The hypothalamus at the crossroads of psychopathology and neurosurgery

Daniel A. N. Barbosa,1,2 Ricardo de Oliveira-Souza, MD, PhD,1,3 Felipe Monte Santo, MD,1,4 Ana Carolina de Oliveira Faria, MSc, PhD,1,3 Alessandra A. Gorgulho, MD, MSc,5,6 and Antonio A. F. De Salles, MD, PhD5,6

1Department of Clinical Neuroscience, D’Or Institute for Research and Education; 2Division of Neurosurgery and 3Department of Neurology and Psychiatry, Gaffrée e Guinle University Hospital, Federal University of the State of Rio de Janeiro; 4Intensive Care Unit, Icaraí Hospital, Niterói, RJ; 5HCor Neuroscience, São Paulo, Brazil; and 6Department of Neurosurgery and Radiation Oncology, David Geffen School of Medicine, University of California, Los Angeles, California

The neurosurgical endeavor to treat psychiatric patients may have been part of human history since its beginning. The modern era of psychosurgery can be traced to the heroic attempts of Gottlieb Burckhardt and Egas Moniz to alleviate mental symptoms through the ablation of restricted areas of the frontal lobes in patients with disabling psychiatric illnesses. Thanks to the adaptation of the stereotactic frame to human patients, the ablation of large volumes of brain tissue has been practically abandoned in favor of controlled interventions with discrete targets.

Consonant with the role of the hypothalamus in the mediation of the most fundamental approach-avoidance behaviors, some hypothalamic nuclei and regions, in particular, have been selected as targets for the treatment of aggressiveness (posterior hypothalamus), pathological obesity (lateral or ventromedial nuclei), sexual deviations (ventromedial nucleus), and drug dependence (ventromedial nucleus). Some recent improvements in outcomes may have been due to the use of stereotactically guided deep brain stimulation and the change of therapeutic focus from categorical diagnoses (such as schizophrenia) to dimensional symptoms (such as aggressiveness), which are nongeneric in terms of formal diagnosis. However, agreement has never been reached on 2 related issues: 1) the choice of target, based on individual diagnoses; and 2) reliable prediction of outcomes related to individual targets. Despite the lingering controversies on such critical aspects, the experience of the past decades should pave the way for advances in the field. The current failure of pharmacological treatments in a considerable proportion of patients with chronic disabling mental disorders is reminiscent of the state of affairs that prevailed in the years before the early psychosurgical attempts.

This article reviews the functional organization of the hypothalamus, the effects of ablation and stimulation of discrete hypothalamic regions, and the stereotactic targets that have most often been used in the treatment of psychopathological and behavioral symptoms; finally, the implications of current and past experience are presented from the perspective of how this fund of knowledge may usefully contribute to the future of hypothalamic psychosurgery.

https://thejns.org/doi/abs/10.3171/2017.6.FOCUS17256

KEY WORDS hypothalamus; deep brain stimulation; mental disorders; psychosurgery

©AANS, 2017

Neurosurg Focus Volume 43 • September 2017
tain detailed electrophysiological recordings in the operating room, enabling the development of increasingly accurate and less radical procedures. Thereafter, more detailed knowledge of the neuroanatomical substrates of specific psychiatric symptoms could be applied to the planning of discrete neurosurgical targets. These operations have also provided novel insights into the neurological underpinnings of psychopathology.

In the last decades of the 20th century, 2 advances provided momentum to the practice of functional neurosurgery. Conceptually, indications for surgery subtly shifted from diagnoses to symptoms. For example, during the years after lobotomy was performed for “schizophrenia,” indications for this procedure increasingly focused on symptoms, such as aggressiveness, which are not diagnosis specific.2 The other advance was technical, as shown by the substantial increase in the accuracy of stereotactic surgery due to major improvements in anatomical and functional imaging coupled with electrophysiological recording as confirmation of electrode placement.2 These techniques are progressively being incorporated into most current protocols of stereotactic psychosurgery.

With a volume of only 4 cm³, the human hypothalamus is an anatomically and functionally heterogeneous region seated at the base of the brain. It contains several nuclei that sustain intricate connections with each other as well as with distant parts of the brain and the endocrine system through the hypophysis.50,51 Creation of lesions and stimulation of discrete regions within the hypothalamus of experimental animals have proven their decisive contribution to the neural organization of fundamental approach (e.g., alimentary and sexual) and avoidance (e.g., fear) behaviors.5,52,57,99,113,114 Targeting specific regions of the human hypothalamus has constituted a major technical challenge due to their location and myriad of passing fibers. Many such drawbacks may be circumvented by the development of novel techniques, such as neuromodulation, radiosurgery, and focused ultrasound.20,55,63

Along with the cingulate gyrus and bundle, the amygdala, the anterior limb of the internal capsule, and the subcaudate white matter, the hypothalamus has been a common target for the treatment of a heterogeneous collection of psychopathological symptoms.64,73,85 Outcomes have ranged from poor to satisfactory to good.23,83,90 However, due to the controversial indications of psychosurgery, ethical objections, and the public backlash, the number of hypothalatomy for psychiatric conditions gradually decreased.90,106 The main sources of controversy have included a contentious theoretical basis (mostly animal-based studies), poor description of preoperative clinical presentations, dubious diagnostic criteria, prior treatment schedules, surgical indications, and classification of outcomes.76,90

Since the establishment of deep brain stimulation (DBS) as a safe, reversible, and ethically acceptable procedure, together with the development of more refined stereotactic techniques and imaging visualization of anatomy, the hypothalamus has risen again as a surgical target for the treatment of specific psychopathological symptoms.6 Hypothalamic DBS has been considered a possible therapeutic option for refractory obesity, panic disorder, and aggressive or disruptive behaviors in patients with mental impairment or brain damage.31,113 For some of those conditions, encouraging results are becoming available in the literature.

This article has 3 objectives: 1) to describe the functional organization of the hypothalamus; 2) to review the stereotactic targets that have been used for the treatment of psychiatric illness and incidentally elicited behavioral changes when stimulated; and 3) to discuss the possible implications of these reports for the future of hypothalamic psychosurgery.

Functional Organization of the Hypothalamus

The human hypothalamus is a small anatomically heterogeneous brain region involved in a gamut of physiological processes ranging from vegetative and endocrine functions to higher-order social behavior.8,18,19,50,97 Strategically placed at the crossroads of multiple functional systems, the hypothalamus is composed of a complex array of nuclei and thin fibers that run chiefly in the medial forebrain bundle, in the fornix, and in the ansa peduncularis.59,79,50,69 In all vertebrate species, the hypothalamus is a paramedian division of the basal diencephalon that lies below the thalamus, where it makes up the floor and lateral walls of the third ventricle.49

The complex anatomy of the hypothalamus is best represented by a combination of coronal, axial, and parasagittal sections alternatively stained for nerve fibers and cell bodies.59 In a rostrocaudal direction (Fig. 1), 3 major regions—preoptic (or chiasmal), tuberal (or infundibular), and mammillary—are easily seen with the naked eye.68 This rostrocaudal partition is supplemented by a tripartite mediolateral division represented by the periventricular, nuclear, and lateral zones, which form parallel zones with a distinctive cellular architecture and hodology.57 Table 1 summarizes the main hypothalamic nuclei that are known to be clinically relevant.

