A SYSTEMATIC REVIEW OF PSYCHOSURGICAL TREATMENTS FOR OBSESSIVE-COMPULSIVE DISORDER: DOES DEEP BRAIN STIMULATION REPRESENT THE FUTURE TREND IN PSYCHOSURGERY?

Bruno Aouizerate, Jean-Yves Rotgé, Corinne Martin-Guehl, Emmanuel Cuny, Alain Rougier, Dominique Guehl, Pierre Burbaud, Bernard Bioulac, and Jean Tignol

Summary

Obsessive-compulsive disorder (OCD) is a relatively frequent anxiety disorder with an estimated lifetime prevalence of 2-3% in the general population. It is generally characterized by a chronic course leading to profound impairment in psychosocial functioning and quality of life. Although its pathophysiology is not completely understood, there is considerable evidence for the role of overactivity in the frontal-subcortical loops originating in the orbitofrontal cortex and the anterior cingulate cortex, respectively. By acting preferentially through the blockage of serotonin reuptake, antidepressants, in addition to psychological treatments, have significantly improved the poor prognosis of the illness. However, these conventional therapeutic strategies fail to sufficiently alleviate obsessive-compulsive symptoms in approximately 25-30% of cases. Several surgical strategies have been successfully investigated for treating resistant forms of OCD, including anterior capsulotomy, anterior cingulotomy, subcaudate tractotomy and limbic leucotomy. They interrupt the orbitofrontal and anterior cingulate loops at either the cortical or subcortical level, which have been found to be disrupted in OCD. Although these lesional techniques have a relatively low incidence of serious complications or undesirable effects, the non-ablative surgical procedure known as deep brain stimulation (DBS), which offers the advantages of reversibility and adjustability, has recently been introduced in the treatment of medically intractable OCD, by primarily targeting the limb part of the internal capsule, the subthalamic nucleus or the ventral striatum. DBS appears to be highly promising providing that its benefit is investigated with all due caution and is confirmed by further research in this area.

Key words: Obsessive-Compulsive Disorder (OCD) – Orbitofrontal Cortex – Anterior Cingulate Cortex – Anterior Capsulotomy – Anterior Cingulotomy – Subcaudate Tractotomy – Limbic Leucotomy – Deep Brain Stimulation (DBS) – Medically Intractable OCD

Declaration of interest: none

Bruno Aouizerate[a,b], Jean-Yves Rotgé [a,b], Corinne Martin-Guehl[a], Emmanuel Cuny[c], Alain Rougier[c], Dominique Guehl[b], Pierre Burbaud[b], Bernard Bioulac[b], and Jean Tignol[a]

[a] Service de Psychiatrie d'Adultes, Université Victor Segalen Bordeaux 2, Centre Hospitalier Charles Perrens, Centre Carreire, 121 rue de la Béchade, 33076 Bordeaux, France.
[b] Service de Neurophysiologie Clinique, Université Victor Segalen Bordeaux 2, CNRS UMR 5543, Centre Hospitalier Pellegrin, Place Amélie Raba-Léon, 33076 Bordeaux, France.
[c] Service de Neurochirurgie, Université Victor Segalen Bordeaux 2, Centre Hospitalier Pellegrin, Place Amélie Raba-Léon, 33076 Bordeaux, France.

Corresponding Author
Bruno Aouizerate Service de Psychiatrie d'Adultes, Université Victor Segalen Bordeaux 2, Centre Hospitalier Charles Perrens, Centre Carreire, 121 rue de la Béchade, 33076 Bordeaux, France. bruno.aouizerate@u-bordeaux2.fr

Obsessive-compulsive disorder (OCD) is a relatively frequent anxiety disorder that affects 2-3% of the general population (Rasmussen and Eisen 1990, 1992). It is characterized by persistent, intrusive and unpleasant thoughts, impulses or images. Recurrent, time-consuming behaviors are performed in a ritualistic fashion according to rigid rules in order to reduce anxiety and severe distress caused by obsessions. OCD markedly impairs social, occupational and other important areas of functioning, and produces a profound deterioration in quality of life (Koran et al. 1996).

Over the last three decades, significant advances in the development of pharmacological and psychological strategies have considerably improved the prognosis of OCD, which generally has a chronic course with low rates of spontaneous remissions (Rasmussen and Tsuang 1986, Skoog and Skoog 1999). Controlled research has largely contributed to establishing the efficacy of antidepressant medications in the treatment of OCD, which have prominent inhibiting effects on serotonin reuptake (SRI). Clomipramine, a tricyclic antidepressant, was initially introduced in the late 1960s (Fernandez-Cordoba and Lopez-Ibor 1967) and exhibits specific anti-obsessional effects independently of its antidepressant action (Thoren et al. 1980, Insel et al. 1983, Mavissakalian et al. 1985). However,

Received November 2006, accepted November 2006

clomipramine possesses relatively potent anti-muscarinic, antihistaminic and anti-α_1-adrenergic properties, resulting in adverse autonomic effects and complex toxic reactions from acute overdosage that limit its use and tolerability. Since the late 1980s, a series of innovative antidepressant agents comprising the so-called "selective serotonin reuptake inhibitor" (SSRI) group has emerged. The SSRIs have been found to present similar anti-obsessional efficacy but fewer side effects or toxicity risks than the tricyclics. SSRIs have today become the first-line agents for the management of OCD. In addition to pharmacological approaches, cognitive-behavioral therapies (CBT) such as exposure and prevention response have proven useful in alleviating obsessive-compulsive symptoms (Foa et al. 1998, 2002). However, up to 25-30% of patients fail to respond adequately to these treatments (Jenike et al. 1998), in part due to the side effects of SSRIs at therapeutic doses as well as to the high levels of anxiety and discomfort involved in CBT, which increase the risk of dropout or non-compliance. Several neurosurgical approaches have been successfully proposed for treating OCD cases unresponsive to traditional treatments. They consist in performing lesions within the frontal-subcortical loops that emanate from the orbitofrontal and anterior cingulate cortices, respectively, which are thought to be of special importance in the genesis of obsessive-compulsive symptoms. In this review article, we first focus on the pathophysiological basis of OCD in the light of phenomenological considerations. An anatomical-functional approach of OCD is succinctly developed on the basis of our increasing knowledge about structure-function relationships in parallel with large functional neuroimaging data sets. Several brain regions such as the orbitofrontal cortex, the anterior cingulate cortex and their subcortical projections to striatum (caudate nucleus) have been identified as playing a central role in the mediation of obsessive-compulsive manifestations. Second, the paper examines neurosurgical strategies that have been most often used for the management of refractory forms of OCD, especially anterior capsulotomy, anterior cingulotomy, subcaudate tractotomy and limbic leucotomy. These lesion-producing procedures have been shown to substantially alleviate obsessive-compulsive symptomatology in 40 to 60% of cases and to cause relatively few deleterious complications. Third, we discuss deep brain stimulation (DBS), a reversible neurosurgical technique, which is emerging as a treatment of choice in severely disabling forms of Parkinson's disease and other movement disorders (Cuny et al. 2002, Mahli and Sachdev 2002, Krack et al. 2003, Fraix et al. 2006, Guehl et al. 2006). DBS has recently been introduced for replacing older lesional procedures in resistant OCD (Nuttin et al. 1999, Mallet et al. 2002, Anderson and Ahmed 2003, Gabriels et al. 2003, Sturm et al. 2003, Abelson et al. 2005, Aouizerate et al. 2004a, 2005a, Greenberg et al. 2006). To date, the encouraging preliminary results have been found to depend particularly on the targeted brain, including the limb part of the internal capsule, the subthalamic nucleus or the ventromedial caudate nucleus. No serious adverse effects resulting from DBS have been reported until now.

