The Nucleus Accumbens: A Target for Deep-Brain Stimulation in Obsessive-Compulsive and Anxiety Disorders

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Summary

We considered clinical observations in patients with obsessive-compulsive and anxiety disorders who underwent bilateral anterior capsulotomy, as well as anatomical and pathophysiological findings. Based on these considerations, we chose the shell region of the right nucleus accumbens as the target for deep-brain stimulation in a pilot series of four patients with severe obsessive-compulsive and anxiety disorders. Significant reduction in severity of symptoms has been achieved in three of the four patients treated. Clinical results, as well as a 15O-H2O-PET study performed in one patient during stimulation, speak in favor of the following hypothesis: As a central relay structure between the amygdala, basal ganglia, mesolimbic dopaminergic areas, mediodorsal thalamus, and prefrontal cortex, the nucleus accumbens seems to play a modulatory role in the flow of information from the amygdaloid complex to the latter areas. If disturbed, an imbalanced information flow from the amygdaloid complex can yield obsessive-compulsive and anxiety disorders. These can be counteracted by blocking the information flow within the shell region of the nucleus accumbens by means of deep-brain stimulation (DBS).

Introduction

Obsessive-compulsive disorder (OCD) is a chronic and disabling condition which severely impairs personal, social, and professional life. Patients with OCD suffer from recurrent obsessive thoughts and uncontrollable compulsive reactions, such as repetitive behavioral or mental acts occurring in response to an obsession. OCD occurs frequently in combination with other anxiety and depressive disorders. It is notorious for both the chronicity and the difficulty of its treatment. In severe cases of treatment-refractory OCD and anxiety disorders, neurosurgical procedures (cingulotomy, limbic leukotomy, subcaudate tractotomy, and anterior capsulotomy) may be indicated [10, 18]. The best results have been obtained with bilateral anterior capsulotomy [12, 15].

Electrical deep-brain stimulation (DBS) at high frequencies has a blocking effect on the stimulated area and mimics the effect of tissue lesioning [2, 3]. DBS is reversible and has a much lower rate of side effects than lesioning with thermocoagulation [21]. Thus, Nuttin and Cosyns [17] used bilateral DBS of the anterior limb of the internal capsule instead of lesioning for treatment of severe OCD. Significant improvement of symptoms was achieved in four patients. However, unusually high stimulation amplitudes had to be used, which resulted in high energy consumption requiring frequent exchange of the portable energy source.

Based on clinical observations as well as on anatomical and pathophysiological considerations, we used the right nucleus accumbens as the primary target for DBS in four patients with the diagnosis of severe, pharmaceutically resistant anxiety disorders and OCD.

Anatomy and Pathophysiology

During the past three decades, basal forebrain areas, especially the ventral striatum, the nucleus accumbens, and the rostral parts of the "extended amygdala" [4, 9], have attracted the growing interest of anatomists, pharmacologists, and clinicians. The dopamine theory of schizophrenia has focused on the nucleus accumbens and its role in psychiatric diseases [14, 23]. The nucleus is located immediately underneath the anterior limb of the internal capsule and covers a large area of the basal forebrain rostral to the anterior commissure.

Medially adjacent to it is the vertical part of the diagonal band of Broca, while laterally adjacent to it are the claustrum and piriform cortex. Dorsally, neighboring structures include rostral extensions of the globus pallidus and the anterior limb of the internal capsule. The nucleus accumbens extends dorsolaterally into the ventral putamen, dorsomedially into the ventral caudate, i.e., the ventral striatum sensu stricto, without a sharp demarcation.

The nucleus accumbens is divided into two principal parts: a central core and a peripheral shell. The former is associated with the extrapyramidal motor, the latter with the limbic system. While the core-shell dichotomy is well-established in rodents, in the primate, especially in man, both parts are poorly characterized. However, there is a consensus that the shell region is confined to the ventromedial margin of the nucleus (for review see Heimer [8]).

