira MJ, Marino R. Stereotactic disconnection of hypothalamic hamartoma to control seizure and behavior disturbance: case report and literature review. *Neuromur Rev.* 2008;31(3):343-349.

126. Hernandez V, Pastor J, Pedrosa M, Peña E, Sola RG. Low-frequency bilateral hypothalamic stimulation for treatment of drug-resistant aggressiveness in a young man with mental retardation. *Stereotact Funct Neurosurg.* 2008;86(4):219-223.

127. Kuhn J, Lenartz D, Mai JK, Huff W, Klosterkoetter J, Sturm V. Disappearance of self-aggressive behavior in a brain-injured patient after deep brain stimulation of the hypothalamus: technical case report. *Neurosurgery.* 2008;62(5):E1182; discussion E1182. doi:10.1227/01.neu.0000325889.84785.69.

128. Maley JH, Alvarna JE, Valle EP, Richardson D. Deep brain stimulation of the orbitofrontal projections for the treatment of intermittent explosive disorder. *Neurouf Focus.* 2010;29(2):E11. doi:10.3171/2010.5.FOCUS10102.

129. Franzini A, Broggi G, Cordella R, Dones I, Messina G. Deep-brain stimulation for aggressive and disruptive behavior. *World Neurosurg.* 2013;80(3-4):S29.e11-S29.e14.

130. Torres C V, Sola RG, Pastor J, et al. Long-term results of postero medial hypothalamic deep brain stimulation for patients with resistant aggressiveness. *J Neurosurg.* 2013;119(2):277-287.

131. Benedetti-Isaac JC, Torres-Zambrano M, Vergas-Toscano A, et al. Seizure frequency reduction after postero medial hypothalamus deep brain stimulation in drug-resistant epilepsy associated with intractable aggressive behavior. *Epilepsia.* 2015;56(7):1152-1161.

132. Anand B, Brobek J. Hypothalamic control of food intake in rats and cats. *Yale J Biol Med.* 1951;24(2):123-140.

133. Sabatino JJ, Werner JK, Newsome SD. A rare case of hyponatremia from a hypothalamic lesion in a patient with multiple sclerosis. *Mult Scler.* 2015;21(5):662-665.

134. Ranson S, Fisher C, Ingram W. Hypothalamic regulation of temperature in the monkey. *Arch Neuropsych.* 1937;38(3):445-466.

135. Franzini A, Messina G, Cordella R, Marra C, Broggi G. Deep brain stimulation of the postero medial hypothalamus: indications, long-term results, and neurophysiological considerations. *Neurosurg Focus.* 2010;29(2):E13. doi:10.3171/2010.5.FOCUS1094.

136. Lapachak PA. Scientific rigor recommendations for optimizing the clinical applicability of translational research. *J Neurol Neurophysiol.* 2012;3(5):e111.

137. Ballantine HT. Historical overview of psychosurgery and its problematic. *Acta Neurochir Suppl (Wien).* 1988;44:125-128.

138. Neumaier F, Paterno M, Alpdogan S, et al. Surgical approaches in psychiatry: a commentary. *Stereotact Funct Neurosurg.* 2010;29(2):E13. doi:10.3171/2010.5.FOCUS1094.

139. Older J. Psychosurgery: ethical issues and a proposal for control. *Am J Orthopsychiatry.* 1974;44(4):661-674.

140. Mpakopoulou M, Gatos H, Broits A, Paterakis KN, Fountas KN. Stereotactic amygdalotomy in the management of severe aggressive behavioral disorders. *Neurosurg Focus.* 2008;25(11):E6. doi:10.3171/FOC/2008/25/11/E6.

141. Earp JD. Psychosurgery: the position of the Canadian Psychiatric Association. *Can J Psychiatry.* 1979;24(4):553-565.

142. Woerdeman PA, Willems PWA, Noordmans HJ, Berkelbach van der Spreenkel JW, van Rijen PC. Frameless stereotactic subcortical tractotomy for intractable obsessive-compulsive disorder. *Acta Neurochir (Wien).* 2006;148(6):633-637; discussion 637.

143. Park HR, Kim IH, Kang H, et al. Nucleus accumbens deep brain stimulation for a patient with self-injurious behavior and autism spectrum disorder: functional and structural changes of the brain: report of a case and review of literature. *Acta Neurochir.* 2017;159(1):137-143.

144. Alho EJL, Alho ATDL, Grimberg L, et al. High thickness histological sections as alternative to study the three-dimensional microscopic human sub-cortical neuroanatomy. *Brain Struct Funct.* 2018;223(3):1121-1132. doi:10.1007/s00429-017-1548-2.

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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, all that 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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