1. Pathophysiological basis of OCD

Over the last 30 years, there has been considerable progress in neuroscience leading to better understanding of the pathophysiological determinants of OCD. For this purpose, a general two-step strategy has been used resulting from: 1) the investigation of cognitive and emotional processes, which can be considered as disrupted regarding phenomenological aspects; and 2) the identification of brain regions that are more specifically implicated in the production of obsessive-compulsive symptoms on the basis of neurophysiological research. This approach is now briefly discussed.

1.1. Phenomenological aspects

The core of the obsessional process is the experienced sensation that "something is wrong" (Schwartz 1998, 1999). In other words, obsessions may be understood as the consequence of an excessive attribution of negative consequences upon exposure to certain behavioral situations. (Salkovskis 1985, 1999). The pathological doubt, a prominent phenomenon in OCD, may be related to the permanent perception of a mistake and/or error in the initial representation referring to a cognitive overestimation of the likelihood of aversive events occurring in response to the subject's action. Pathological doubt may be considered not only in terms of cognitive constructs but also the subject's emotional reaction to feelings of uncertainty generated by perceived "error detection" signals (Foa et al. 1998, Tolin et al. 2003). Compulsions may be construed as behavioral responses intending to relieve the tensions or anxiety caused by high levels of self-doubt. If obtained, this relief may be felt as a form of reward. Nevertheless, it is only transient, thereby increasing anxiety severity and emotional distress. This leads to immediately reproducing the behavior in a cyclic manner on the basis of an internal motivational state through an expectation of the reward. Moreover, attention is selectively directed towards the compulsive behavior the subject is undertaking. Although it is certainly simplistic, this phenomenological view is of interest because several processes are apparently disrupted within the OCD, including cognitive appraisal and representation, anticipation, maintenance of concentration and attention, error detection, emotion and activational motivation (e.g. activations for initiation and sustaining behavioral reactions and tendency to work for reward). Therefore, a dysfunction of the brain regions heavily involved in these cognitive and emotional processes may occur in OCD (Aouizerate et al. 2004b, 2005b).

1.2. Anatomo-functional approach

Considerable contributions from animal work and human functional neuroimaging studies have provided detailed information of the prefrontal systems that appear to be important in OCD. As proposed above, it has been postulated that disruption in the frontal-subcortical circuits originating in the orbitofrontal cortex (OFC) and the anterior cingulate cortex (ACC), respectively, play a crucial role in the emergence of obsessive-compulsive symptoms (Aouizerate et al. 2004b, 2005b). These loops share common general structures. Both OFC and ACC send projections to the ventral striatum, including the nucleus accumbens and the ventromedial portion of the caudate nucleus. The ventral striatum has efferent connections to the dorsomedial and ventral pallidum before reaching the paramedian portions of the ventral anterior and medial nuclei of the thalamus. The thalamic relay sends back projections to the OFC and ACC, thus completing the circuits. Although they are part of a parallel model of organization, the orbitofrontal and anterior cingulate loops are anatomically and functionally interrelated (Cummings et al. 1993).

1.2.1. Functional properties of the OFC, ACC and ventral striatum

The OFC is thought to intervene in both cognitive and emotional processing. The anterior and ventrolateral sectors appear to play a pivotal role in a wide range of cognitive processes, including the selection, comparison and judgment of stimuli held in short-term and long-term memory, task switching, coordination of two or more separate cognitive operations, information transfer between operations and relational integration of the results of multiple operations (Ramnani and Owen 2004), and monitoring of error recognition (Rosenkilde et al. 1981, Thorpe et al. 1983). Moreover, the OFC and ventromedial areas are highly involved in emotional and motivational processes. They participate in the assessment, appraisal and determination of the emotional significance of environmental stimuli, the generation and modulation of complex specific affective states and emotional experiences (feelings) leading to behavioral responses that are contextually appropriate (Tremblay et al. 1999, Phillips et al. 2003, Roesch and Olson 2004). Finally, the OFC is thought to be important for the affective aspects of decision making and the capacity to anticipate by the representation of elementary positive and negative emotional states when immediate elicitors are not present (Davidson et al. 1999, Krawczyk 2002, Matsumoto et al. 2003).

The ACC has been functionally divided into two major subdivisions that appear especially relevant in processing cognitive and emotional information, respectively. The dorsal region, which has bidirectional connections with the dorsolateral prefrontal cortex (DLPFC), parietal cortex, and premotor and supplementary motor areas, in involved in various cognitive functions including attention to action, working memory, anticipation of incoming information and error detection (Niki and Watanabe 1979, Devinsky et al. 1995, Shima and Tanji 1998, Schwartz 1999, Bush et al. 2000, 2002, Akkal et al. 2002, Shidara and Richmond 2002). It has also been shown that the dorsal ACC plays a key role in non-routine situations where conflicts intervene between plans of action and the high likelihood of making an error. The detection of conflicts by the ACC leads to the recruitment of cognitive control in the DLPFC (Botvinick et al. 1999, 2004, Kerns et al. 2004, Matsumoto and Tanaka 2004). Cognitive control reflects a configuration of the cognitive system during performance in specific tasks. It requires an effort and blocks habitual behavior in favor of the execution of less familiar behavior (Botvinick et al. 1999, 2004, Kerns et al. 2004, Matsumoto and Tanaka 2004). The ventral region of the ACC is intimately linked to the limbic system, especially the OFC, amygdala, ventral striatum and hippocampus, and has connections to the hypothalamus, which is essential for the regulation of autonomic and neuroendocrine responses. The ventral ACC contributes to emotional processing by which an internal emotional and motivational state is consciously perceived (Devinsky et al. 1995, Bush et al. 2000).

The striatum lies at the crossroads of three vast anatomo-functional systems: limbic, associative and motor. A modular design remaps cortical inputs onto distributed local modules of striatal projections neurons comprised of a dispersed set of neurochemically specialized patchy zones, the striosomes, within a large matrix compartment called the matrisomes (Gerfen 1984, Graybiel et al. 1994). Striosomes are more numerous in the ventromedial part than in the dorsolateral region of the striatum. They primarily receive inputs related to the limbic system and project to the dopamine-containing substantia nigra pars compacta. The two parts of the prefrontal cortex that densely innervate striosomes are the OFC and ACC. Matrisomes preferentially receive inputs from associative and sensorimotor cortical areas and project to the output nuclei of the basal ganglia (Gerfen 1984, Graybiel et al. 1994, Eblen and Graybiel 1995, Baxter 1999). The striatum reduces the dimensionality of sparse information from the entire neocortex, which is then integrated in planning aspects and motor execution (Bar-Gad and Bergman 2001). On one hand, the dorsal striatum seems to be involved in the procedural learning of behavioral routines that are performed almost without conscious effort. Habit formation may result from a dynamic reorganization within this region underlying "motor readiness" and "release" functions that may be thought as altered in OCD, in which patients have particular difficulties in interrupting the performance of routinized behavioral sequences, with deficit in shifting ability from one sequence to another (Baxter 1999, Jog et al. 1999, Aouizerate et al. 2004b). On the other hand, the ventral striatum is important for the preparation, initiation and control of voluntary behaviors oriented towards reward delivery (Hollerman et al. 1998, Tremblay et al. 1998, Hassani et al. 2001). Reward-driven learning requires extraction of reward-related information from a large variety of stimuli (Schultz 2000, Bar-Gad and Bergman 2001). The tonically active neurons (TANs), which seem to be located at the striosome-matrix borders of the striatum (Graybiel et al. 1994, Schwartz 1998), participate in the integration of motivationally significant events during learning (Aosaki et al. 1994, Schwartz 1998, Apicella 2002). Dopamine neurons carry information on the presence and values of rewards, and their predictability, which are essential in a reinforcement learning process (Fiorillo et al. 2003, Tobler et al. 2005). They are modeled as the "critic" providing a feedback to the "actor" by evaluation of the consequences of a given action on the environment, and which generates an error signal when differences are perceived between predictions and reality. In this way, the "critic" modulates the subsequent "actor's" behavior so as to obtain or optimize the magnitude of reward (Bar-Gad and Bergman 2001). Moreover, there are differential contributions of dopaminergic projections to the ventral and dorsal parts of striatum corresponding to the "critic" and the "actor", respectively (O'Doherty et al. 2004). Thus, OCD may be considered as the consequence of an excessive "critic", resulting in the emergence of compulsive behaviors (Aouizerate et al. 2004b, 2005b).

