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Chapter 7

Posterior hypothalamus as a target in the treatment of aggression: From lesioning to deep brain stimulation

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Abstract

Intermittent explosive disorder can be described as a severe "affective aggression" condition, for which drugs and other supportive therapies are not fully effective. In the first half of the 19th century, experimental studies progressively increased knowledge of aggressive disorders. A neurobiologic approach revealed the posterior hypothalamic region as a key structure for the modulation of aggression. In the 1960s, patients with severe aggressive disorder, frequently associated with intellectual disability, were treated by bilateral stereotactic lesioning of the posterior hypothalamic area, with efficacy. This therapy was later abandoned because of issues related to the misuse of psychosurgery. In the last 2 decades, however, the same diencephalic target has been selected for the reversible treatment by deep brain stimulation, with success. This chapter presents a comprehensive approach to posterior hypothalamic surgery for the treatment of severely aggressive patients and discusses the experimental steps that allowed this surgical target to be selected. Surgical experiences are reported, together with considerations on target features and related encephalic circuits.

INTRODUCTION

A number of behaviors have been considered instances of aggression, including instinctual displays (such as hissing, baring of teeth and claws), fighting (wrestling, punching, pushing, etc.) and killing (as in predatory behaviors), as well as a range of human behaviors whose instinctual foundations are less clear, ranging from military actions to unwelcome sexual behaviors and everything in between, including arguing, yelling, sarcasm, teasing, and general assertiveness. The categories of aggression that have been proposed to account for these behaviors include impulsive, reactive, hostile, affective, explosive, irritable, defensive, controlled, proactive, instrumental, predatory, offensive, territorial, inter-male, and maternal. Which behaviors belong to which category? Which categories are valid? Are there any other behaviors or categories which should be included, or excluded?

These considerations were expressed by the eminent neurobiologist Jaak Panksepp, inherently introducing limits regarding the definition of aggression. In this complex setting, Panksepp's main scientific and cultural effort relied on studying neurobiologic correlates of emotions (Panksepp and Zellner, 2004). He hypothesized that mammalians present with seven primary (or basic) affective systems: *seeking*, *fear*, *rage*, *lust*, *care*, *panic/grief*,

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and *play*. The previously mentioned types of aggression have been described in the *rage* and the *seeking* systems (and also in *lust*), highlighting the proteiform manifestations of aggression (Panksepp and Biven, 2012).

The neurobiology of emotions deals with similarities between human and other mammalian forebrains, but also with mesencephalic structures. This concept was probably first introduced by Charles Darwin, in 1872, in the work *Expression of the Emotions in Man and Animals*, in which a set of basic emotions was described to be unvaried across species (Darwin, 1872/1965; Dalgleish, 2004). One of the forebrain portions displaying the highest homologies across all mammalians is the limbic system, also known as the paleomammalian complex, in which affective functions dwell. The limbic system also represents the phylogenetically ancient part of the forebrain (MacLean, 1949, 1954; Panksepp and Zellner, 2004).

Animal models have been considered as a suitable option to enhance our knowledge of human emotional aspects by studying the limbic system (Panksepp and Zellner, 2004; Hrabovszky et al., 2005; Haller and Kruk, 2006).

Through experimental studies, it was possible to grossly define two types of aggression: predatory attack and affective defense (Moyer, 1968; Flynn et al., 1970; Weinshenker and Siegel, 2002; Kruk et al., 1998; Haller and Kruk, 2006). These studies have been translated into the clinical field, attempting to define human correlates of aggression (Meloy, 1988). Predatory aggression reveals controlled, predatory, proactive, and instrumental attitudes, encompassing also subtle manifestations of goal-directed behaviors. Affective defense includes irritable, impulsive, reactive, explosive, territorial, and maternal features, which can be directed toward a real threat or a perceived one (Weinshenker and Siegel, 2002; Panksepp and Zellner, 2004). Predatory aggression is mainly described by the seeking system, which activates to satisfy needs and ambitions. In this case, autonomic system arousal is not observed. Affective defense is commonly associated with the rage system, whose hallmark physiologic feature relies on autonomic system activation (in particular, the orthosympathetic response), following frustrations or threats. On the other hand, these simplifications are required to understand aggression, but come with limitations: these two types of aggression, which would represent two distinct but integrated encephalic circuits, can intervene in a combined manner, in a series of daily-life behaviors (Panksepp and Zellner, 2004). Moreover, in more evolved mammals, the complexity of cortical regions plays a relevant role in top-down modulation of limbic system subcortical regions (Fulton and Ingraham, 1929; Fulton, 1951), which represent the core of the primary affective systems.

Literature contributions reveal that the bulk of the animal studies on this topic are related to the "affective defense" since it is more straightforward to measure than predatory attack. Again, experiences of clinical correlates of rage system activation are also more frequent and easier to observe (Panksepp and Biven, 2012).

CLINICAL CORRELATES OF AGGRESSION

The patients described in this chapter present with severe affective aggression, and drugs are not effective in symptom control. "Intermittent explosive disorder (IED)" is the most appropriate diagnostic category used to describe affective aggression in humans. IED belongs to the "disruptive, impulse-control, and conduct disorders" chapter of DSM-V (American Psychiatric Association, 2013), which includes all self-control disorders. Despite the relevant theoretic and psychometric shortcomings of this category (Weinshenker and Siegel, 2002), it represents the most suitable one to define these patients.