The Periventricular Zone

The periventricular zone (PVZ) is rudimentary in humans, in comparison with that of other mammals, consisting of a 1-mm-thick layer of subependymal neuron clusters without a clear structural organization; the PVZ is continuous with the periaqueductal gray substance with which it is connected through the dorsal longitudinal fascicle of Schütz.98 Despite the comparatively rudimentary structure of the human PVZ, its role in behavior is far from simple or unimportant. For example, Foerster and Gagel, in their 1933 publication,26 related that following removal of a cyst from the third ventricle of the patient in their Case 4, every time the surgeon gently wiped coagulated blood from the ventricle floor the patient burst out laughing, whistled, made jokes, and uttered obscene remarks. These fits of mania recurred as many times as the ventricle floor was swabbed, ceasing as contact was suspended. In 1957, Angelergues et al.3 reported a case of persistent euphoria in a patient who suffered a bilateral infarct of the PVZ without extension to the nuclear and lateral zones. Cases like those reported by Foerster and Gagel and Angelergues et al., although anecdotal, offer direct evidence for the critical role of a well-defined ana-
The hypothalamus as a psychosurgical target

Neurosurg Focus Volume 43 • September 2017

The hypothalamus as a psychosurgical target

Neurosurg Focus Volume 43 • September 2017

3

Tomical division of the hypothalamus in mood regulation, a fact that may bear important therapeutic and surgical applications. The importance of the PVZ for overall body homeostasis is also shown by its unique relationship with the adenohypophysis. The collection of neurons located in the arcuate and paraventricular nuclei (the “hypophysiotrophic area”) project to the portal system of the median eminence, where they secrete the hypothalamic hormones. At this point, the whole endocrine system is potentially open to all kinds of neural modulation issuing from multiple regions of the brain.

The Nuclear Zone

In contrast to the PVZ, the nuclear and lateral zones are larger (relative to overall brain volume) and more complex in humans compared with other mammals. The fornix divides these 2 zones as it pierces the hypothalamus on its way to the mammillary body.

TABLE 1. Main hypothalamic nuclei in the rostrocaudal direction

| Hypothalamic Division & Nucleus | Functional Associations |
|--------------------------------|------------------------|
| Preoptic or chiasmal | Thermal regulation, endocrine regulation of sexual behavior |
| Preoptic | | |
| Paraventricular | Regulation of antidiuretic hormone & oxytocin secretion, integration of neuroendocrine & autonomic response to stress |
| Suprachiasmatic | Regulation of circadian rhythms |
| Supraoptic | Secretion of neurohypophyseal hormones |
| Tuberal or infundibular | | |
| Arcuate | Food intake, cardiovascular regulation, monitoring of adipose tissue fat |
| Dorso medial | Daytime feeding schedule, emotional responses to stress/panic-related behavior, libido |
| Ventromedial | Food intake, weight gain/loss, lipolysis, sexual behavior |
| Mammillary | | |
| Posterior | Sympathetic responses, defensive & aggressive behaviors |
| Tubermammillary | Wakefulness; motivated behaviors in relation to food, water, sex, & drugs |
| Mammillary | Episodic memory encoding |
The anterior hypothalamus is located medial to the optic chiasm. Most rostral are the preoptic nuclei, which are involved in thermal regulation and in the endocrine regulation of sexual behavior. Caudal to the preoptic nuclei is the paraventricular nucleus, a vertical column of large cells in close relationship with the wall of the third ventricle medially and the column of the fornix laterally. This nucleus takes part in the secretion of antidiuretic hormone and oxytocin by the posterior pituitary; it is also essential for the integration of the neuroendocrine and autonomic response to stress. The supraoptic nucleus is slightly lateral, with a short extension rostral to the optic tract; like the paraventricular nucleus, it is also associated with the secretion of neurohypophysial hormones.

The tuberal (or infundibular) hypothalamus is rostrally continuous with the dorsal part of the anterior hypothalamus. The infundibular (or arcuate) nucleus is located anteroventrally, behind the optic chiasm, and forms the anterior wall of the infundibulum. It is involved in food intake, cardiovascular regulation, and the monitoring of adipose tissue fat. This region is also the location of the dorsomedial nucleus (DMN) and ventromedial nucleus (VMN), the latter being bounded dorsolaterally by the fornix. Lesions to the VMN modulate sexual behavior and lead to overeating and weight gain. DBS with electrodes located in this region increases lipolysis and leads to rejection of food and weight loss in animals and humans. The DMN is bounded rostrally by the paraventricular nucleus and has been implicated in daytime feeding and the emotional responses to stress, such as panic-related behavior. Surgical lesions of this nucleus in both male and female patients have caused persistent impotence and loss of libido unrelated to the blood levels of sexual hormones. High-frequency stimulation of this zone leads to sexual arousal.

The posterior hypothalamus includes the posterior nucleus, the tuberomammillary nucleus, and the mammi-
The hypothalamus as a psychosurgical target

Historically associated with sympathetic responses and defensive and aggressive behaviors, the posterior nucleus is limited caudally by the mammillothalamic tract. It is located above the tuberomammillary nucleus, which contains histaminergic neurons that have been implicated in the promotion of wakefulness and motivated behaviors in relation to food, water, sex, and drugs. The mammillary bodies constitute one of the major nodes of the classical circuit of Papez, which is essential for episodic memory encoding. The posterior hypothalamus and adjoining brainstem regions are critical for behavioral wakefulness, as originally proposed by von Economo based on clinicopathological cases of lethargic encephalitis.

The Lateral Zone

The lateral hypothalamus represents the associative zone of the hypothalamus; a number of complex fiber systems make their way through this zone toward and from the hypothalamic nuclei in relation to distant regions of the forebrain and brainstem. The most conspicuous fiber systems that pass through the lateral hypothalamus comprise the medial forebrain bundle, the fornix, and the ansa peduncularis. The lateral hypothalamic area (LHA) also contains the lateral hypothalamic nucleus, which is ventrally and medially limited by the tuberomammillary nucleus. The lateral and ventromedial nuclei constitute the classical “feeding center” because they exert reciprocal functions in eating behavior. Thus, bilateral lesions of the LHA produce weight loss in experimental animals, while electrical stimulation of this region increases appetite and food intake.