1.2.2. Functional neuroimaging

Progress in functional neuroimaging technology has offered the opportunities for elucidating the anatomic substrates of OCD. Positron emission tomography, single photon emission computed tomography and functional magnetic resonance imaging studies have predominantly compared brain activation between patients with OCD and normal healthy subjects, as well as within patients with OCD either during symptom provocation conditions or before and after therapy. Converging lines of evidence indicate cerebral blood flow and metabolic glucose abnormalities in several cortical and subcortical brain regions. Most research groups have found an increased functional activity in the OFC, ACC, head of the caudate nucleus and thalamus (Saxena et al. 1998, Baxter 1999, Aouizerate et al. 2004b, 2005b). These functional abnormalities have been shown in baseline conditions and during symptom provocation paradigms. Moreover, the reducing effects of antidepressants and CBT on OCD severity seem to be associated to a progressive decline in activity of the OFC, ACC and the caudate nucleus, thereby supporting the hypothesis of a putative functional deterioration in the orbitofrontal and anterior cingulate cortex system in OCD (Saxena et al. 1998, Baxter 1999, Aouizerate et al. 2004b, 2005b).

For the most part, neuroimaging studies of OCD have been conducted in patients with multiple and heterogeneous symptoms. In this respect, recent efforts have provided a classification of patients with OCD according to their respective clinical phenotype. Factor analytic studies have reduced the symptoms of OCD to four reliable and temporally stable dimensions: 1) aggressive/sexual/religious/somatic obsessions and checking compulsions; 2) obsessions with need for symmetry/exactness and ordering/arranging/counting compulsions; 3) contamination obsessions and cleaning/washing compulsions; and, 4) hoarding obsessions and collecting compulsions (Baer 1994, Leckman et al. 1997, Summerfeldt et al. 1999, Mataix-Cols et al. 1999, 2002). The identified symptom subgroups have been found to be linked to distinct patterns of brain activation (Mataix-Cols et al. 2003, 2004, Saxena et al. 2004). Findings from these studies indicate an excess activity in either dorsal cortical areas (DLPFC and dorsal ACC) upon presentation of provocative checking-related pictures or ventral cortical areas (OFC and ventrolateral prefrontal cortex), in response to hoarding-related pictures, or both upon exposure to washing-related pictures (Mataix-Cols et al. 2003, 2004). However, hoarding symptoms have been associated with lower activation in subcortical regions such as the caudate nucleus and thalamus (Saxena et al. 2004).

A critical issue is to examine the possibility of altered error detection process in OCD. An overactivation in both OFC and ACC of patients with OCD was found when errors were made during a high-conflict behavioral task (exaggerated error signals), but also when trials were correctly completed (false error signals) (Fitzgerald et al. 2005, Maltby et al. 2005). These results suggest the importance of an excessive monitoring for the occurrence of error generated by the ACC in the pathogenesis of OCD.

In conclusion, abundant data from various complementary approaches (neurophysiology and functional neuroimaging) have provided strong evidence for the hypothesis of a functional deterioration in the orbitofrontal and anterior cingulate cortex system in OCD.

2. Neurosurgical treatments of OCD

The idea of brain surgery as a means of improving psychiatric disorders started around 1890, when Frederich Goltz, a German researcher, removed a portion of his dogs' temporal lobes and found them to be calmer and less aggressive. This was swiftly followed by application in humans when Gottlieb Burkhardt, a Swiss psychiatrist, attempted similar surgeries on six of his schizophrenic patients. Some were indeed calmer but two died. That might have been the end of the story but in 1935 at a London conference of neurologists, Fulton and Jacobsen of Yale University demonstrated the effects of removing the frontal lobe of animals. They had performed a lobectomy on a chimpanzee called Becky who prior to the procedure would get agitated and frustrated during experiments. After the brain surgery, Becky displayed a radical change in behavior. She was apparently incapable of becoming frustrated or agitated. One year later, inspired by the effects of the frontal cortical ablation, the Portuguese neurologist Egas Moniz, working together with the neurosurgeon Almeida Lima, performed and developed the first human lobotomy ("prefrontal leucotomy") which greatly influenced the work of Walter Freeman, a U.S. neurologist and his associate, James Watts, a neurosurgeon. The first lobotomy was performed in the U.S. in 1936. Despite Freeman's passionate support for the procedure, psychosurgery fell into disrepute during the 1950s because of the marked complications often produced and the introduction of psychotropic medications for the management of psychiatric conditions beginning in 1954 with chlorpromazine (Binder and Iskandar 2000, Feldman et al. 2001). However, the still scarce agents available at this time failed to sufficiently improve some psychiatric patients who experienced undesirable effects. Thus, there was a renewed interest in psychosurgery in the 1960s with the development of stereotactic lesioning. The four currently used procedures, called anterior capsulotomy, anterior cingulotomy, subcaudate tractotomy and limbic leucotomy, have been successfully applied in severe, chronic and refractory cases of psychiatric illnesses, such as OCD. Recently, the reversible surgical procedure DBS, which constitutes a highly effective treatment of advanced forms of Parkinson's disease, has been proposed as a therapeutic alternative for intractable OCD. We describe each procedure regarding its rationale, results and safety.

2.1. Anterior capsulotomy

Starting with the pioneering work of the neurosurgeon Lars Leksell at the Karolinska Institute (Sweden) in the 1950s, anterior capsulotomy targets the anterior limb of the internal capsule in which fibers connecting the ventral anterior and medial dorsal nuclei of the thalamus to the OFC and ACC pass (Mindus and Jenike 1992, Bentivoglio et al. 1993, Jenike 1998, Binder and Iskandar 2000, Feldman et al. 2001, Malhi and Sachdev 2002, Greenberg et al. 2003, Mashour et al. 2005). Two major surgical procedures have been implemented: radiofrequency thermolesion and radiosursurgical or gamma capsulotomy.