IED is described as recurrent aggressive outbursts with either verbal and/or physical aggression with or without damage or destruction of property and/or physical injury against animals or individuals (pantoclastic episodes). Moreover, these patients pose a significant risk of self-harm. As defined, the outbursts are not premeditated and are not committed to achieving a tangible objective (American Psychiatric Association, 2013).

As described in the following paragraphs, the population to be discussed also presents with intellectual disability (ID) (Sano, 1962; Franzini et al., 2013). Aggression and ID are frequently observed together: the prevalence rate of challenging behavior in ID patients is reported to be as high as 45% (Emerson et al., 2001; Lowe et al., 2007; Grey et al., 2010). One of the main reasons for persons with ID to be referred to psychiatric services is pathologic aggression, and this is not surprising. Referral occurs, in fact, when their behavior becomes a problem for someone else (i.e., caregivers).

Pharmacologic therapy, including neuroleptics, anticonvulsants, antidepressants, anxiolytics, and mood stabilizers, can be effective in treating acute symptoms (Aman et al., 2002). Few studies on the long-term pharmacologic treatment of these patients have been performed, and often fail to show benefit (Willner, 2015). Early interventional strategies, in particular during childhood, through educational and psychologic methods (Davies and Oliver, 2013) could help patients negotiate relational and social hurdles that, if not successfully dealt with, are often followed by life breakdown (Antonacci et al., 2008).

LABORATORY EXPERIENCES: ROOTS OF SURGICAL APPROACH FOR AGGRESSIVE DISORDERS

In the historical period during which Darwin observed that a set of "basic" emotions appears similarly across

species and cultures (Darwin, 1872/1965), eminent clinicians and scientists were engaged in a debate on the feasibility of brain function localization. In 1870, Prussians Fritsch (1838–1927) and Hitzig (1838–1907) described the effects of direct current stimulation over different parts of dog brain cortex (Fritsch and Hitzig, 1870). They first suggested that brain presents with specialized regions, at least for motor functions. This aspect was later confirmed by the Queen Square Institute group, through experimental studies (Taylor and Gross, 2003; York III and Steinberg, 2011), and in humans, in 1885 (Tan and Black, 2002). On the other hand, Goltz (1834–1902), in Halle and then in Strasbourg, held a misleading unitary view of brain functions based on dog brain experiments (Tyler and Malessa, 2000). However, he first depicted rage as a consequence of brain manipulation, following complete extirpation of the dog neocortex (Goltz, 1892; Siegel, 2007).

A few decades later, the American physiologist Cannon (1871–1945) and his doctoral student Bard (1898–1977) reproduced Goltz's experiments on dog decortication to investigate the origin of emotions (they developed the so-called Cannon–Bard theory of the origin of emotions). Bard et al. demonstrated that rage-like behavior elicited by decortication disappeared following a disconnection between the rostral end of the superior colliculi and the posterior hypothalamus (in particular, the posterior edge of the mamillary bodies). After this observation, the caudal hypothalamus was supposedly the "center" of rage responses once released from cortical control (Bard, 1928, 1939; Bard and Rioch, 1937). At that time, this type of rage was described as "sham" (without the commensurate subjective affect), in a cultural milieu in which behaviorist positions did not encourage discussion on emotional experiences (Panksepp and Biven, 2012). Brain lesioning experiments for the study of emotions advanced, so that a cortical top-down control over the hypothalamus was reported. In particular, the orbital cortex was considered to have a role in rage responses in cat and monkey (Fulton and Ingraham, 1929; Fulton, 1951). This was also the case with the amygdala, whose lesioning resulted in contradictory results, with either evoking or taming of aggressive behavior, again in both cat and monkey (Spiegel et al., 1940; Bard and Mountcastle, 1948; Thomson and Walker, 1950). All of these considerations contributed to illustrious neurobiologic theories regarding emotions. Papez (1883–1958) in 1937 suggested that the hypothalamus, anterior thalamic nuclei, hippocampus, and gyrus cinguli act as anatomic substrates for emotion expression (Papez, 1937). Later, Yakovlev (1894–1983), delineating a network underlying emotion and motivation, confirmed a role for the orbitofrontal cortex and amygdala, adding the insular cortices and the anterior temporal lobe (Yakovlev, 1948). MacLean (1913–2007) synthesized the previous theories, in a whole cortico-subcortical network called the "visceral brain," later to be called the limbic system (MacLean, 1954).