The Hypothalamus as a Stereotactic Target

Lessons From the Past: The Hypothalamosotomies

Four groups published the main papers on the hypothalamus as a psychosurgical target to treat refractory aggressive behavior. Sano, in a 1962 article, was the first to define this hypothalamic target as the site of maximum sympathetic response elicited by electrical stimulation, an area that is currently known as the “ergotropic, or Sano’s triangle.” This procedure, initially called “sedative neurosurgery,” was more efficient than other approaches, leading to calming effects in the first 22 cases. These results were confirmed in a series of 42 cases in which the patients were followed for 2 to 7 years, with outcomes categorized as “excellent” (12 patients became calm, with no violent, aggressive, or restless behavior, requiring no care or supervision) or “good” (28 patients became calm and tractable with only occasional irritability, requiring no constant care or supervision). In 1988, Sano and Mayanagi reported on the long-term outcome (10–25 years) for 37 of the 60 patients operated on from 1962 to 1977. The results were considered satisfactory in 29 cases (78%); 18 of these 29 patients presented no violent or aggressive behavior postoperatively, allowing familial and social adaptation. A South American group presented a series of 11 cases in which patients were treated with bilateral or unilateral (1 case) posteromedial (PM) hypothalamotomy: 5 patients suffered from mental retardation, 2 patients were diagnosed with psychopathic personality, and 1 patient was diagnosed with schizophrenia. After 6–48 months of follow-up, 10 patients had satisfactory results, with social adaptation and complete disappearance of violent behavior in 7 cases. From 1970 to 1972, Arjona performed stereotactic lesions of the posteromedial hypothalamus (PMH) to treat aggressive behavior in 11 pediatric patients with mental retardation (age range 3–13 years) who did not respond to other treatments. After cryogenic lesions to the PMH (unilateral in 1 case), aggressive behavior and agitation improved in all patients, and they were later able to live at home and mix with other children.

One group from India presented results of amygdalotomy and hypothalamotomy in the treatment of refractory aggressive behavior. One report published in 1975 included 49 patients who underwent PM hypothalamotomy, performed after failure of amygdalotomy in 33 cases. The results in the 8 cases in which primary bilateral PM hypothalamotomy was performed were considered “good.” Unilateral primary hypothalamotomy had good results in 5 of 8 patients, while unilateral secondary procedures were considered useful in 15 of 20 patients. The authors suggested that unilateral hypothalamotomy may work well only in patients who have previously undergone amygdalotomy.

Later, in an article published in 1988, Ramamurthi (from the same group) described his experience with 603 operations (122 hypothalamotomies) and concluded that about two-thirds of children with refractory aggressive behavior may benefit from amygdalotomy, hypothalamotomy, or a combination of both.

In the 1970s, based on evidence from animal studies and clinical observations, stereotactic lesions to the ventromedial hypothalamic nucleus (VMH) were also applied in the neurosurgical treatment of drug addiction. One case of intractable drug and alcohol addiction was included in Müller’s series of hypothalamic psychosurgery. A 30-year-old man with a history of delirium, acute kidney failure, generalized epileptic seizures, and toxic liver damage due to heavy alcohol and drug intake underwent unilateral hypothalamotomy involving the right nucleus of Cajal and the lateral field of the tuber cinereum. Despite promising early effects on his addiction and lack of adverse effects (including changes in libido), he had to be committed to a psychiatric hospital 10 months after the surgery due to a relapse of alcoholism. In a series of 13 patients treated with ventromedial (VM) hypothalamotomy (bilateral in 6 cases) for alcohol and drug addiction, 3-year follow-up showed increased self-control, but the patients also had increased appetite, weight gain, and reduced sexual drive. These unwanted effects made the treatment impractical, and it was abandoned.

In 1974, a Danish group reported on a series of 5 patients with gross obesity who underwent exploratory electrical stimulation of the lateral hypothalamic area (LHA). A convincing hunger response was elicited in 3 cases. Right-sided hypothalamotomy of this region was performed in these patients. One of the patients also underwent an additional contralateral electrocoagulation procedure 3 months later. Even though the patients’ body weight did not change significantly, the treated patients showed a considerable, although transient, decrease in spontaneous calorie intake, which was not observed in the other 2 patients who had only undergone exploratory
surgery. The rationale for this operation was based on the harmful consequences of obesity together with the unsatisfactory results of other therapeutic options.72

From the mid-1960s to the late 1970s, the indications for hypothalamotomy were extended to include the treatment of sexual deviations.23,64,77–80 The main stereotactic target was the VMH (or Cajal’s nucleus), which was destroyed bilaterally in some cases.23,80 Some of the conditions being treated were not well defined by the authors, and others (e.g., homosexuality) are no longer considered paraphiliases.35,76 Hence, even though authors often speak of “improvement or cure of the sexual deviation,” their cases and series must be analyzed with caution.

The first successful treatment of uncontrollable pedophilia by means of VM hypothalamotomy was performed in 1962.77 Although only limited outcome information is provided, aberrant sexual impulses were affirmed to be suppressed for the 3 years of follow-up. Interestingly, the patient also became incapable of indulging in erotic fancies and stimulating visions.77 From that time until 1979, a total of 75 patients considered sexually abnormal were reported to have been subjected to hypothalamotomies in West Germany.80 In 1973, Müller et al. presented a case series of 22 patients, 20 of whom underwent VM hypothalamotomy for a variety of so-called “sexual deviations,” mostly with good outcome. For undisclosed reasons, the ventromedial preoptic area was also lesioned in cases of heterosexual deviations in this series. One patient with pedophilic disorder who was considered successfully treated presented with hyperphagia and obesity at the 3-month follow-up visit; he had gained 32 kg from the operation.64

Increased appetite and weight gain were also observed in 5 patients and were considered to have great decreases in aggressive sexual traits and compulsions after surgery, allowing more harmonious family management and improvement in social interactions.12,27,29,30 Three years after the first favorable results of these studies, 2 other case reports of PMH DBS for aggressive behavior were published.38,44 A group from Madrid described the case of a male patient with idiopathic mental retardation and daily refractory aggressive crises who had good response to low-frequency stimulation as determined by evaluation with the Inventory for Client and Agency Planning (ICAP). At 18 months of follow-up, the patient had had 4 periods of aggressiveness, each lasting 2–3 days.38 Kuhn et al. reported on a case of a 22-year-old woman with severe self-mutilating behavior after traumatic brain injury. Under high-frequency PMH DBS, she experienced a pleasant sense of inner peace and showed complete elimination of self-aggressive behavior during a 4-month observation period.44