The shell region has histological and biochemical properties similar to those of the central amygdaloid nucleus, which, together with the medial amygdaloid nucleus, gives origin to the extended amygdala system (de Olmos and Heimer 1999; Alheid et al. 1998). It contains a larger proportion of relatively small cells with high concentrations of D1- and D3-receptors and a denser distribution of many neuropeptides such as VIP, CCK, enkephalins, substance P, and neurotensin, than other regions of the nucleus accumbens and the ventral striatum (Heimer 2000).

Within the nucleus accumbens, information is transmitted from shell to core. Together with the ventral striatum, the nucleus accumbens, especially the shell region, receives a strong dopaminergic input from the VTA and the dorsal tier of the substantia nigra and projects back to major parts of the dorsal and ventral tier (dorsal and and densocellular parts of the substantia nigra pars compacta) as described by Haber et al. [7].

In the human being, the nucleus accumbens receives strong afferents from the basolateral amygdala via the ventral amygdalofugal pathway, and most probably also from the central and medial amygdaloid nuclei, via the sublenticular and supracapsular parts of the extended amygdala [1, 4]. Its main efferents innervate the pallidum, striatum, mediodorsal thalamus, prefrontal, including cingulate cortex and, as mentioned above, mesolimbic dopaminergic areas.

The nucleus accumbens thus attains a central position between limbic and mesolimbic dopaminergic structures, the basal ganglia, the mediodorsal thalamus, and the prefrontal cortex.

Since dopamine is a major transmitter in the nucleus accumbens, a modulating function on amygdaloid-basal ganglia-prefrontal cortex circuitry can be assumed [5, 16, 19].

Implications for Psychiatric Surgery

In the 1960s, Leksell and Talairach introduced anterior capsulotomy as a treatment for severe OCD and anxiety disorders. Fiber tracts connecting the mediodorsal thalamus reciprocally with the prefrontal cortex were interrupted by thermocoagulation or focused stereotactic irradiation bilaterally in the anterior limb of the internal capsule [12, 15]. Significant reduction of OCD-related behavior, fear, and anxiety has been achieved in the majority of patients, but "frontal" symptoms have been observed occasionally, most probably because fibers projecting to the dorsolateral prefrontal cortex have been interrupted, in addition to fibers terminating in orbitofrontal regions.

Based on growing experience with DBS for Parkinson's disease [2, 24], Nuttin and Cosyns [17] replaced the lesioning procedures, with their irreversible effects, by stimulation at high frequencies, which has a blocking effect that is fully reversible. Bilateral DBS of the anterior limb of the internal capsule by Nuttin and Cosyns yielded significant improvement of OCD symptoms in four patients, but unusually high stimulation amplitudes had to be used, which caused high energy consumption of the impulse generators and consequently their frequent servicing.

The fact that the distal lead of the electrodes used (Medtronic, Minneapolis, USA) is placed into the ventral edge of the internal capsule, where it abuts the nucleus accumbens, and the high stimulation amplitudes make functional blocking of accumbens activity highly probable.

The extensive experience of the Karolinska group [15], as well as our own observations with anterior capsulotomy for treating OCD and anxiety disorders, show that lesioning of the ventrocaudal part of the internal capsule is decisive for successful treatment.

Similar conclusions have been made by Rasmussen and Greenberg (2002, personal communication) for gamma-capsulotomy. Thermocoagulation and radiation necrosis in the ventral edge of the internal capsule are likely to affect the nucleus accumbens as well, including its shell region.

Target Selection and Clinical Findings

Considering the central position of the nucleus accumbens between the amygdaloid complex, basal ganglia, mediodorsal thalamic nucleus, and prefrontal cortex, all of which are involved in the pathophysiology of anxiety disorders [22] and OCD [20], the beneficial clinical effects of anterior capsulotomy might well be caused by blocking of the amygdaloid-basal ganglia-prefrontal circuitry at the level of the shell region of the nucleus accumbens, rather than by blocking of the fiber tracts in the internal capsule.

These considerations prompted us to modify the electrode track for DBS. Instead of targeting the anterior limb of the internal capsule alone, we implanted the electrode in a way that permitted stimulation of the ventral part of the anterior limb of the internal capsule as well as of the shell region of the nucleus accumbens with the same electrode and selective stimulation of these structures.