Taking a step back to the past, studies on hypothalamus anatomy and physiology progressed. Based on the work of Karplus (1866–1936) and Kreill (1864–1928), the anatomist Beattie, at the McGill University in Montreal in 1932, reported the division of cat hypothalamus into three groups, given their cellular features: supraoptic, tuber cinerei, and supramamillary (or posterior). Posterior hypothalamus (pHyp) receives afferent connections from medial and ventral thalamic nuclei, sending information to the midbrain and reticular formation (hypothalamic-tegmental tract), which belongs to the autonomic system (Beattie et al., 1930). Hess (1881–1973), Nobel prize laureate in 1949 for his study on the role of hypothalamus as coordinator of organ activities, described the hypothalamus as also having a central role in autonomic activities (Hess, 2008). PHyp (and rostral midbrain) was described as a "dynamogene zone" or "ergotropic sektor," with a role in sympathetic response generation. The anterior hypothalamus, but also the preoptic and septal nuclei, were delineated as parasympathetic outputs (trophotrop-endophylaktischer sektor). An overlap between the two "sektors" was later admitted. In that period, the Osaka group proposed mediolateral segregation of autonomic responses instead of anteroposterior segregation, based on rabbit diencephalon studies (Sano, 1962; Ban, 1966; Sano et al., 1966, 1970). Following the Grünthal conception of a, b, and c "Zellgebiete" (Grünthal, 1929), the medial and lateral regions (a and c zones) presented with parasympathetic activity, with a sympathetic area between them (b zone), having the dorsal longitudinal fasciculus as output. In particular, according to Ban et al., stimulation of the b zone induced raging behaviors, while the c zone elicitation caused sleep (Sano, 1962). Another relevant contribution was that of Tokizane, in Tokyo, who described cat pHyp as a hippocampus-activating region, with influence over neocortex throughout the reticular formation (Tokizane et al., 1964).

In those years, Keiji Sano (1920–2011) (Fig. 7.1) was engaged in the study of psychic consequences of tumors located at the level of the limbic system. He observed that posterior orbital area and anterior hypothalamus lesions generated euphoria, hyperactivity, or even irritability and rage, whereas lesions at the level of the cingulate gyrus, thalamus, and pHyp caused apathetic and somnolent symptoms. On the other hand, temporal lobe lesions could generate contradictory symptoms (Sano, 1962). Based on these considerations, he proposed two separate circuits having a central role in autonomic responses and expression of emotions. He considered the main components of the Papez circuit (namely pHyp, anterior thalamic nuclei, cingulate gyrus, and hippocampus) as the actors of the "ergotropic circuit," and anterior hypothalamus, posterior orbital region, insula, uncus, and

Fig. 7.1. Professor Keiji Sano, the pioneer of surgery for aggressive behavior. Photo courtesy of the Department of Neurosurgery, University of Tokyo.

amygdala as the parasympathetic system generators. In particular, he hypothesized that aggressive disorder emerged as a consequence of an unbalance between these circuits, with the ergotropic one dominating the other (Sano, 1962).

This overview reveals that the pHyp plays a central role in aggressive attitude generation and autonomic system activation. Thus pHyp is thought to be a key anatomic node of the ergotropic (Papez) circuit, as well as a functional substrate of the rage system as described by Panksepp, which is at the base of "affective defense" (Panksepp and Biven, 2012).

AT THE DAWN OF SURGERY FOR AGGRESSIVE DISORDERS: THE LESIONAL ERA

Sano is considered a pioneer in the field of functional neurosurgery (Takakura, 2011). He carefully examined the research steps described in the previous section, to find a method for the neurosurgical treatment of aggressive disorders (Sano, 1962). His surgical efforts led him to sift through various stereotactic targets at different levels of the ergotropic circuit: anterior cingulum, thalamus, fornix, but also the upper mesencephalic reticular formation (Fig. 7.2). Sano selected the posteromedial hypothalamus as the best target in terms of efficacy and reported the most detailed and consistent surgical series concerning patients with aggressive behavior treated by

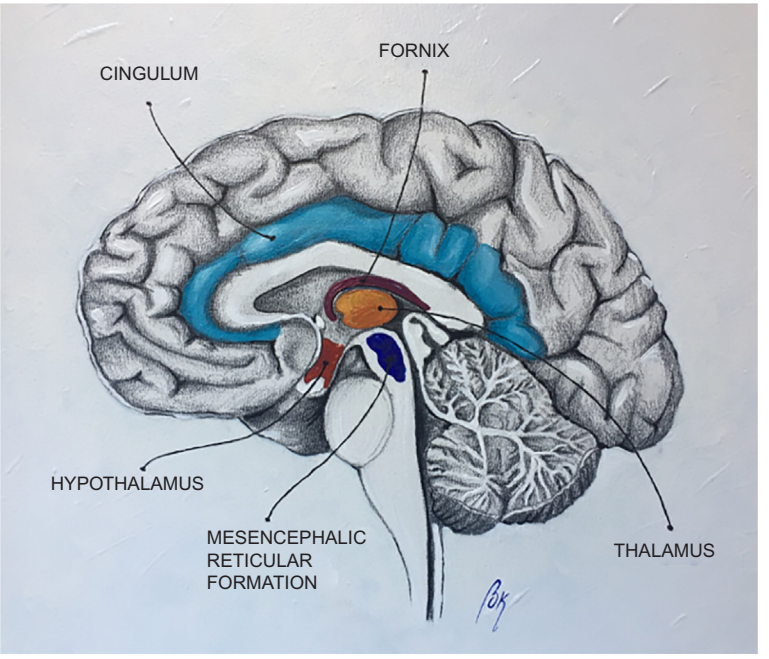

Fig. 7.2. The five targets employed by Sano for the treatment of aggressive disorder. Acrylic on canvas performed by Kenny Bianchini.

radiofrequency lesioning of the pHyp (Sano et al., 1970; Sano and Mayanagi, 1988). Patients were synthetically described as "…so violent, aggressive, and restless in behavior that their families had to keep a constant watch over them and sometimes the police had to take care of them" (Sano et al., 1970).