In 2013, the same group from Madrid also presented long-term results of PMH DBS for intractable aggressiveness in a series of 6 patients with mental retardation.103 Five showed a significant reduction in aggressiveness evaluated with the ICAP, while improvements in social interactions and sleep patterns were observed in 3 and 4 patients, respectively. Interestingly, the authors refer to similar responses with low- and high-frequency stimulation.103 In another series, 4 patients with moderate to severe cognitive compromise underwent PMH DBS for aggressive behavior associated with Sotos syndrome and nongenetic causes. Aggressive behavior improved in these patients as assessed by the Modified OAS (MOAS) as well as by the Quality of Life Scale (QOLS).104

In 2008, Hamani et al. reported on the case of a morbidly obese patient treated with bilateral DBS of the ventral hypothalamus. No weight change was observed in the first 6 months with high-frequency (130-Hz) stimulation; however, the patient lost 12 kg following a 5-month period of low-frequency (50-Hz) stimulation. The weight loss was seemingly due to a reduction in food craving and a decreased tendency to binge eat, with no intentional changes in his diet or changes in his exercise habits. Without stimulation, the binge-eating episodes returned, and the patient regained the weight he had lost.36

Following the reports by Hamani et al.36 and others,73,113 an FDA-approved pilot study on DBS targeting the LHA for the treatment of refractory obesity was performed.112

Behavioral Effects of Hypothalamic Stimulation in the DBS Era

The development of DBS and modern stereotactic techniques has allowed the resurgence of the hypothalamus as a target for ethically accepted psychosurgical interventions. The chief application of hypothalamic DBS for psychiatric patients has been refractory aggressive behavior in mentally impaired patients. Nevertheless, other potential uses of these procedures are increasingly being explored. A brief literature review on hypothalamic DBS for behavioral symptoms is summarized in Table 2.

The DBS target for aggressive behavior follows the coordinates described decades ago by Keiji Sano.83 Four groups of authors have reported on results of bilateral PM hypothalamic DBS in a total of 19 patients. Franzini and collaborators presented a series of 7 patients with severe mental retardation who were operated on between 2002 and 2010.27 Six of these patients benefited from high-frequency stimulation of the PM hypothalamus with marked reduction in aggressive behavior as assessed by the Overt Aggression Scale (OAS), followed by simplification of family management and improvement in social interactions.12,27,29,30 Three years after the first favorable results of these studies, 2 other case reports of PMH DBS for aggressive behavior were published.38,44 A group from Madrid described the case of a male patient with idiopathic mental retardation and daily refractory aggressive crises who had good response to low-frequency stimulation as determined by evaluation with the Inventory for Client and Agency Planning (ICAP). At 18 months of follow-up, the patient had had 4 periods of aggressiveness, each lasting 2–3 days.38 Kuhn et al. reported on a case of a 22-year-old woman with severe self-mutilating behavior after traumatic brain injury. Under high-frequency PMH DBS, she experienced a pleasant sense of inner peace and showed complete elimination of self-aggressive behavior during a 4-month observation period.44

In 2013, the same group from Madrid also presented long-term results of PMH DBS for intractable aggressiveness in a series of 6 patients with mental retardation.103 Five showed a significant reduction in aggressiveness evaluated with the ICAP, while improvements in social interactions and sleep patterns were observed in 3 and 4 patients, respectively. Interestingly, the authors refer to similar responses with low- and high-frequency stimulation.103 In another series, 4 patients with moderate to severe cognitive compromise underwent PMH DBS for aggressive behavior associated with Sotos syndrome and nongenetic causes. Aggressive behavior improved in these patients as assessed by the Modified OAS (MOAS) as well as by the Quality of Life Scale (QOLS).104

In 2008, Hamani et al. reported on the case of a morbidly obese patient treated with bilateral DBS of the ventral hypothalamus. No weight change was observed in the first 6 months with high-frequency (130-Hz) stimulation; however, the patient lost 12 kg following a 5-month period of low-frequency (50-Hz) stimulation. The weight loss was seemingly due to a reduction in food craving and a decreased tendency to binge eat, with no intentional changes in his diet or changes in his exercise habits. Without stimulation, the binge-eating episodes returned, and the patient regained the weight he had lost.36

Following the reports by Hamani et al.36 and others,73,113 an FDA-approved pilot study on DBS targeting the LHA for the treatment of refractory obesity was performed.112
At a mean duration of follow-up of 35 months, no serious long-term adverse effects (including unwanted psychological consequences) had been observed. After metabolically optimized LHA DBS settings, promising weight loss trends accompanied by a decreased urge to eat and increased subjective feelings of energy were reported. These effects proved reversible when the stimulator was turned off in a blinded fashion. A larger follow-up report focusing on efficacy and metabolic results is expected. Furthermore, sudden unexpected behavioral changes during implantation of DBS electrodes in the hypothalamus were reported in the literature (Table 3). Bejjani et al. reported on a case of a patient with advanced Parkinson’s disease successfully treated by bilateral stimulation of the subthalamic nucleus who developed acute transient aggressive behavior during intraoperative electrical test stimulation. The authors suggest that the site where stimulation produced the rage episode was located on the exploratory medial track, at the lateral border of the PMH. This fortuitously evoked response paved the way for the rebirth of hypothalamic surgery for the treatment of aggressive behavior in mentally retarded patients.

Other effects of hypothalamic DBS may also provide insights to tackle other psychiatric symptoms. The first reported series of ventroposterior hypothalamic (VPH) DBS for treatment of refractory chronic cluster headache (CCH) featured a male patient with signs of mild hypersexual and hyperphagic behavior, which seemed to be resolved with stimulation; he lost 25 kg at 18-month follow-up. In other 2 reports of ipsilateral VPH DBS for CCH, a total of 3 patients presented panic attacks during stimulation. Schoenen et al. reported that one of their 6 patients needed to

| TABLE 2. Brief review of literature on hypothalamic DBS for behavioral disorders |
| Authors & Year | No. of Pts (sex) | Study Type | Target | Indication | Outcome |
|----------------|------------------|------------|--------|------------|--------|
| Hamani et al., 2008 | 1 (M) | Case report | Ventral hypothalamus (bilat) | Refractory morbid obesity | Reduced food cravings, decreased tendency to binge* |
| Hernando et al., 2008 | 1 (M) | Case report | PMH (bilat) | Refractory aggressive behavior associated with mental retardation | Reduced aggressive behavior & improved social interactions, simplification of familiar management |
| Kuhn et al., 2008 | 1 (F) | Case report | PMH (bilat) | Refractory self-aggressive behavior after brain injury | Subjective experience of inner peace, disappearance of self-aggressive behavior |
| Franzini et al., 2005, 2007, 2013 | 7 (6 M, 1 F) | Case series | PMH (bilat) | Refractory aggressiveness & severe mental retardation | Reduced aggressiveness at 1 yr in 6 of 7 pts, improved family & social interactions |
| Torres et al., 2012 | 6 (4 M, 2 F) | Case series | PMH (bilat) | Refractory aggressive behavior related to mental retardation | Reduced aggressive behavior in 5 of 6 pts, improved social interactions in 3 of 6 pts & sleep patterns in 4 of 6 pts |
| Whiting et al., 2013 | 3 (1 M, 2 F) | Pilot study | LHA (bilat) | Refractory morbid obesity | Decreased urge to eat, increased energy levels |
| Micieli et al., 2016 | 4 (3 M, 1 F) | Case series | PMH (bilat) | Refractory aggressive behavior related to mental retardation | Reduced aggressive behavior & improved quality of life§ |