In the radiofrequency thermolesion technique, the intervention is performed under local anesthesia and light sedation. Coordinates of the target in the anterior limb of the internal capsule are determined with preoperative magnetic resonance imaging (MRI). Small bilateral burr holes are made and monopolar electrodes are inserted into the target area. Thermolesioning by heating the uninsulated tip of the electrode to 75°C for 75 seconds produces a lesion approximately 4 mm wide and 15-18 mm long. In radiosurgical or gamma capsulotomy, lesions are created by cross-firing 201 narrow beams of ^{60}CO g-radiation from a stereotactic gamma unit onto the target site. General anesthesia is not needed, and only a slight premedication is used. Craniotomy and shaving are unnecessary. The biologic effect of each gamma beam is negligible (Mindus and Jenike 1992, Jenike 1998, Binder and Iskandar 2000, Feldman et al. 2001).

2.1.1. Efficacy

Herner (1961) was the first to assess the effects of capsulotomy in OCD. In a sample of 18 patients with obsessional neurosis, 14 (78%) had markedly improved symptoms over the follow-up period ranging from 24 to 80 months. Later, Bingley et al. (1977) reported that 16 (45.7%) of the 35 OCD patients treated were considered as free from symptoms, nine (25.7%) were much improved and 10 (28.6%) were slightly improved or unchanged at the end of the follow-up period of 35 months. Of the 24 patients who were entirely unable to work before surgery, 20 (83.3%) recovered partly or fully working capacities postoperatively. Similarly, Kullberg (1977) found that one (12.5%) of the eight patients with OCD who underwent this surgical procedure showed a complete regression of symptoms, two (25.0%) experienced a considerable reduction of symptom severity, three (37.5%) exhibited moderate-to-slight reduction of symptom severity, and the remaining two (25.0%) had no change in symptom intensity at the end of the 1 to 9 years of follow-up. This was paralleled by considerable improvement in social functioning. Fodstad et al. (1982) reported that the two patients operated with OCD felt substantially better within 24 months following surgery. In the more recent study by Mindus et al. (1994) using the Comprehensive Psychopathogical Rating Scale-Obsessive-Compulsive subscale (CPRS-OC) for assessment of changes in symptom severity, seven (32.0%) of the 22 patients undergoing capsulotomy for refractory OCD had improved by 75% to 100%, three (13.0%) by 51 to 75%, five (23.0%) by 26% to 50% and the remaining two (9.0%) by 1% to 25% at the 8-year follow-up. Lippitz et al. (1999) also found a good therapeutic response, as defined by a 50% reduction or more in scores on the CPRS-OC or the Yale-Brown Obsessive Compulsive scale (Y-BOCS), in 16 (55.2%) of the 29 patients after 8 years of follow-up.

Taken together, these findings suggest that anterior capsulotomy leads to successful outcome in around two-thirds of patients suffering from severely distressing and incapacitating forms of OCD.

2.1.2. Complications, side-effects

In the report by Herner et al. (1961), the operation caused no mortality in all 116 patients who underwent this procedure for a wide spectrum of psychiatric conditions, such as schizophrenia, depression, anxiety and obsessional neuroses. Three of these patients (2.5%) died at 11, 28 and 33 months after surgery respectively but two from suicide and the third from cardiac infarction. Seven (27.0%) of the 26 patients undergoing capsulotomy for severely disabling anxiety disorders other than OCD had attempted suicide after surgery, as shown by Rück et al. (2003). Operative complications were markedly few: subcortical hemorrhage (transient hemiparesis) in two (4.4%) of the 35 patients by Bingley et al. (1977), stenosis of the aqueduct of the mid-brain in one (0.8%) and comitiality in four cases (3.4%) of the 116 patients by Herner (1961). In the recent study by Rück et al. (2003), two (7.6%) of the 26 patients experienced postoperative seizures requiring carbamazepine treatment in one (3.8%). The other side-effects recorded were much less serious, including urinary and fecal incontinence and weight increase (+ 11.6% of the preoperative bodyweight in the OCD group at 24- to 80-month follow-up) (Herner, 1961). Recently, Rück et al. (2003) confirmed weight change with a more pronounced gain in the women (+ 15.1 kg at the one-year follow-up).

Kullberg (1977) reported transient confusion with temporal spatial disorientation lasting less than three weeks after the operation in all eight patients with OCD. Blunted affects with inactivity and apathy were described in most patients (62.5%), particularly during the first two weeks of the post-operative period. These adverse effects appear to normalize in the long-term. In investigating personality changes, Bingley et al. (1977) and Fodstad et al. (1982) gave the Eysenck Personality Inventory (EPI). No personality deterioration was noted up to one year after the operation. Normalization of personality traits, as measured with the Karolinska Scales of Personality, even occurred in all 15 patients treated with capsulotomy at either one or eight years after surgery (Mindus et al. 1999). However, Fodstad et al. (1982) using a comprehensive battery of neuropsychological tests showed a slight impairment in reasoning ability in one (50.0%) of the two capsulotomized patients for OCD. Nyman and Mindus (1995) reported that five (50.0%) of the 10 patients treated with capsulotomy for intractable anxiety disorders, including OCD, committed more perseverative errors on the Wisconsin Card Sorting Test. Seven (27.0%) of the 26 patients by Rück et al. (2003) also showed significant adverse symptoms with apathy and dysexecutive behavior, which were strongly correlated with performance on neuropsychological tests of executive and working memory functions. Such disturbances in clinical frontal lobe functioning were found at one year after surgery.

Therefore, it can be concluded that anterior capsulotomy is a relatively safe surgical technique, although long-term dysfunction of systems involving the frontal lobes was identified in more than one third of psychiatric cases treated with this surgical procedure.

2.2. Anterior cingulotomy

Originally performed by Whitty (Oxford, UK) in 1952, modern stereotactic bilateral anterior cingulotomy was developed under the direction of Thomas Ballantine at Massachusetts General Hospital in Boston (U.S.) between 1965 and 1986. In this surgical procedure, the targets are located in the ventral and rostral regions of ACC (Brodmann areas 24 and 32) (Whitty et al. 1952, Ballantine et al. 1987, Mindus and Jenike 1992, Jenike 1998, Binder and Iskandar 2000, Feldman et al. 2001, Malhi and Sachdev 2002, Greenberg et al. 2003, Mashour et al. 2005).

Under general anesthesia, the operation requires minimal hair shaving. Thermocoagulation electrodes are introduced stereotactically into each target site through bilateral burr holes, approximately 12 mm in diameter. Initially, ventriculography was used to help visualize the targets. In 1991, this was replaced by MRI guidance. The uninsulated tips of the electrodes are heated to 80-85°C for 100 sec by a radiofrequency current. The lesions are 1 cm wide and 2 cm long (Ballantine et al. 1987, Mindus and Jenike 1992, Jenike 1998, Binder and Iskandar 2000, Feldman et al. 2001).