Sano and his colleagues aimed at evaluating the posterior portion of the "b-zone of Ban" as the relevant target, through intraoperative neurophysiologic mapping. This detail shows that Sano considered both schools of thought (Bard-Hess on one side, Japanese on the other) concerning the autonomic hypothalamic organization. The b zone was inspected at 1–5 mm from the medial wall of the third ventricle, where stimulation evoked sympathetic responses. Hypothalamus functional maps were developed, based on the Schaltenbrand-Bailey atlas. In that cultural milieu, Sano proposed the concept of an ergotropic triangle (later known as the triangle of Sano, a zone defined by "the midpoint of the intercommissural line, the rostral end of the aqueduct, and the anterior border of the mamillary body") (Fig. 7.3) (Sano et al., 1970), the high-frequency stimulation of which elicited sympathetic activity, which became a sign of correct electrode placement. Implantations involved other brain areas, such as mesial temporal structures, temporal pole, and other frontal regions, in the same surgical session. Scalp EEG electrodes were also inserted at the level of frontal, temporal, and parietal regions. The "asleep-awake-asleep" anesthetic protocol allowed performance of the neurophysiologic assessment in a light-sedation condition. The following stimulation parameters were used: a voltage of 10–20 V, a pulse width of 1000 ms, a frequency of 100 Hz, with a duration of 5–10 s. A rise in blood pressure, tachycardia, and hyperpnea were observed after stimulation, principally 2–3 mm lateral from the wall of the third ventricle. Pupillary dilation was seen in a slightly wider area if compared to the previous dilation. Stimulation near the wall of the ventricle evoked an ipsilateral downward gaze (an ipsilateral inward gaze was caused by the stimulation of a ventrocaudal region, with an opposite conjugate deviation if the lateral portion was stimulated). PHyp and medial subthalamic nucleus stimulation also evoked the contraction of ipsilateral sternocleidomastoid and posterior neck muscles, probably because of stimulation of the medial longitudinal fasciculus. Red nucleus stimulation, probably related to parasympathetic functions, caused the lowering of blood pressure and pupillary constriction. Other consequences of stimulation were an increase of nonesterified fatty acids (in four cases) and growth hormone (in three cases). EEG desynchronization was observed in neocortex and allocortex, but not in the hippocampus, where theta waves were occasionally elicited. Delta waves sometimes appeared

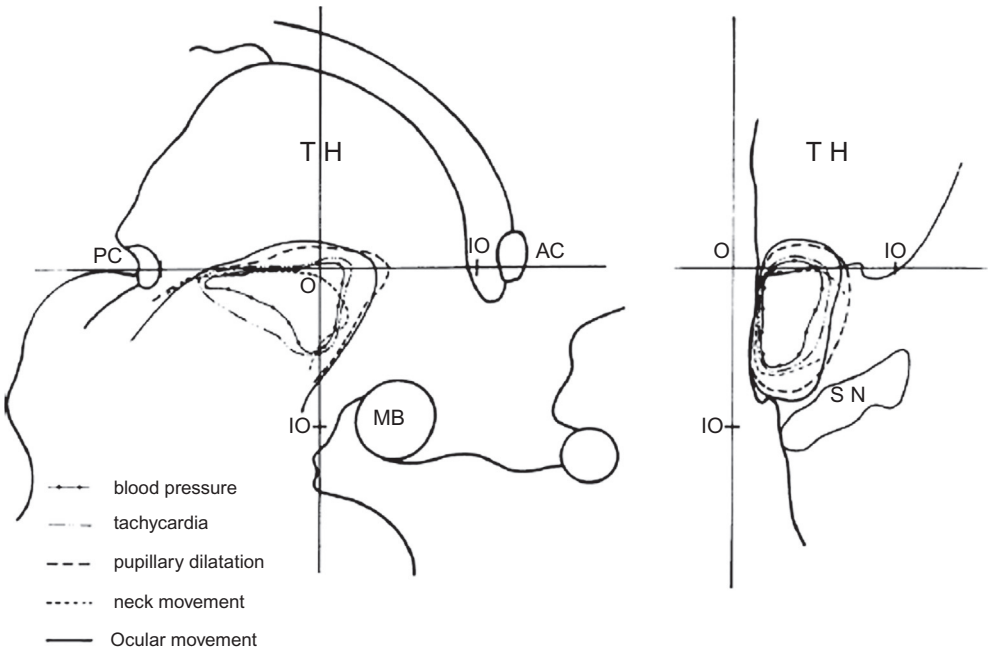

Fig. 7.3. Ergotropic (or Sano's) triangle. Summary of autonomic and somatomotor responses upon electrical stimulation of Sano's triangle (rise in blood pressure, tachycardia, maximal pupillary dilatation, and neck and ocular movements). Bilateral electrocauterization at this level resulted in a striking improvement of the aggressive disorder. *TH*, thalamus; *MB*, mamillary body; *SN*, substantia nigra; IO, 10 mm. Reprinted from Sano, K., Mayanagi, Y., Sekino, H., et al., 1970. Results of stimulation and destruction of the posterior hypothalamus in man. J Neurosurg 33, 689–707. Published with permission.