* Only during the 5 months after the system was set to a lower frequency during which the patient kept the stimulation constantly turned on. These effects were not observed in high-frequency stimulation during the initial 6-month period.
† Assessed by ICAP.
‡ Assessed by OAS.
§ Assessed by MOAS and QOLS.

| TABLE 3. Unexpected behavioral changes evoked by DBS to the hypothalamus |
| Authors & Year | No. of Pts (sex) | Study Type | DBS Indication | Stimulation Site | Main Unexpected Effect |
|----------------|------------------|------------|----------------|------------------|-----------------------|
| Bejjani et al., 2002 | 1 (M) | Case report | PD | Lat part of PM hypothalamus | Induction of aggressive behavior |
| Franzini et al., 2003 | 5 (4 M, 1 F) | Case series | CCH | VPH (ipsilateral) | Sex & food intake normalization in 1 male pt* |
| Schoenen et al., 2005 | 6 (5 M, 1 F) | Case report | CCH | VPH (ipsilateral) | Induction of panic attacks in 1 pt |
| Rasche et al., 2006 | 1 (F) | Case report | CCH | VPH (ipsilateral) | Induction of panic attacks |
| Bartsch et al., 2008 | 6 (4 M, 2 F) | Case series (multicenter) | CCH | VPH (ipsilateral) | Induction of panic attacks in 2 pts |
| Hamani et al., 2008 | 1 (M) | Case report | Obesity | Ventral hypothalamus (bilat) | Evocation of detailed autobiographical memories |
| Wilent et al., 2010 | 1 (F) | Case report | Obesity | VMH (bilat) | Induction of panic attacks |

PD = Parkinson’s disease.
* Signs of mild hypersexual and hyperphagic behavior were observed in this patient prior to the operation; he had lost 25 kg by the 18-month follow-up visit.
† Estimated to be in close association with the fornix.
have the implantation procedure interrupted due to a panic attack associated with polypharmacy, tachycardia, and moderate hypertension. After the operation, the patient’s vital signs returned to normal. In a multicenter case series reported by Bartsch et al., 2 of 6 patients experienced panic as a side effect of DBS. Such episodes were not further described in this study. A similar case was reported by Rasche et al., 35 a 39-year-old woman developed tachycardia, diplopia, and panic attacks during intraoperative test stimulation of the left ventroanterior for CCH. Some authors consider these side effects typical of this procedure. 4,5

In 2010, Wilent et al. reported panic attacks in response to stimulation of the VMH in a 50-year-old woman undergoing bilateral implantation of DBS leads into the lateral hypothalamus for the treatment of obesity. 6,13 The patient had a dramatic increase in anxiety, blood pressure, and heart rate, accompanied by hyperventilation and nausea. While stimulation of this area in either hemisphere led to the aforementioned response, stimulation appeared to be more effective at the center of the VMH.

A unique behavioral effect reported by Hamani and colleagues 36 in a patient treated with DBS for obesity was the elicitation of detailed autobiographical memories and déjà vu experiences during bilateral stimulation of contacts located in the ventral hypothalamus, which were estimated to be close to the fornix. An associative memory task administered in a double-blind stimulation on/off protocol indicated that stimulation increased recollection but not familiarity-based recognition, indicating a functional engagement of the hippocampus. Electroencephalographic source localization demonstrated that stimulation of this region in either hemisphere modulates activity in mesial temporal lobe structures related to memory. 36

Implications for the Future

The hypothalamus has been used as a stereotactic target throughout the decades of the neurosurgical endeavor to ameliorate the mind and behavior in a host of otherwise hopeless psychiatric disorders. 10,16,56,100 Neuroscience researchers have employed different techniques to reveal the minutiae of the functions of the hypothalamus, ranging from the tracing of fiber pathways to advanced molecular analysis. 48,5099 The hypothalamus mainly exerts an integrative role; that is, it receives a range of afferent inputs and effectuates autonomic, endocrine, and behavioral responses to achieve homeostasis through allostasis. 87 Accordingly, the hypothalamus has been implicated in psychiatric diseases related to feeding, sexual behavior, aggression, and fear. Moreover, it can evoke self-related memories, usually described as pleasant experiences. 96

Stereotactic approaches to specific nuclei or regions of the hypothalamus have provided a unique background for a better understanding of the neural basis of several behavioral disorders (obesity, aggressive behavior, panic disorder, addiction, and paraphilic disorders). 11,23,26,33,36,112 A better understanding of the underlying circuitry of specific behavioral functions—i.e., feeding, drug consumption, aggression, sexuality, and fear—together with the implementation of neuromodulation paradigms (e.g., optogenetic stimulation, radiosurgery, focused ultrasound, intraoperative electrophysiological mapping) and the prediction of the network-level response to different focal stimulations of hypothalamic nuclei or white matter fibers (i.e., with simulation studies) may lead to the development of novel and optimized stereotactic targets and clinical trials of neurosurgery for psychiatric disorders. 4,20,55,63

Summary and Conclusions

Interest in the hypothalamus as a potential target for psychosurgery dates back to the beginning of the 20th century. 18,19,39 This interest was channeled into practical action following the adaptation of the stereotactic apparatus to human patients, allowing neurosurgeons to aim at the hypothalamus with unprecedented precision. 66 Initially, the choice of specific targets was largely based on inferences from animal studies and on a few cases of relatively discrete war injuries of the basal forebrain. 41,83 In the 1960s and 1970s, hypothalamotomies were performed for intractable aggressiveness associated with mental retardation, morbid obesity, sexual deviations, and alcohol and drug dependence. 33,54,73,83 Despite a lack of consistent scientific support and the fierce opposition put up by both medical professionals and the mass media, hypothalamotomy and, for that matter, psychosurgery as a whole, became increasingly popular from 1935 to the late 1950s. During this period, surgery for the treatment of mental illness was performed in several countries, including Brazil; although its frequency decreased dramatically in the mid-1950s after reserpine and chlorpromazine were introduced into clinical practice, surgical treatment continued to be performed in a few medical centers. 10,16,56,100