2.2.1. Efficacy

In the earliest case report, Whitty et al. (1952) found beneficial effects of cingulotomy in three (75.0%) of the four patients diagnosed with obsessional neurosis. Two were considered as having pronounced improvement and the remaining one was reported as somewhat "improved" at the end of the follow-up ranging from $1^{3/4}$ to $2^{3/4}$ years. This promising finding failed to be confirmed by Kullberg (1977) who showed a relatively modest reduction in symptom severity in the three OCD patients at 1 to 8 years after the operation. Fodstad et al. (1982) also reported that two patients with incapacitating forms of OCD were clinically unchanged two years after surgery was performed. However, Ballantine et al. (1987) who performed cingulotomy on a larger series of 32 patients with OCD, noted that eight (25.0%) were functionally well, 10 (31.0%) experienced marked improvement, and 14 (44.0%) showed slight or no improvement over the mean postoperative follow-up period of 8.6 years. Jenike et al. (1991) retrospectively analyzed the outcome for 14 operated patients using the Y-BOCS, which has become the most commonly accepted instrument for determining obsessive-compulsive symptom intensity. Eight (57.0%) showed moderated-to-marked improvement, as indicated by a 50 % or greater decrease in Y-BOCS score. The remaining six (43.0%) experienced no clinical change at a mean follow-up of 13.1 years. Among the eight patients who responded favorably, two associated their improvement rather with their current pharmacological treatment and behavioral therapy, while one other still had significant obsessive-compulsive symptoms, as suggested by a Y-BOCS score above 16. In a prospective study of 44 OCD patients, Dougherty et al. (2002) found relatively consistent results. At the long-term follow-up of 32 months after one or more cingulotomies, 14 (32.0%) of the 44 OCD patients were classified as responders, determined as at least 35% improvement on the Y-BOCS and a Clinical Global Improvement (CGI) score of 1 (very much improved) or 2 (much improved). Six others (14%) were considered as partial responders, defined as at least 35% improvement on the Y-BOCS or a CGI score of 1 (very much improved) or 2 (much improved).

Although initial studies of the efficacy of anterior cingulotomy showed beneficial effects in approximately 60% of OCD patients, more recent investigations have provided much less encouraging results with a response rate of 30%. This may be related to: 1) the surgical procedure based on more selective lesions of CCA; 2) the use of standard instruments for clinical assessment of therapeutic response; and 3) the study population who met current criteria for treatment non-response in OCD.

2.2.2. Complications, side-effects

Ballantine et al. (1987) were the first to carefully evaluate the risks and complications of selective stereotactic lesions made in the ACC on their series of patients who met various psychiatric diseases, particularly including affective disorders (unipolar, bipolar, and schizoaffective), OCD and other anxiety disorders, schizophrenia and personality disorders. The authors showed a low incidence of serious complications. No death occurred among the 696 cases of cingulotomy performed during the 25 years of this study. There were hemiplegias due to intracerebral hematomas in 0.3%. Postoperative seizures, which were usually well controlled with phenytoin, were observed in 1.0%. Although Fodstad et al. (1982) also recorded modifications in EEG patterns in the immediate postoperative phase in the two OCD patients treated with this surgical procedure, all EEGs were normal at the follow-up examinations (12-36 months). Jenike et al. (1991) described occasional seizures in three (9.0%) of the 33 patients treated with cingulotomy for refractory forms of OCD. In the study by Dougherty et al. (2002), one patient (2.0%) also developed seizures, which were successfully treated with anticonvulsivant medication. In the report by Whitty et al. (1952), 12 (41.4%) of the 29 operated cases showed urinary and/or fecal incontinence, which was restricted to the first postoperative week. No significant change in autonomic functions was found between three weeks before and three months after surgery. Weight was relatively stable over the six postoperative months of monitoring, except for some psychotic patients who experienced an increase in body weight.

Kullberg (1977) described immediate psychic disturbances in four (30.7%) of the 13 patients who underwent cingulotomy for anxiety disorders including OCD. These cognitive, emotional and behavioral alterations (confusion, blunted affects, apathy and motor retardation) disappeared within 3-4 weeks after intervention. Dougherty et al. (2002) also reported apathy with decreased energy in one patient (2.0%). However, this effect resolved over a longer period of six months. Conversely, Jenike et al. (1991) mentioned that one patient (3.0%) exhibited a manic episode whereas another (3.0%) felt much less severe symptoms with excessive energy and sleeping difficulties for several weeks after the operation was performed. In the study by Ballantine et al. (1987), 18 (9.0%) of the 198 psychiatrically disabled patients committed suicide over the mean follow-up period of 8.6 years. The annual suicide rate was therefore 1.0%. However, all these patients had suicidal ideation before surgery and 13 (72%) even made suicide attempts before cingulotomy. There was also one case (2.0%) of death by suicide among the 44 OCD patients, which occurred within 6 months after cingulotomy, as the consequence of concomitant major depression with past history of suicide attempt (Dougherty et al. 2002). Postoperative neuropsychological tests showed that general intellectual functions are at the same levels at 6 months, as compared before surgery in the two OCD patients who underwent this surgical technique (Fodstad et al. 1982). Better testing results were even obtained after the operation (Ballantine et al. 1987). Despite the increase in performance on memory tests found by Fodstad et al. (1982), memory deficits were recently reported in two OCD patients (5.0%), which resolved within 6-12 months after the operation (Dougherty et al. 2002). This is consistent with previous work by Cohen et al. (1999) showing that most attentional and executive impairments at 3 months after surgery disappeared after 12 months.

Thus, these findings suggest that anterior cingulotomy causes relatively few serious somatic complications. The risk for mental adverse events or negative effects upon cognitive functions is highest in the initial postoperative period and then declines progressively over time.

2.3. Subcaudate tractotomy

Developed by Geoffrey Knight (London, UK) in 1964, this neurosurgical approach intended to limit undesirable effects by reducing the size of the lesion made under the head of the caudate nucleus in the substance inominata (Knight 1969, Mindus and Jenike 1992, Jenike 1998, Binder and Iskandar 2000, Feldman et al. 2001, Malhi and Sachdev 2002, Greenberg et al. 2003, Mashour et al. 2005). Anatomically, this subcortical region is reciprocally connected to the OFC and directly projects to the ventral caudate. The substance inominata is also located close to the ventral portion of the internal capsule. Therefore, lesions produced by subcaudate tractotomy interrupt the orbitofrontal-subcortical connections, and cause degeneration of fibers passing through the ventral part of the internal capsule and linking the ventral anterior and medial dorsal nuclei of the thalamus to the OFC and ACC (Meyerson 1998).

The operation is performed under general anesthesia. Bilateral burr holes 16 mm in diameter are made. Lesions are then created using the stereotactically guided placement radioactive ^{90}Yttrium rods, 1 mm wide and 7 mm long, into the posterior ventral white matter of the frontal lobe. The target area, which is visualized by means of a ventriculogram, is later recognized as containing small islands of cells named the substance inominata. The half-life of the beta emitter is 60 hours, after which time the rods become inert. They are arranged as an array in two or three rows covering a volume approximately 20 mm wide, 18 mm long and 5 mm thick (Knight 1969, Mindus and Jenike 1992, Jenike 1998, Binder and Iskandar 2000, Feldman et al. 2001).

2.3.1. Efficacy

There have been relatively few reports assessing the efficacy of subcaudate tractotomy in OCD. In the early study by Ström-Olsen and Carlisle (1971), 20 patients with very severe OCD underwent this surgical procedure. At a follow-up ranging from 16 months to 4 years, they were rated as follows: I. Completely recovered for seven (35.0%); II. Improved but with slight residual symptoms for three (15.0%); III. Improved but with persistent symptoms for three (15.0%); IV. Unchanged for six (30.0%); and V. Worse for the remaining one (5.0%). Among the seven cases who entirely recovered, two (28.6%) felt immediate postoperative relief from their symptoms, while the five others (71.4%) experienced delayed alleviation of their symptoms between 2 and 10 months after the operation. Bridges et al. (1973) reported that good outcome (ratings I and II) was observed in 16 (66.7%) of the 24 patients operated, while the remaining eight (33.3%) showed poor response (ratings III, IV and V) at the follow-up of at least 3 years. Two years later, Göktepe et al. (1975) reviewed the therapeutic effects of subcaudate tractotomy in 18 patients suffering from obsessional illness. At a follow-up of 2.5 years on average, nine (50.0%) had recovered or were very much improved (ratings I and II) while the nine others (50.0%) were partially improved, unchanged or worse (ratings III, IV and V). Bridges et al. (1994) added to previous work by including 15 additional OCD patients treated with this surgical procedure. Five (33.3%) were grouped into categories I and II, five (33.3%) into category III, and the remaining five (33.3%) into categories IV and V at 1 year postoperatively.