a few minutes after desynchronization. In some epilepsy cases, the hippocampus could present with spiking. After stimulation mapping, radiofrequency lesions were created in the area that showed a sympathetic response at a frequency of 1 MHz and a power of 2–3 W for 3–4 min, the estimated size of the lesions being 3–4 mm. The procedure was carried out at the level of the contralateral hemisphere 7–10 days after the first surgical session; 51 patients were operated on, with a follow-up longer than 1 year in 42 of them, and 95% of these patients presented with an improvement of the aggressive behavior (outcomes were excellent in 12 patients and good in 28). The patients were described as markedly calm, passive, and tractable, with decreased spontaneity. Patients' IQ improved, probably due to their increased cooperation. Unfortunately, validated scales were not reported together with the outcome (the most detailed paper was published in 1970). Out of the 42 patients who were followed up for at least 1 year, 22 presented with seizures before surgery. One patient became seizure-free after surgery, while 41% (9 patients) showed a reduction in seizure frequency and intensity. Some of the patients were allowed to have drug tapering. A general weight gain tendency was observed. Again, a parasympathicotonia tendency was observed, following a mecholyl test (Sano et al., 1970).

The long-term outcomes of this population of patients were revisited in 2017 (Barbosa et al., 2017), with a long-term follow-up of 10–25 years. Results were considered satisfactory in 29 patients: 18 out of 29 patients did not show aggressive behavior anymore, allowing familial and social adaptation (Sano and Mayanagi, 1988).

Sano's explanation of the renowned efficacy of pHyp lesioning, as compared to other targets (anterior cingulum, thalamus, fornix, but also upper mesencephalic reticular formation), was that surgery of lower-order areas produces more marked and lasting clinical effects than surgery on higher-order areas, because the "overlapping of the circuits is more marked in the neocortex than in the limbic cortex, and in the limbic cortex than the diencephalon" (Sano, 1962). Thus diencephalic selectivity, in the context of the ergotropic circuit, would be the most relevant "predictor of outcome."

In those years other groups reported experiences in stereotactic lesioning for the treatment of aggressive behaviors, following the conceptual wave of treating symptoms (aggression) more than the disease (schizophrenia) (Barbosa et al., 2017). Arjona et al. reported improvement at personal and social levels following posteromedial hypothalamus cryogenic lesioning in 11 children having IDs (Arjona, 1974). Another Japanese group, based in Sapporo, successfully treated four patients (three with IDs) with radiofrequency lesioning (Miyazaki et al., 1965), in addition to other groups (Diaz Perez et al., 1968; Matera et al., 1972; Sramka and Nádvorník, 1975). An Indian team headed by Ramamurthi proposed posteromedial hypothalamotomy in those cases in which bilateral amygdalotomy failed to relieve aggressive attitude (Ramamurthi, 1988).

The hypothalamus was also targeted in other disorders of behavior (Barbosa et al., 2017). In 1952, Spiegel and Wycis targeted the lateral hypothalamic region, near the subthalamic area, in one patient with psychotic symptoms (Spiegel and Wycis, 1952).

A STEP INTO BRAIN STIMULATION: THE DBS ERA

At the beginning of the 1970s, psychosurgical procedures had been almost all abandoned, either because of the worldwide diffusion of antipsychotic drugs as an effective "noninvasive" therapy, or because of the perception of surgery as a brain-disabling treatment, also having been used to control minorities (Valenstein, 1977; United States Department of Health, Education, and Welfare, 1978). In addition, in another field (that of movement disorders), the introduction of levodopa-based therapies caused the fall into disuse of stereotactic lesional surgery (Gardner, 2013). Later, by the mid-1980s, dopaminergic drugs started to show fading efficacy in the long-term management of parkinsonian patients, paving the way for a renaissance of surgical procedures (Gardner, 2013). Some groups started to repropose lesional approaches as a treatment complement (Bergman et al., 1990; Laitinen et al., 1992). Benabid's group, in Grenoble, was also engaged in implementing deep brain stimulation (DBS) technology for the treatment of a few neurologic and psychiatric disorders, including Parkinson's disease (PD) (Benabid et al., 1987). Advancements in the available technology allowed verification of the safety and efficacy of DBS for PD symptoms (Benabid et al., 1991), paving the way for the future success of this methodology, with some new aspects as compared to lesional surgery: adaptability of stimulation parameters, a safer surgical profile, and relative reversibility (Tasker et al., 1997).

Over the years, DBS indications encompassed many disorders, including those of the psychiatric domain (Franzini et al., 2012). The C. Besta Neurological Institute in Milan obtained promising results in the treatment of severe, drug-resistant, chronic cluster headache (CCH), through pHyp DBS (Leone et al., 2001; Franzini et al., 2010), with the target choice in accordance with PET hypermetabolism during CCH attack (May et al., 1998). In light of Sano's experience, but also the acquired knowledge correlating pHyp to other emotional structures and, especially, the observation of the occasional onset of aggressive behavior during CCH attacks in some patients, the Besta group was led to consider pHyp as a key node for aggressive disorders (Franzini et al., 2005).