For the first patient treated in the pilot series we implanted the DBS electrodes bilaterally. Alternating activation of various contact combinations of the right, left, or both electrodes was performed during a testing period of several weeks following electrode implantation. We observed that bipolar stimulation over the two distal leads of the right electrode (0 negative, 1 positive), which were placed within the right nucleus accumbens, yielded significant reduction in symptoms. Bilateral stimulation did not improve the effects. Activation of leads placed in the internal capsule had not been effective. Consequently, in the following three patients we implanted the electrode only unilaterally into the right nucleus accumbens (◘ Fig. 16.1).

The DBS electrode implantation is performed stereotactically. The positioning of the electrode is

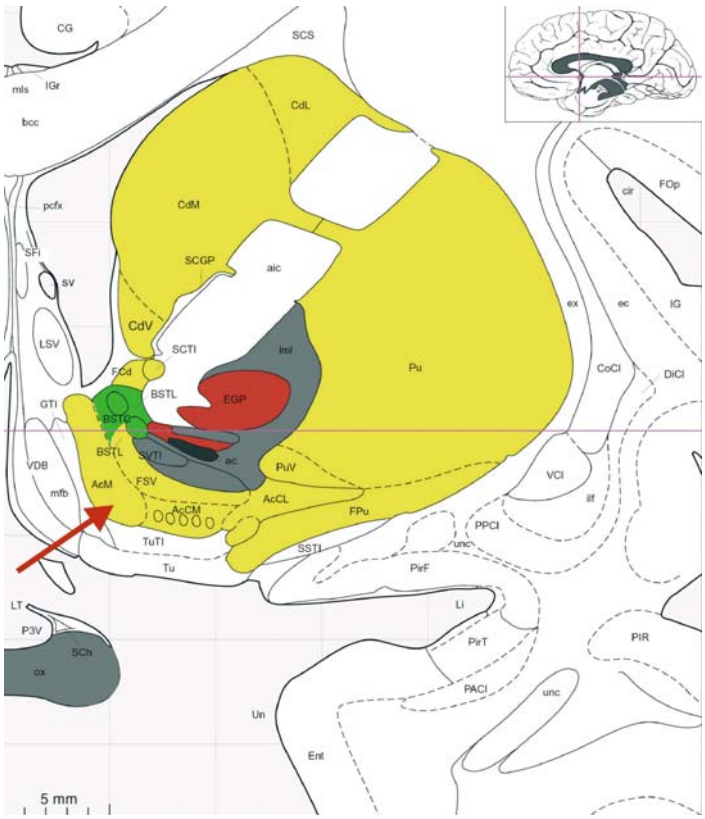

Fig. 16.1. Frontal section of the human brain at the level of the target point in the ventro-medio-caudal part of the nucleus accumbens. Arrow indicates target point. Coordinates: 2.5 mm rostral anterior border of AC, 6.5 mm lateral of midline, 4.5 mm ventral AC. (Mai et al. 1997)