To conclude, all these studies suggest that subcaudate tractotomy is associated with relatively high success rates in reducing obsessive-compulsive symptoms substantially in around half the cases.

2.3.2. Complications, side-effects

In the first report on the efficacy and safety of subcaudate tractotomy, Ström-Olsen and Carlisle (1971) found no immediate postoperative mortality. Ten

(6.7%) of the 150 severely disabled psychiatric patients undergoing this surgical technique died between 2 and 10 months after the intervention, three from heart disease, two from cerebral thrombosis, four from pneumonia, and one successfully committed suicide. However, it cannot be excluded that the operation might have contributed to the cause of death in some of these ten patients. Nineteen others (12.7%) died from 1 to 6 years after surgery, nine (6.0%) from cardiovascular disorders, two (1.3%) from senility, two (1.3%) from malignant disease, and three (2.0%) from pneumonia. There were three additional deaths, one (0.7%) by suicide and two (1.3%) accidentally. Suicide might be attributed to the forms of depressive illnesses uncontrolled by subcaudate tractotomy. Göktepe et al. (1975) reported 25 cases of death (12.0%) among the 208 patients operated for intractable psychiatric disorders. There was one death (0.5%) from the operation itself by major seed displacement. Three deaths (1.4%) were by suicide. The other causes of death (bronchopneumonia, cardiac failure, carcinoma...) were unrelated to the operation and occurred after more than 6 months. Bridges et al. (1994) estimated the suicide rate at 1.0% of the 303 psychiatric patients treated with this surgical technique over the follow-up period from 3 to 13 years. Postoperative seizures were reported in 1.6 to 2.2% of cases. However, some of these patients had a history of a fit or more before operation, and only those who postoperatively suffered from more than one fit received anticonvulsivant therapy (Ström-Olsen and Carlisle 1971, Bridges et al. 1973, Göktepe et al. 1975, Bridges et al. 1994). Ström-Olsen and Carlisle (1971) found tiredness and lethargy lasting up to three months after surgery. Confusion was observed in approximately 10.0% of patients of 50 years or over during less than one month (Bridges et al. 1994). There was also an increased body weight in 13 (8.7%) of the 150 operated patients (+9.5-12.7 kg) at the end of the follow-up period of 4 years or less. Other complaints were persistent headaches in one patient (0.7%) and loss of smell in one other (0.7%). There was no reported case of urinary incontinence (Ström-Olsen and Carlisle, 1971).

Psychological and behavioral changes were noted in 21 (14.0%) of the 150 psychiatric patients who underwent subcaudate tractotomy. The commonest symptoms were irritability, outspokenness and volubility, which markedly interfered with social and family relationships in four (2.7%) of the 21 patients (Ström-Olsen and Carlisle 1971). Bridges et al. (1973) also described three (6.3%) cases of irritability, volubility and social disinhibition among the 48 patients treated with this surgical procedure. In the first prospective study of the effects of subcaudate tractotomy on neuropsychological functions, Kartsounis et al. (1991) used tests of general intelligence, memory, language, visuospatial analysis, speed and attention as well as focal cognitive tests, which are reflective of frontal lobe dysfunction. This complete battery of tests was administered 1 week before, and then 2 weeks and 6 months after surgery. An apparently transient impairment on memory and recognition tasks and tests of frontal lobe dysfunction was observed. This is presumably due to the reversible postoperative edema within the brain regions targeted in the operation.

Therefore, subcaudate tractotomy causes relatively rare major complications and adverse personality traits. Although there is a temporary deterioration in frontal lobe functions postoperatively, this surgical procedure produces no significant long-term deleterious cognitive effect.

2.4. Limbic leucotomy

Proposed by Desmond Kelly et al. (London, UK) in 1973, limbic leucotomy is essentially a multi-target technique based on making stereotactic lesions in the anterior cingulotomy, in combination with those of the original subcaudate tractotomy (Kelly et al. 1973, Mindus and Jenike 1992, Jenike 1998, Binder and Iskandar 2000, Feldman et al. 2001, Malhi and Sachdev 2002, Greenberg et al. 2003, Mashour et al. 2005).

After hair shaving, and under local or general anesthesia, bilateral burr holes are made. As in the above mentioned procedures for cingulotomy and subcaudate tractotomy, limbic leucotomy makes use of a ventriculogram for target localization. Intra-operative stimulation of autonomic responses may be necessary as an aid to target placement, at least in the substance inominata site, although its usefulness has been questioned. The lesions in the ACC are created by means of radiofrequency-heated electrodes (Kelly et al. 1973, Mindus and Jenike 1992, Jenike 1998, Binder and Iskandar 2000, Feldman et al. 2001).

2.4.1. Efficacy

One of the earliest reports was by Kelly and Mitchell-Heggs (1973) where 16 patients with OCD who underwent this operation were rated as symptom-free (category I) in one (6.2%), much improved (category II) in six (37.5%), improved (category III) in seven (43.8%), while the remaining two (12.5%) were unchanged (category VI) at 6 weeks of follow-up. Mitchell-Heggs et al. (1976) confirmed the favorable effects of limbic leucotomy in intractable OCD over a protracted period of 16-month follow-up. Among the 27 OCD patients treated with this surgical procedure, 24 (89.0%) were reported to have clinically improved (categories I, II and III) at 16 months, 18 (67.0%) of them being rated as symptom-free (category I) or much improved (category II). However, Montoya et al. (2002) found that only five (42.0%) of the 12 patients undergoing limbic leucotomy for refractory OCD, were classified as responders, as defined by a CGI score of 1 (very much improved) or 2 (much improved) after a mean follow-up period of 26 months. Moreover, when Y-BOCS was used to measure the overall severity of obsessive-compulsive symptoms in 11 of these patients, four (36.4%) met standard criteria for clinical response, as indicated by a 35% decrease in the total Y-BOCS score.

Thus, the first reports of patients suffering from OCD who had undergone limbic leucotomy demonstrate clinical improvement in up to 90%. However, response rates fall by nearly one half in more recent studies based on the now available comprehensive assessment of OCD.

2.4.2. Complications, side-effects

Although there was no death attributable to this surgical procedure in the initial experience of Kelly and colleagues with approximately 66 psychiatric cases (Kelly and Mitchell-Heggs 1973, Mitchell-Heggs et al. 1976), Montoya et al. (2002) reported two (9.5%) deaths by suicide (one patient with major depression and one with OCD) at the end of the 26-month follow-up. However, relationships between limbic leucotomy and increased risk for suicide remain to be established. First, both patients experienced suicidal ruminations and made serious suicide attempts before surgery. Second, there was no information about the period of time elapsing from the operation to suicide. Third, poor response to surgery could have precipitated suicide in these predisposed patients. One (4.8%) of the 21 patients surgically treated for intractable OCD had a postoperative infectious episode at the burr hole site, which was well controlled by local debridement and antibiotic therapy (Montoya et al. 2002).