Based on these considerations, Franzini et al. performed a bilateral pHyp DBS in a series of seven patients with "pathological aggressive and disruptive behavior" and "mental retardation" (Franzini et al., 2013). The first procedure was reported in 2005 (Franzini et al., 2005). All these patients, before DBS, were carefully evaluated to verify the inefficacy of previous pharmacologic and behavioral therapies and to assess the extremely severe, chronic, treatment-resistant conditions. Stimulation parameters were as follows: voltage between 1 and 3 V; pulse width between 60 and 90 ms; frequency 185 Hz, with a monopolar configuration (case positive). A 65% mean improvement in the Overt Aggression Scale (OAS) was observed (Franzini et al., 2013). In one case (postischemic aggressive behavior), no effect on aggressive attitude was noted; however, an improvement in sleep pattern and a stable reduction in blood pressure values occurred. Another patient relapsed after a temporary battery shutdown. Once stimulation was restored, however, the therapeutic effect declined, despite parameter adjustment (Rizzi et al., 2017). Patients were observed for a follow-up of between 3 and 11 years, with stable results (Franzini et al., 2013; Messina et al., 2016; Rizzi et al., 2017). In particular, as Sano observed in his series (Sano et al., 1970), relational aspects of these patients improved, with great benefit for caregivers as well.

Other groups successfully reproduced the Besta experience, using low- and high-frequency stimulation, with either monopolar or bipolar patterns, equally beneficial in controlling aggressive outbursts. Kuhn et al. successfully treated, through pHyp DBS, a 22-year-old patient presenting with self-aggressive behaviors following severe head injury (Kuhn et al., 2008). A relevant and stable improvement was reached in a single case, with the following, peculiar, stimulation parameter settings: monopolar on the left side and bipolar on the right side, a very low frequency (15 Hz), and longer pulse width (450 ms) (Hernando et al., 2008). Torres et al. displayed a series of 6 patients with aggressive behavior and severe ID (only 1 patient had normal development until the age of 14 years). They reported similar results using both low voltage (1 V), a longer pulse width (450 ms), and low frequency (between 15 and 60 Hz), and higher voltage (between 1.8 and 2.5 V), shorter pulse width (between 60 and 210 ms), and higher frequency (between 130 and 185 Hz) (Torres et al., 2008). Benedetti-Isaac et al. treated 5 patients with medically intractable aggressive behavior and seizures. The OAS score improved similarly to that of the Besta group, with significant improvement in the quality of life for both patients and caregivers. Seizure outcome was also impressive (Benedetti-Isaac et al., 2015) (Table 7.1).

It is worth reporting that, in all series, adverse neurovegetative effects were encountered with increasing voltage intensity. This aspect represents the main limit for the therapeutic window of pHyp DBS (Rizzi et al., 2017).

Other groups have investigated other surgical targets, such as the ventral capsule (VC) and ventral striatum (VS). Maley et al. (2010) and Giordano et al. (2016) highlighted the role of the orbitofrontal cortex in anger control, through bilateral VC/VS DBS, with clinical benefit. Globus pallidus interna (GPi) DBS was successfully

Table 7.1

Summary of literature focusing on pHyp DBS for the treatment of aggressive disorders

Series	Patients	Follow-up	Stimulation parameters at last follow-up	Clinical results
Kuhn et al. (2008)	1	4 months	Monopolar 130 Hz, 90 μs, 1.5 V	Complete resolution
Hernando et al. (2008)	1	18 months	Monopolar/bipolar 15 Hz, 450 μs, 0.6–0.9 V	Persistent improvement
Franzini et al. (2013)	7	2–11 years	Monopolar 185 Hz, 60–90 μs, 1–3 V	65% mean improvement on OAS scale (range: 0%–100%); 50% DRE reduction in 2 patients
Torres et al. (2013)	6	6–82 months	Monopolar/bipolar 15–185 Hz, 60–450 μs, 1.3–2.5 V	47% improvement on ICAP scale for general aggressiveness 30% reduction DRE (in 1 patient)
Benedetti-Isaac et al. (2015)	5	2–48 months	Cyclic (1 min ON, 5 min OFF) 185 Hz, 90 μs, 2.4–3 V	65% mean improvement on OAS scale (0%–100%) 89.6 mean seizure frequency reduction (50.8%–100%)

Abbreviations: *DRE*, drug-resistant epilepsy; *OAS*, Overt Aggression Scale.

performed in a patient with Lesch Nyhan syndrome and dystonia, presenting with self-mutilating behavior, drawing attention to the possible involvement of motor circuits in the pathogenesis of self-aggressive syndromes (Taira et al., 2003). These results were replicated (Deon et al., 2012; Abel et al., 2014).

FROM THE TARGET TO THE CIRCUIT

Debate around the target: "Posterior hypothalamus" or "A region posterior to the hypothalamus"?

The exact location of electrodes in pHyp DBS has been a matter of debate, since many groups have demonstrated that their position is posterior to the posterior hypothalamic region (Starr, 2008; Fontaine et al., 2010; Akram et al., 2017). These considerations have been outlined in the CCH DBS series, taking into account that CCH and aggressive disorders share the same DBS target.