Notwithstanding the lack of consensus in critical areas, the experience of the past 80 years should provide a valuable contribution to the understanding of the neurology of mental illnesses and the trails to be followed in the pursuit of novel therapeutic strategies. The slow resurgence of psychosurgery in the past decades has been propelled by its increasing acceptance by lay people as well as by the recognition of the failure of pharmacological treatments in at least 20% of patients with the severest forms of mental disorders. It may seem ironic that we stand today in a situation that in some ways resembles the one we faced in the initial decades of the twentieth century, when legions of human beings were hopelessly disabled by mental illness. 107 The time could hardly be more auspicious for the development of novel ways of treating them and alleviating their suffering. The rebirth of psychosurgery is a promising avenue in this direction. 50

References

1. Alt KW, Jeunesse C, Buitrago-Téllez CH, Wächter R, Boës E, Pichler SL: Evidence for stone age cranial surgery. *Nature* 387:360, 1997
2. Alterman RL, Sterio D, Beric A, Kelly PJ: Microelectrode recording during posteroventral pallidotomy: impact on target selection and complications. *Neurosurgery* 44:315–323, 1999
3. Anand BK, Brobeck JR: Hypothalamic control of food intake in rats and cats. *Yale J Biol Med* 24:123–140, 1951
4. Anderson DJ: Optogenetics, sex, and violence in the brain: implications for psychiatry. *Biol Psychiatry* 71:1081–1089, 2012
5. Angerlegues R, De Ajuriaguerra J, Hecaaen H: [Paralysis of
The hypothalamus as a psychosurgical target

Neurosurg Focus Volume 43 • September 2017

23. Dieckmann G, Schneider-Jonietz B, Schneider H: Deep brain stimulation for psychiatric disorders: beyond Portugal and the United States. Acta Neurochir Suppl 23:48–55, 2013

26. Foerster O, Gagel O: [A case of colloid cyst of the third ventricle. A input to the question of the relationship between psychiatric disorders and the brainstem.] Z Gesamte Neurol Psychiatr 149:312–344, 1933 (Ger)

27. Franzini A, Broggi G, Cordella R, Dones I, Messina G: Deep-brain stimulation for aggressive and disruptive behavior. World Neurosurg 80:S29.e11–S29.e14, 2013

28. Franzini A, Ferroli P, Leone M, Broggi G: Stimulation of the posterior hypothalamus for treatment of chronic intractable cluster headaches: first reported series. Neurosurgery 52:1095–1101, 2003

29. Franzini A, Marras C, Ferroli P, Bugiani O, Broggi G: Stimulation of the posterior hypothalamus for medically intractable impulsive and violent behavior. Stereotact Funct Neurosurg 83:63–66, 2005

30. Franzini A, Marras C, Tringali G, Leone M, Ferroli P, Bussone G, et al: Chronic high frequency stimulation of the posteromedial hypothalamus in facial pain syndromes and behaviour disorders. Acta Neurochir Suppl 97:399–406, 2007

31. Franzini A, Messina G, Cordella R, Marras C, Broggi G: Deep brain stimulation of the posteromedial hypothalamus: indications, long-term results, and neurophysiological considerations. Neurosurg Focus 29(2):E13, 2010

32. Fulgraff G, Barbey I: [Stereotactic neurosurgery for anosmic sexual behavior.] Abschlussbericht der Kommission beim Bundesgesundheitsamt. Berlin: Reimer, 1978 (Ger)

33. Fuss J, Auer MK, Biedermann SV, Briken P, Hacke W: Deep brain stimulation to reduce sexual drive. J Psychiatry Neurosci 40:429–431, 2015

34. Gooley JJ, Schomer A, Saper CB: The dorsomedial hypothalamic nucleus is critical for the expression of food-entrainable circadian rhythms. Nat Neurosci 9:398–407, 2006

35. Halász B, Popp L, Uhlarik S: Hypophysiotrophic area in the primate hypothalamus. J Neuroendocrinol 14(6):93–101, 1975

36. Hamani C, McAndrews MP, Cohn M, Oh M, Zumsteg E, Sturm V: Disappearance of self-aggressive behavior in a brain-injured patient after deep brain stimulation of the amygdala and anterior thalamic nucleus is critical for the expression of food-entrainable circadian rhythms. Nat Neurosci 9:398–407, 2006

37. Herman JP, McKlveen JM, Ghosal S, Kopp B, Wulsin MA, et al: Regulation of the hypothalamic-pituitary-adrenal axis by stress. J Clin Endocrinol Metab 86:195–244, 1940

38. Hernando 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 86:219–223, 2008

39. Ingram WR: Nuclear organization and chief connections of the anterior temporal cortex in the human brain. J Comp Neurol 115:333–369, 1960

40. Jarema M: Biological treatment in psychiatry: beyond pharmacology. Neuro Endocrinol Lett 29 (Suppl 1):7–68, 2008

41. Kleist K: [War injuries of the brain and their implications for neuroanatomy and neuropathology.] Handbuch der ärztlichen Erfahrungen im Weltkriege 1914/1918. Leipzig: Barth, 1934 (Ger)

42. Klingler J, Gloor P: The connections of the amygdala and of the anterior temporal cortex in the human brain. J Comp Neurol 115:333–369, 1960