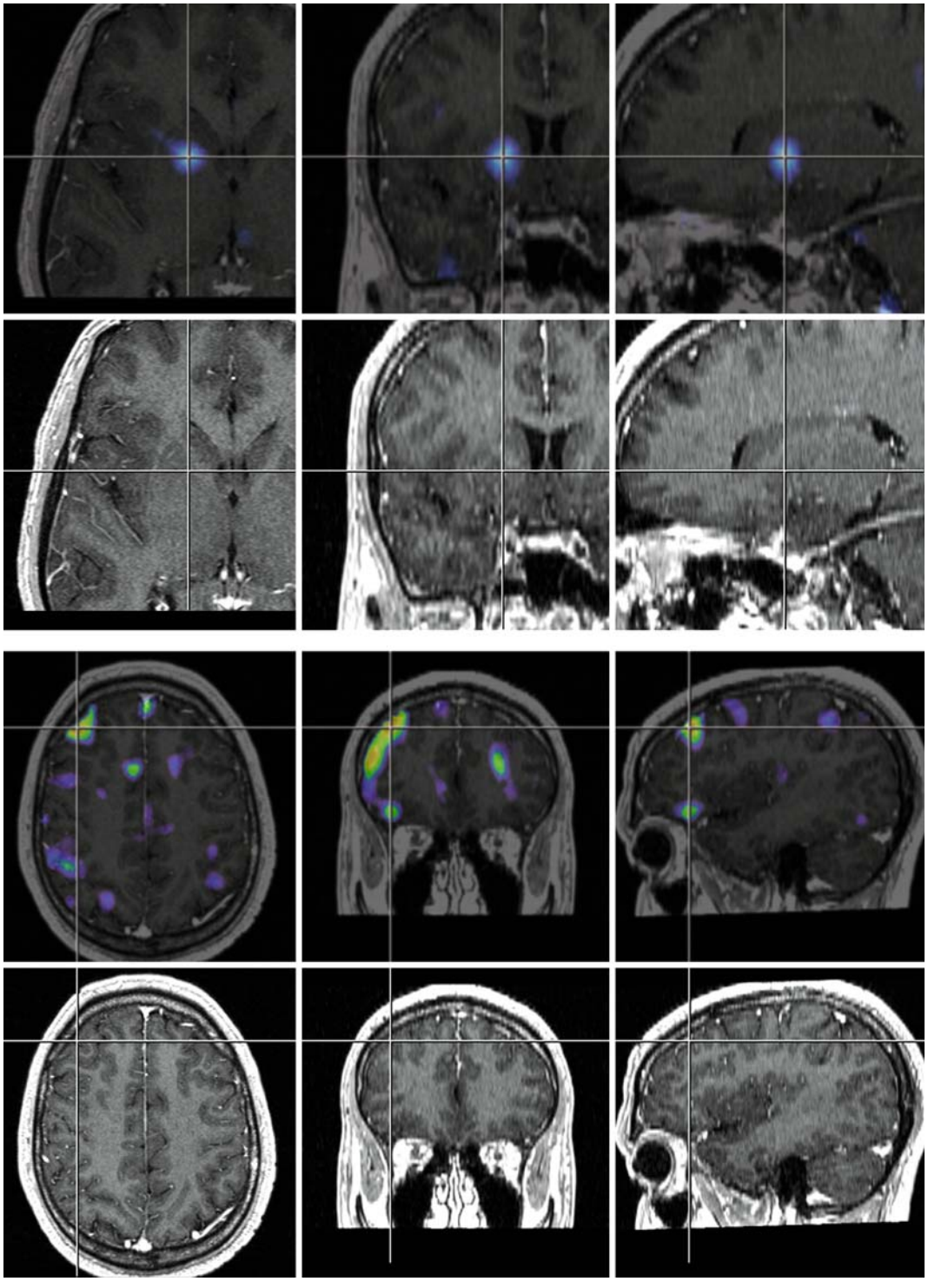

Fig. 16.2. Upper image: region of neuronal inhibition as measured by 15O-H2O-PET superimposed onto the preoperative MR image. Lower image: frontal cortex shows neuronal activation as a result of DBS in the ipsilateral (right) shell of the nucleus accumbens

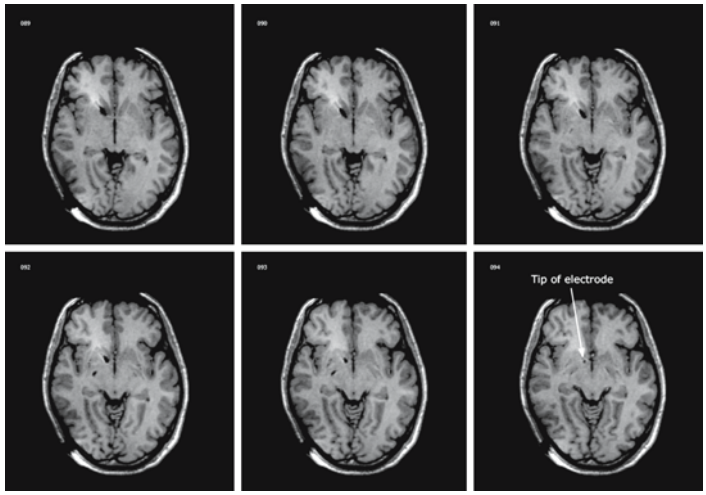

Fig. 16.3. Postoperative T1-weighted MRI depicts exact electrode placement in the desired target area. Note the dark artifact surrounding the electrode, which is due to disturbance of the local magnetic field by the electrode and not caused by tissue damage

verified by intraoperative X-ray. Target point and trajectory have been assessed using stereotactic MR and CT imaging (◘ Figs. 16.2 and 16.3).