In 2008, Starr, commenting on the Besta group series, stated that active contacts are located "several millimeters posterior to the mamillothalamic tract (MTT). In some anatomical texts, the MTT defines the posterior boundary of the hypothalamus, which would put the CCH DBS target in the anterior periventricular grey matter. Other atlases, however, show the hypothalamus continuing posteriorly to the MTT." On the other hand, hypothalamus, periventricular, and periaqueductal gray structures display in a continuous rim on the third ventricle wall, without clear borders between them (Starr, 2008), so that the distinction between structures at this level can suffer from an arbitrary division.

A French multicenter study in 2010 (Fontaine et al., 2010) reported on a series of 10 patients with CCH treated by pHyp DBS, using the target of Franzini (Leone et al., 2001). They performed an enlightening retrospective study on active contacts locations, aiming at clarifying the stimulated anatomic structures. The center of active contacts was projected in a 2-slice Schaltenbrand and Bailey atlas and into a volumetric 4.7 T brain-MR images atlas of the diencephalon-mesencephalic junction. Hypothesizing a given volume of tissue activated by the stimulation, all the contacts were located posterior to the mamillary bodies and MMT. It is curious to state that, according to Sano's drawing of the ergotropic triangle and blood pressure by electrical stimulation (Sano et al., 1970), the gross targeted region is generally behind the mamillary bodies (Figs. 7.3 and 7.4).

Despite the poor definition of the diencephalic–mesencephalic atlases in humans and the small population sampling, these reports have relevant additions. Based on correlation with the majority of human atlases, pHyp DBS results in a "posterior hypothalamic region DBS" or a "DBS of the retro-hypothalamic region" (Starr, 2008; Fontaine et al., 2010).

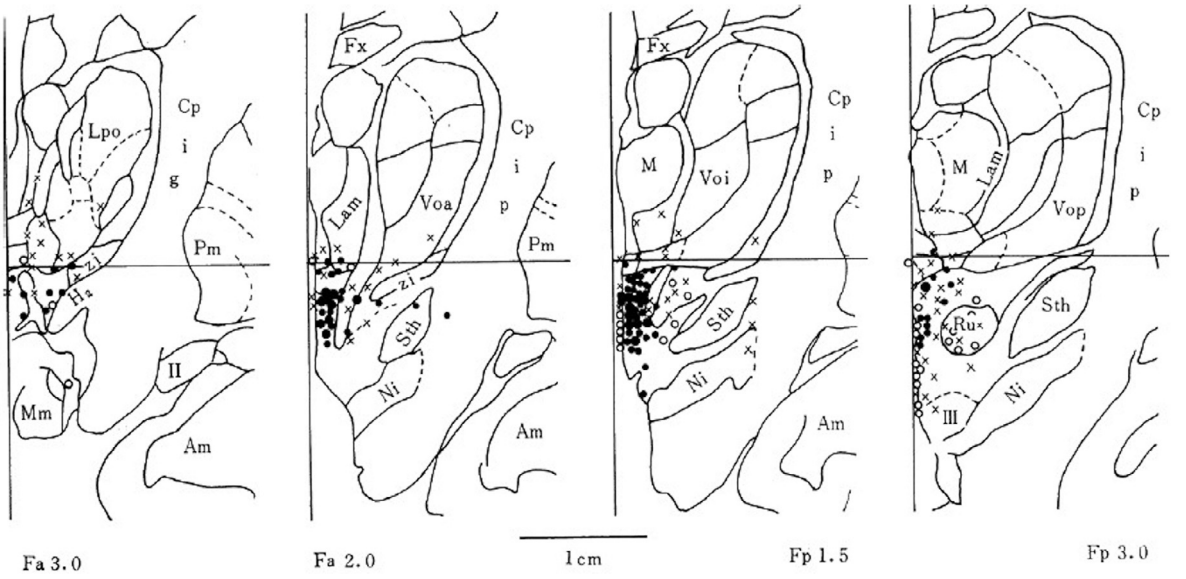

Fig. 7.4. Blood pressure (BP) changes induced by electrical stimulation of the posterior hypothalamic region. *Black circles* = rise in BP; *open circles* = decrease in BP; *X* = no change. *Am* = amygdaloid nuclei; *Cp i g* = capsula interna, genu; *Cp i p* = capsula interna, crus posterius; *Fx* = fornix; H_2 = campus Forelii; *II* = tractus opticus; *III* = oculomotor nerve; *Lam* = lamella medialis thalami; *Lpo* = supranucleus lateropolaris thalami; *M* = nucleus dorsomedialis; *Mm* = nucleus mamillaris medialis; *Ni* = substantia nigra; *Pm* = pallidium mediale; *Ru* = nucleus ruber; *Sth* = corpus subthalamicum; *Voa* = nucleus ventro-oralis anterior; *Voi* = nucleus ventro-oralis internus; *Vop* = nucleus ventro-oralis posterior; *Zi* = zona incerta. Reprinted from Sano, K., Mayanagi, Y., Sekino, H., et al., 1970. Results of stimulation and destruction of the posterior hypothalamus in man. J Neurosurg 33, 689–707. Published with permission.