43. Kotowicz Z, Gottlieb Burckhardt and Egas Moniz—two beginnings of psychosurgery. Gesnerus 62:77–101, 2005

44. 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 62(2):E1182, 2008

45. Laicéan G, De Salles AA, Gorgulho AA, Krahl SE, Frichtetto
L., Behnke EJ, et al: Modulation of food intake following deep brain stimulation of the ventromedial hypothalamus in the vervet monkey. J Neurosurg 108:336–342, 2008
46. Lang J: Stereotaxic anatomy of the hypothalamus. Acta Neurochir (Wien) 75:5–22, 1985
47. Le Gros Clark WE: The topography and homologies of the hypothalamic nuclei in man. J Anat 70:203–214, 3, 1936
48. Lein ES, Hawrylycz MJ, Dollar P, Lee H, Lein ES, Perona P, et al: Functional identification of an aggression locus in the mouse hypothalamus. Nature 445:168–176, 2007
49. Lemaire JJ: Related circuitry and synaptic connectivity in psychiatric disorders, in Sun B, De Salles A (eds): Neurosurgical Treatments for Psychiatric Disorders. New York: Springer, 2015, pp 1–20
50. Lemaire JJ, Frew AJ, McArthur D, Gorgulho AA, Alger JR, Salomon N, et al: White matter connectivity of human hypothalamus. Brain Res 1371:43–64, 2011
51. Lemaire JJ, Nezzar H, Sakkia L, Boirie Y, Fontaine D, Coste A, et al: Maps of the adult human hypothalamus. Surg Neurol Int 4 (Suppl 3):S156–S163, 2013
52. Lin D, Boyle MP, Dollar P, Lee H, Lein ES, Perona P, et al: Functional identification of an aggression locus in the mouse hypothalamus. Nature 470:221–226, 2011
53. Lu L, Wang X, Kosten TR: Stereotactic neurosurgical treatment of drug addiction. Am J Drug Alcohol Abuse 35:391–393, 2009
54. Manjila S, Rengachary S, Xavier AR, Parker B, Guthikonda M: Modern psychosurgery before Egas Moniz: a tribute to Gottlieb Burckhardt. Neurosurg Focus 25(1):E9, 2008
55. Martin E, Jeanmonod D, Morel A, Zadicario E, Werner B: High-intensity focused ultrasound for noninvasive functional neurosurgery. Ann Neurol 66:858–861, 2009
56. Massiero AL: [Lobotomy and leucotomy in Brazilian mental hospitals.] Hist Cienc Saude Manguinhos 10:549–572, 2003 (Portuguese)
57. Meleaga WP, Lacan G, Gorgulho AA, Behnke EJ, De Salles AA: Hypothalamic deep brain stimulation reduces weight gain in an obesity-animal model. PLoS One 7:e30672, 2012
58. Meyers R: Evidence of a locus of the neural mechanisms for libido and penile potency in the septo- fornico-hypothalamic region of the human brain. Trans Am Neurol Assoc 86:81–85, 1961
59. Meyers R: Three cases of myoclonus alleviated by bilateral anotomy, with a note on postoperative alibido and impotence. J Neurosurg 19:71–81, 1962
60. Miceli R, Rios AL, Aguilar RP, Posada LF, Hutchison WD: Single-unit analysis of the human posterior hypothalamus and red nucleus during deep brain stimulation for aggressivity. J Neurosurg 126:1158–1164, 2017
61. Minor RK, Chang JW, de Cabo R: Hungry for life: How the arcuate nucleus and neuropeptide Y may play a critical role in mediating the benefits of calorie restriction. Mol Cell Endocrinol 299:79–88, 2009
62. Moniz E: Prefrontal leucotomy in the treatment of mental disorders. Am J Psychiatry 93:1379–1385, 1937
63. Mulgaonkar AP, Singh RS, Babakhian M, Culjat MO, Grundfest WS, Gorgulho A, et al: A prototype stimulator system for noninvasive low intensity focused ultrasound delivery. Stud Health Technol Inform 173:297–303, 2012
64. Müller D, Roeder F, Orthner H: Further results of stereotaxis in the human hypothalamus in sexual deviations. First use of this operation in addiction to drugs. Neurochirurgia (Stuttg) 16:113–126, 1973
65. Musicik ES, Holtzman DM: Mechanisms linking circadian clocks, sleep, and neurodegeneration. Science 354:1004–1008, 2016
66. Nangunoori RK, Tomycz ND, Oh MY, Whiting DM: Deep brain stimulation for obesity: from a theoretical framework to practical application. Neural Plast 2016:7971460, 2016
67. Nauta WJ: Hypothalamic regulation of sleep in rats; an experimental study. J Neurophysiol 9:285–316, 1946
68. Nauta WJH, Domestic VB: Ramifications of the limbic system, in Matthesy S (ed): Psychiatry and the Biology of the Human Brain: A Symposium Dedicated to Seymour S. Kety, New York: Elsevier, 1981, pp 165–188
69. Nauta WJ, Haymaker W: Hypothalamic nuclei and fiber connections, in Haymaker W, Anderson E, Nauta WJ (eds): The Hypothalamus. Springfield, IL: Charles C Thomas, 1969, pp 136–200
70. Oomura Y, Ono T, Ooyama H, Wayner MJ: Glucose and osmoosensitive neurones of the rat hypothalamus. Nature 222:282–284, 1969
71. Permentier R, Kolbaev S, Klyuch BP, Vandel D, Lin JS, Selbach O, et al: Excitation of histaminergic tuberomammillary neurones by thyrotropin-releasing hormone. J Neurosci 29:4471–4483, 2009
72. Quade F: Stereotaxy for obesity. Lancet 1:267, 1974 (Letter)
73. Quade F, Vaermet K, Larsson S: Stereotaxic stimulation and electrocoagulation of the lateral hypothalamus in obese humans. Acta Neurochir (Wien) 30:111–117, 1974
74. Ramamurthi B: Stereotactic operation in behaviour disorders. Amygdalotomy and hypothalatomyotomies. Acta Neurochir Suppl (Wien) 44:152–157, 1988
75. Rasche D, Foethke D, Glemroth J, Tronnier VM: [Deep brain stimulation in the posterior hypothalamus for chronic cluster headache. Case report and review of the literature.] Schmerz 20:439–444, 2006 (Ger)
76. Rieber I, Sigusch V: Psychosurgery on sex offenders and sexual “deviants” in West Germany. Arch Sex Behav 8:523–527, 1979
77. Roeder FD: Stereotaxic lesion of the tubular cinereum in sexual deviation. Confin Neurol 27:162–163, 1966
78. Roeder F, Müller D: [On stereotaxic cure of pedophilic homosexuality.] Dtsch Med Wochenschr 94:409–415, 1969 (Ger)
79. Roeder F, Müller D, Orthner H: [Further experiences with the stereotactic management of sexual perversion.] J Neurol Transm Suppl 10:317–324, 1971 (Ger)
80. Roeder F, Orthner H, Müller D: The stereotaxic treatment of pedophilic homosexuality and other sexual deviations, in Hitchcock E, Laitinen L, Vaernet LC, Vaernet KC (eds): Psychosurgery. Springfield: Charles C Thomas, 1972, pp 87–111
81. Sagar SM, Martin JB: Hypothalamohypophyseal peptide systems, in Bloom FE (ed): Handbook of Physiology. Section 1: The Nervous System, Volume IV: Intrinsic Regulatory Systems of the Brain. New York: Oxford University Press, 1986, pp 413–462
82. Salcman M: The cure of folly or The operation for the stone by Hieronymus Bosch (C. 1450-1516). Neurosurgery 59:935–937, 2006
83. Sano K: Sedative neurosurgery with special reference to postero-medial hypothalatomyotomy. Neurosurg Med (Tokyo) 4:112–142, 1962
84. Sano K, Mayanagi Y: Postero-medial hypothalatomyotomy in the treatment of violent, aggressive behaviour. Acta Neurochir Suppl (Wien) 44:145–151, 1988
85. Sano K, Mayanagi Y, Sekino H, Ogashiwa M, Ishijima B: Results of stimulation and destruction of the posterior hypothalamus in man. J Neurosurg 33:689–707, 1970
86. Sano K, Yoshita M, Ogashiwa M, Ishii J, Ohya C: Postero-medial hypothalatomyotomy in the treatment of aggressive behaviors. Confin Neurol 27:164–167, 1966
87. Saper CB: Hypothalamic regulation of sleep in rats; an experimental study. J Neurophysiol 9:285–316, 1946
88. Saper CB, Paxinos G (eds): The Human Nervous System, ed 3. London: Academic Press, 2011, pp 548–583
89. Saper CB, Lowell BB: The hypothalamus. Curr Biol 24:R1111–R1116, 2014
The hypothalamus as a psychosurgical target