Unilateral DBS of the right accumbens was performed in four patients. They were suffering from severe anxiety disorders and OCD and no longer responding to medical treatment and psychotherapy. DBS treatment, applied with permanent pulse-train stimulation (square-wave impulses of 90 μs duration, 130 Hz, and amplitudes between 2 and 6.5 V) yielded nearly total recovery from both anxiety and OCD symptoms without any side effects in three of four patients with follow-up periods of 24–30 months. Clinical improvement occurred a few days to several weeks after the beginning of DBS. In the fourth patient no beneficial effect was achieved. A recently performed MRI investigation in that patient revealed that the target area had been missed owing to a displacement of the electrode in the caudoventral direction, which explains the therapeutic failure.

In one patient a 15O-H2O-PET study in conditions "stimulation on vs. stimulation off" was performed. High-frequency stimulation of the shell of the nucleus accumbens inhibited the activity of the ipsilateral dorsolateral rostral putamen but activated the right dorsolateral prefrontal and cingulate cortex.

One patient had a severe relapse of OCD and anxiety symptoms 30 months after electrode implantation and permanent DBS. Following exchange of the pacemaker, the patient recovered very well and was able to return to "normal" life 3 days later.

This article focuses on a possible rationale for DBS in the nucleus accumbens in the treatment of anxiety and obsessive-compulsive disorder. A detailed presentation of the clinical and PET data (not yet published) would exceed the scope of the present communication.

Discussion

The significant improvement of symptoms due to severe anxiety and OC disorders obtained with unilateral high-frequency stimulation of the shell of the right n. accumbens indicates a major role for this nucleus as a central relay between the amygdaloid complex, the basal ganglia, the mediodorsal thalamus, and the prefrontal cortex. The amygdaloid complex, especially the lateral nucleus, is well-known to be involved in anxiety and fear reactions [11, 22]. Disinhibition of the lateral amygdaloid nucleus has been shown to be decisive for the development of Pavlovian learned fear, depending on a deficiency of gastrin-releasing peptide receptors on GABA-ergic interneurons, which in turn causes disinhibition of principal neurons in the lateral-amygdaloid nucleus [22].

Pathological information flow from the lateral amygdaloid nucleus can be propagated to basolateral and central amygdaloid nuclei, to finally converge in the shell region of the accumbens via both the ventral amygdalofugal pathway and the extended amygdala. The shell region could thus represent a "bottleneck" for impulse propagation from the amygdaloid complex to the basal ganglia, mediodorsal thalamus, and prefrontal cortex, areas involved in the pathophysi-

ology of OCD, as shown with functional imaging [22]. This was supported by our PET data, briefly described above.

The PET findings seemed to correlate well with the symptoms of the patient, which were aggravated in the stimulation-off period and relieved in the stimulation-on period. A placebo effect cannot be excluded because the investigated patient had not been blinded.

The good results in our anxiety and OCD patients might be explained by blocking of this hypothetical pathological impulse flow through chronic high-frequency stimulation of the shell of the N. accumbens. It is noteworthy that unilateral stimulation of the right n. accumbens was sufficient. This finding is in line with the results of Lippitz et al. [12], who found that capsulotomies in the right hemisphere were decisive for a favorable therapeutic outcome.

Inputs from the amygdaloid complex to the nucleus accumbens "gate" both fronto-striatal and hippocampo-striatal circuitry [5, 16, 19]. It might thus be speculated that a dysfunction of the nucleus accumbens, resulting in an impairment to adequately modulate amygdalo-basal ganglia-prefrontal circuitry, might be at the origin of anxiety disorders and OCD.

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