Circuit modulation

Given the concept of "DBS of the retro-hypothalamic region" and that of the volume of tissue activated (Maks et al., 2009), it is relevant to analyze the observations of the French group (described earlier) on the stimulated structures. Apart from the red nucleus, which is involved in migraine pathophysiology (Cao et al., 2002) but not in CCH (Goadsby, 2002), they described the fascicle retroflexus of Meynert, which links the habenula with the interpeduncular nucleus, belonging to the limbic system; both longitudinal fascicles (the dorsal longitudinal fascicle was also thought to have a role in Sano's work (Sano et al., 1970)); and they connect hypothalamus with brainstem autonomic centers (Riley, 1943; Nieuwenhuys et al., 1988; Carpenter, 1991). Mesencephalic gray substance was also taken into account, which has already been used for lesional chronic pain stereotactic surgery (Nauta, 1969; Carpenter, 1991). These descriptions revealed that pHyp DBS is acting at the level of multiple systems, including a general (orexinergic) or a more specific (projecting to the caudal trigeminal nucleus) antinociceptive system.

Also taking into account the past laboratory experiences mentioned in a previous section, pHyp surgery does not seem to rely on the mere destruction or stimulation of a discrete deep area per se. On the contrary, it probably generates a modulation of a series of networks or circuits (Rizzi and Marras, 2017). The pHyp area is a lower-order region (Sano et al., 1970), which gathers several pathways, at least fibers belonging to emotional, autonomic, and nociceptive systems. This aspect is likely at the base of the reported efficacy of pHyp DBS in clearly different diseases or symptoms, including CCH and aggressive disorders, but also epilepsy (Franzini et al., 2010).

A more recent study gave additional clarification to the neural networks elicited through pHyp DBS, thereby described as VTA DBS (Akram et al., 2016). They described an anteriorly driven streamline, traversing hypothalamus and splitting in an inferolateral pathway toward the amygdalar complex (amygdalofugal), and an anterosuperior pathway toward the anterior limb of the internal capsule and prefrontal areas. A posterior streamline, running medial to the red nucleus, reaches the "periaqueductal gray and then caudally through the pons and upper medulla in a dorsolateral position toward the trigeminal tract and nuclei" (Akram et al., 2017). The potential involvement of many different structures and circuits raises doubts about the segregation between the rage and seeking systems. The pHyp region seems to be strongly connected to the amygdala, which represents a key terminus of the rage circuit, and to prefrontal cortices, throughout dopaminergic pathways (the "medial forebrain bundle") (Rizzi et al., 2017; Coenen et al., 2018), representing key structures of the seeking system. It is known that patients prone to exhibiting aggression without remorse present with diminished "arousability" of frontal lobe areas (Raine et al., 2002). Moreover, a seeking system contribution to affective aggression is likely, also given the extended possibility of cortical control in humans. Panksepp and Zellner proposed that rage and seeking systems would interact through an intrahypothalamic connection, between medial and lateral hypothalamus regions (respectively assumed to have a role in rage and seeking) (Panksepp and Zellner, 2004). Medial and lateral hypothalamus have mutual GABA-mediated inhibitory projections (Siegel et al., 1999). It is also worth reflecting on data coming from amygdalotomy (Narabayashi et al., 1963; Fountas and Smith, 2007) and VC/VS DBS (Giordano et al., 2016) for the treatment of clinically similar patients. To summarize, ablation or stimulation of structures belonging to both rage and seeking systems are reported to be beneficial (Rizzi et al., 2017). All these reports implicitly question pHyp surgery selectivity on the ergotropic circuit. Limits of structure categorization at this level (i.e., the concept that a well-defined function corresponds to a well-defined nucleus or bundle), but also the theoretic description of the different types of aggression, are highlighted. These complex aspects need to be clarified, through experimental and clinical studies.

CONCLUSIONS

Neurobiologic studies have made outstanding contributions to the comprehension of aggressive disorder pathophysiology (Panksepp and Biven, 2012; Kruk, 2014). Affective neuroscience is based on experimental studies disseminated over the last 150 years. The step-by-step elucidation of the factors that clarified which targets could be considered for the treatment of severe aggressive disorders provides a synopsis for those, whether clinicians or researchers, who want to propose established or novel therapeutic options. The key figure in this process is Keiji Sano, who first translated into clinical practice decades of experimental knowledge (Sano, 1962; Sano et al., 1970). Thanks to his experience, pHyp was considered as the primary deep target for the surgical treatment of IED. After a period of scarce attention from the scientific community, a new surge was possible due to DBS methodology (Barbosa et al., 2017), which is perceived as more acceptable by both clinicians and patients. Nevertheless, only a few series or single-case reports of pHyp DBS were reported in the last 2 decades (Rizzi et al., 2017). This is probably due to the ethical questions related to potential mind manipulation, together with the legacy of old-fashioned psychiatric surgery (Hariz and Hariz, 2012). In other domains of surgery

for psychiatric disorders (i.e., obsessive–compulsive or major depression disorders; Tourette syndrome), several groups are working to overcome this obstacle, reporting detailed surgical series with success (Mallet et al., 2008; Tyagi et al., 2019; Johnson et al., 2019). Future directions also include a more detailed definition of those patients who could benefit from pHyp DBS. Postprocessing analysis of brain imaging, such as morphometric quantitative analysis, could help in better defining structural hallmarks of IED, as in other neurologic fields (Sidhu et al., 2018).

The impressive efficacy of pHyp surgery for severe aggressive disorders, including over the long term (Rizzi et al., 2017), represents the most relevant point in favor of this approach in those selected patients not responding to drugs.

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