Somatic complications were relatively infrequent and transient. A short period of confusion, headache and extreme laziness lasting for one to several days was described as common (Kelly and Mitchell-Heggs 1973, Mitchell-Heggs et al. 1976, Montoya et al. 2002). Mild lethargy was persistent in eight (12.1%) of 66 operated patients at 16 months of follow-up (Mitchell-Heggs et al. 1976). Urinary and sometimes fecal incontinence was also seen in the majority of patients for a few days after surgery. Such sphincter disturbances were completely resolved beyond the initial postoperative phase (Kelly and Mitchell-Heggs 1973, Mitchell-Heggs et al. 1976), except for three (14.3%) of the 21 patients treated with this surgical technique at the 26-month follow-up (Montoya et al. 2002). None of the patients developed epilepsy postoperatively in the early studies by Kelly and associates (Kelly and Mitchell-Heggs 1973, Mitchell-Heggs et al. 1976). However, Montoya et al. (2002) reported that four patients (19.0%) exhibited postoperative seizures requiring anticonvulsant treatment in one case (4.8%). None of these four subjects had any previous history of epilepsy. No change in body weight was observed over the year of follow-up (Kelly and Mitchell-Heggs 1973, Mitchell-Heggs et al. 1976).

No major adverse effect on cognitive functions and personality characteristics was reported (Kelly and Mitchell-Heggs 1973, Mitchell-Heggs et al. 1976), apart from five patients (24.0%) who experienced memory impairment (Montoya et al. 2002). An increase in performance on tests of intellectual function was even described at 6 weeks, which remained stable after 16 months of follow-up (Kelly and Mitchell-Heggs 1973, Mitchell-Heggs et al. 1976). Reduction in initiative and emotional drive was not a problem after the first few postoperative weeks. There was no case of aggression and irritability or emergence of impulsive behavior. The Leyton Obsessional Inventory, which provides a useful measure of obsessional symptoms and traits, showed significant improvement at 6 weeks (Kelly and Mitchell-Heggs 1973, Mitchell-Heggs et al. 1976).

Therefore, these conclusions based on observations made on groups of psychiatric patients suggest that limbic leucotomy is characterized by low occurrence rates of deleterious somatic complications and long-term negative consequences on cognition, personality and behavior.

2.5. Deep brain stimulation: the future of psychosurgery?

Over the last four decades, the development of modern lesional procedures, leading to an interruption of reciprocal connections between the frontal lobes and subcortical structures, has been considerably helpful for the management of medically refractory cases of OCD. These techniques have been demonstrated to be of substantial benefit for 40 to 60%, with relatively few serious undesirable effects. However, DBS is becoming of special interest because this surgical procedure is reversible, adjustable, and offers new opportunities in terms of targeting brain regions that the ablative techniques cannot reach.

DBS uses electrodes with four platinium/iridium contacts on each lead, which is stereotactically and bilaterally implanted into specific brain targets. Entry- and target-points and trajectory are determined using stereotactic MR- and CT-imaging. The electrode positioning is verified by peroperative X-ray. DBS consists of the delivery of a high-frequency current through the quadripolar electrodes connected to a battery powered pulse-generating device, which is typically placed in the chest. Chronic stimulation is programmable and adjusted by varying electrode and/or contact selection, frequency, amplitude and pulse width, within safety limits (Cuny et al. 2002, Malhi and Sachdev 2002, Greenberg and Rezai 2003). Although its mechanism of action is still far from clear, DBS is thought to block neural activity within the stimulated target area, thereby reproducing the effects of tissue lesioning (Malhi and Sachdev 2002, Greenberg and Rezai 2003, Mashour et al. 2005).

To date, chronic bilateral high-frequency stimulation constitutes a major therapeutic advance for devastating forms of Parkinson's disease, with on–off fluctuations and levodopa-induced dyskinesias, and potentially for other movement disorders as well (Cuny et al. 2002, Mahli and Sachdev 2002, Krack et al. 2003, Fraix et al. 2006, Guehl et al. 2006). This surgical approach has recently been proposed as a potential therapeutic alternative in resistant OCD. In a short-term, double-blind, on-off design, the efficacy and safety of DBS in the anterior limb of the internal capsule as a substitute for anterior capsulotomy were examined in four patients suffering from extremely severe and refractory OCD. Three (75.0%) of them felt instantaneous relief after DBS was started. The high amplitude of currents used in one patient caused headache for 10 seconds. However, there was no change in sustained attention measured by standardized neuropsychological tests (Nuttin et al. 1999). Open, long-term outcome studies have confirmed the favorable effects of chronic anterior capsular stimulation. Two of the three patients who initially reported alleviation of obsessive-compulsive symptoms had maintained their clinical improvement, as defined by a 35% or more reduction in Y-BOCS scores, during the 33-month period of follow-up. At 1-year DBS, there was no deleterious effect or harmful consequence on neuropsychological functioning and personality traits (Gabriels et al. 2003). Anderson and Ahmed (2003) also found that chronic bilateral anterior capsular stimulation produced a gradual decline in OC symptom severity until recovery (Y-BOCS scores < 8), which was obtained within the first 3 months of DBS. At the end of the 10-month follow-up period, the patient was even able to return to work (Anderson and Ahmed 2003). However, Abelson et al. (2005) failed to completely replicate these findings. Only one (25.0%) of the four patients who underwent DBS for intractable OCD experienced a significant reduction of at least 50% in Y-BOCS score under both blinded, on-off and long-term, open conditions. A second subject (25.0%) showed a positive response (> 35% decline in Y-BOCS) during the open phase of study. There was no evidence of cognitive impairment on neuropsychological tests and no report of any change in personality characteristics. Recently, Greenberg et al. (2006) found much better results, as attested by a 35% or greater reduction in Y-BOCS score in four (50.0%) of eight OCD patients after 36 months of DBS. Concomitantly, there was a substantial increase in Global Assessment of Functioning (GAF) score from 36.6 (± 1.5) at baseline to 53.8 (± 0.6) at the end of the follow-up period. Surgical adverse effects were limited to a single case of asymptomatic hemorrhage, generalized tonic-clonic seizure, or superficial infection. Approximately one half of the patients experienced psychological side-effects, including transient hypomanic symptoms, increased anxiety and flushing, and clinical worsening after discontinuation of DBS by stimulator battery depletion. However, there was no significant decline in cognitive functioning when assessed at 10 months after surgery.

Other brain regions have been proposed as targets for DBS. Mallet et al. (2002) reported that DBS of the subthalamic nucleus resulted in a profound reduction in Y-BOCS scores by more than 60% in two Parkinsonian patients with comorbid OCD at the immediate postoperative phase and 2 weeks later. The nucleus accumbens, which represents the most ventral and medial part of the caudate nucleus, has also been targeted. There was a clinical improvement in three of the four patients with OCD and other anxiety disorders, which was achieved a few days to several weeks after the beginning of DBS. No side effect was reported during the 24- to 30-month period of follow-up (Sturm et al. 2003). Our group also found favorable effects of DBS of the ventral caudate nucleus, including the nucleus accumbens and the ventromedial portion of the head of the caudate nucleus in one patient suffering from resistant OCD with comorbid major depression (Aouizerate et al. 2004a). DBS progressively improved depressive and anxiety symptoms until remission was achieved at 6 months (HDRS ≤ 7 and HARS ≤ 10) (2). There was also a marked but delayed reduction in OCD symptom severity on Y-BOCS from baseline 25 to 10 and 14 at 12- and 15-month DBS, respectively. The level of functioning on GAF gradually increased from 35 to 60 over the first 15 months of the postoperative period (Aouizerate et al. 2004a). Failure of the pulse generator battery, which was discovered following a clinical impairment, did not affect depressive and anxiety symptom intensity but worsened OC manifestations (Y-BOCS = 21) with a slight deterioration of global functioning (GAF = 55) at 18 months. A return to remission levels for OCD (Y-BOCS < 16) was observed 3 months after generator replacement and remained stable until the end of the 27-month follow-up (final Y-BOCS = 12). This was paralleled by an improvement in psychosocial functioning (final GAF = 65). Interestingly, no neuropsychological alteration or any adverse clinical effect was reported (Aouizerate et al. 2005a).