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Barbosa, de Oliveira-Souza, Monte Santo, De Salles. Acquisition of data: Barbosa, de Oliveira-Souza, de Oliveira Faria, Gorgulho. Analysis and interpretation of data: Barbosa, de Oliveira-Souza, de Oliveira Faria, De Salles. Drafting the article: Barbosa, de Oliveira-Souza, de Oliveira Faria, Monte Santo. Critical revising the article: Barbosa, de Oliveira-Souza, Monte Santo, Gorgulho, De Salles. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Barbosa. Study supervision: de Oliveira-Souza, Gorgulho, De Salles.

Correspondence

Daniel Alves Neiva Barbosa, D’Or Institute for Research & Education (IDOR), Rua Diniz Cordeiro, 30, 2nd Fl., Botafogo, Rio de Janeiro-RJ 22281-100, Brazil. email: danielbarbosa9@hotmail.com.

89. Sapru HN: Role of the hypothalamic arcuate nucleus in cardiovascular regulation. *Auton Neurosci* 175:38–50, 2013
90. Schmidt G, Schorsch E: Psychosurgery of sexually deviant patients: review and analysis of new empirical findings. *Arch Sex Behav* 10:301–322, 1981
91. Schoenen J, Di Clemente L, Vandenheede M, Fumal A, De Pasqua V, Mouchamps M, et al: Hypothalamic stimulation in chronic cluster headache: a pilot study of efficacy and mode of action. *Brain* 128:940–947, 2005
92. Schwartz JR, Driollet R, Rios E, Betti O: Stereotactic hypothalamotomy for behaviour disorders. *J Neurol Neurosurg Psychiatry* 35:356–359, 1972
93. Schwartz MW, Seeley RJ, Campfield LA, Burn P, Baskin DG: Identification of targets of leptin action in rat hypothalamus. *J Clin Invest* 98:1101–1106, 1996
94. Shekhar A, DiMicco JA: Defense reaction elicited by injection of GABA antagonists and synthesis inhibitors into the posterior hypothalamus in rats. *Neuropharmacology* 26:407–417, 1987
95. Soriano-Mas C, Redolar-Ripoll D, Aldaunt-Verla L, Morgado-Bernal I, Segura-Torres P: Post-training intracranial self-stimulation facilitates a hippocampus-dependent task. *Behav Brain Res* 160:141–147, 2005
96. Spiegel EA, Wycis HT, Marks M, Lee AJ: Stereotaxic apparatus for operations on the human brain. *Science* 106:349–350, 1944
97. Sternson SM: Hypothalamic survival circuits: blueprints for defense reaction elicited by injection of GABA antagonists and synthesis inhibitors into the posterior hypothalamus in rats. *Neuropharmacology* 26:407–417, 1987
98. Stuber GD, Wise RA: Lateral hypothalamic circuits for feeding and reward. *Nat Neurosci* 19:198–205, 2016
99. Swanson LW, Hartman BK: The central adrenergic system. An immunofluorescence study of the location of cell bodies and their efferent connections in the rat utilizing dopamine-beta-hydroxylase as a marker. *J Comp Neurol* 163:467–505, 1975
100. Swayze VW II: Frontal leukotomy and related psychosurgical procedures in the era before antipsychotics (1935–1945): a historical overview. *Am J Psychiatry* 152:505–515, 1995
101. Tokunaga K, Fukushima M, Kemnitz JW, Bray GA: Comparison of ventromedial and paraventricular lesions in rats that become obese. *Am J Physiol 251*:R1221–R1227, 1986
102. Torrealba F, Riveros ME, Contreras M, Valdes JL: Histamine and motivation. *Front Syst Neurosci* 6:51, 2012
103. Torres CV, Sola RG, Pastor J, Pedrosa M, Navas M, García-Navarrete E, et al: Long-term results of postero medial hypothalamic deep brain stimulation for patients with resistant aggressiveness. *J Neurosurg* 119:277–287, 2013
104. Torres N, Chabardes S, Piallat B, Devergasa N, Benabid AL: Body fat and body weight reduction following hypothalamic deep brain stimulation in monkeys: an intraventricular approach. *Int J Obes* 36:1537–1544, 2012
105. Ulrich-Lai YM, Herman JP: Neural regulation of endocrine and autonomic stress responses. *Nat Rev Neurosci* 10:397–409, 2009
106. U.S. Department of Health, Education, and Welfare: Protection of human subjects. Use of psychosurgery in practice and research: report and recommendations of National Commission for the Protection of Human Subjects. *Fed Regist* 42:26318–26332, 1977
107. Valenstein ES: *Great and Desperate Cures*. New York: Basic Books, 1986
108. van Praag HM: Two-tier diagnosing in psychiatry. *PSYCHIATRY RES* 34:1–11, 1990
109. Vann SD: Re-evaluating the role of the mammillary bodies in memory. *Neuropsychologia* 48:2316–2327, 2010
110. von Economo C: Sleep as a problem of localization. *J Nerv Ment Dis* 71:249–259, 1930
111. Wheatley MD: The hypothalamus and affective behavior in cats: a study of the effects of experimental lesions, with anatomic correlations. *Arch Neurol Psychiatry* 52:296–316, 1944
112. Whiting DM, Tomycz ND, Bailes J, de Jonge L, Lecoultre V, Wilent B, et al: Lateral hypothalamic area deep brain stimulation for patients with resistant aggressiveness: a pilot study with preliminary data on safety, body weight, and energy metabolism. *J Neurosurg* 119:56–63, 2013
113. Wilent WB, Oh MY, Buetefisch CM, Bailes JE, Cantella D, Angle C, et al: Induction of panic attack by stimulation of the ventromedial hypothalamus. *J Neurosurg* 112:1295–1298, 2010
114. Yang CF, Chiang MC, Gray DC, Prabhakaran M, Alvarado M, Juntti SA, et al: Sexually dimorphic neurons in the ventromedial hypothalamus govern mating in both sexes and aggression in males. *Cell* 153:896–909, 2013
115. Zhang W, Cline MA, Gilbert ER: Hypothalamus-adipose tissue crosstalk: neuropeptide Y and the regulation of energy metabolism. *Nutr Metab (Lond)* 11:27, 2014