In conclusion, dysfunctional frontal-subcortical loops originating in both OFC and ACC have extensively been shown to play a major role in the pathogenesis of OCD. Numerous neuroimaging studies have consistently demonstrated abnormalities in functional activity in the OFC, ACC, ventral striatum and thalamus, which are involved in the cognitive and emotional processes that can be thought as disrupted in OCD in the light of phenomenological considerations. Abundant data collected from psychosurgery have supported the importance of these prefrontal and subcortical regions in the production of OC symptoms. The most widely used approaches (anterior capsulotomy, anterior cingulotomy, subcaudate tractotomy and limbic leucotomy) aiming at producing lesions on the frontothalamic pathways and the limbic system have been shown to be effective in 40 to 60 % of cases, and to be relatively safe. However, chronic DBS of major importance in the treatment of invalidating Parkinson's diseases and other movement disorders has recently been proposed as a reversible and adjustable surgical procedure for the management of refractory OCD. Several brain regions have been chosen as targets, including the anterior limb of the internal capsule, the subthalamic nucleus or the ventral caudate nucleus. Although DBS seems to be the first-line surgical technique since it is the least invasive, there are still unknown factors. On one hand, the most critical issue is to determine the optimal targets both in terms of their possible efficacy and their risks and benefits. On the other hand, the promising anti-obsessional effects and safety of DBS remain to be confirmed by further randomized controlled trials employing standard clinical outcome assessment and current criteria of treatment resistance for the selection of severely ill patients with OCD in larger samples.

References

Abelson JL, Curtis GC, Sagher O, Albucher RC, Harrigan M, Taylor SF, Martis B, Giordani B (2005). Deep brain stimulation for refractory obsessive-compulsive disorder. *Biological Psychiatry* 57, 5, 510-516.

Akkal D, Bioulac B, Audin J, Burbaud P (2002). Comparison of neuronal activity in the rostral supplementary and cingulate motor areas during a task with cognitive and motor demands. *European Journal of Neuroscience* 15, 5, 887-904.

Anderson D, Ahmed A (2003). Treatment of patients with intractable obsessive-compulsive disorder with anterior capsular stimulation. Case report. *Journal of Neurosurgery* 98, 5, 1104-1108.

Aosaki T, Tsubokawa H, Ishida A, Watanabe K, Graybiel AM, Kimura M (1994). Responses of tonically active neurons in the primate's striatum undergo systematic changes during behavioral sensorimotor conditioning. *Journal of*

Neuroscience 14, 6, 3969-3684.

Aouizerate B, Cuny E, Martin-Guehl C, Guehl D, Amieva H, Benazzouz A, Fabrigoule C, Allard M, Rougier A, Bioulac B, Tignol J, Burbaud P (2004a). Deep brain stimulation of the ventral caudate nucleus in the treatment of obsessive-compulsive disorder and major depression. Case report. *Journal of Neurosurgery* 101, 4, 682-686.

Aouizerate B, Guehl D, Cuny E, Rougier A, Bioulac B, Tignol J, Burbaud P (2004b). Pathophysiology of obsessive-compulsive disorder: a necessary link between phenomenology, neuropsychology, imagery and physiology. *Progress in Neurobiology* 72, 3, 195-221.

Aouizerate B, Martin-Guehl C, Cuny E, Guehl D, Amieva H, Benazzouz A, Fabrigoule C, Bioulac B, Tignol J, Burbaud P (2005a). Deep brain stimulation for OCD and major depression. *American Journal of Psychiatry* 162, 11, 2192.

Aouizerate B, Guehl D, Cuny E, Rougier A, Burbaud P, Tignol J, Bioulac B (2005b). Updated overview of the putative role of serotoninergic system in obsessive-compulsive disorder. *Neuropsychiatric Disease and Treatment* 1, 3, 231-243.

Apicella P (2002). Tonically active neurons in the primate striatum and their role in the processing of information about motivationally relevant events. *European Journal of Neuroscience* 16, 11, 2017-2026.

Baer L (1994). Factor analysis of symptom subtypes of obsessive compulsive disorder and their relation to personality and tic disorders. *Journal of Clinical Psychiatry* Suppl 55, 18-23.

Ballantine HT, Jr., Bouckoms AJ, Thomas EK, Giriunas IE (1987). Treatment of psychiatric illness by stereotactic cingulotomy. *Biological Psychiatry* 22, 7, 807-819.

Bar-Gad I, Bergman H (2001). Stepping out of the box: information processing in the neural networks of the basal ganglia. *Current Opinion in Neurobiology* 11, 6, 689-695.

Baxter LR (1999). Functional imaging of brain systems mediating obsessive-compulsive disorder: Clinical studies. In Charney DS, Nestler EJ, Bunney BS (Eds) *Neurobiology of mental illness*, pp. 534-547. Oxford University Press, New York.

Bentivoglio M, Kultas-Ilinsly K, Ilinsly I (1993). Limbic thalamus: Structure, intrinsic organization, and connections. In Vogt BA, Gabriel M (Eds) *Neurobiology of cingulate cortex and limbic thalamus: A comprehensive handbook*, pp. 71-122. Birkhäuser, Boston.

Binder DK, Iskandar BJ (2000). Modern neurosurgery for psychiatric disorders. *Neurosurgery* 47, 1, 9-21.

Bingley T, Leksell L, Meyerson BA, Rylander G (1977). Long-term results of stereotactic anterior capsulotomy in chronic obsessive-compulsive neurosis. In Sweet WH, Obrador S, Martin-Rodriguez JG (Eds) *Neurosurgical treatment in Psychiatry*, *Pain and Epilepsy,* pp. 287-299. University Park Press, Baltimore.

Botvinick M, Nystrom LE, Fissell K, Carter CS, Cohen JD (1999). Conflict monitoring versus selection-for-action in anterior cingulate cortex. *Nature* 402, 6758, 179-181.

Botvinick MM, Cohen JD, Carter CS (2004). Conflict monitoring and anterior cingulate cortex: an update. *Trends in Cognitive Sciences* 8, 12, 539-546.

Bridges PK, Goktepe EO, Maratos J (1973). A comparative review of patients with obsessional neurosis and with depression treated by psychosurgery. *British Journal of Psychiatry* 123, 577, 663-674.

Bridges PK, Bartlett JR, Hale AS, Poynton AM, Malizia AL, Hodgkiss AD (1994). Psychosurgery: stereotactic subcaudate tractomy. An indispensable treatment. *British Journal of Psychiatry* 165, 5, 599-611.

Bush G, Luu P, Posner MI (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Sciences* 4, 6, 215-222.

Bush G, Vogt BA, Holmes J, Dale AM, Greve D, Jenike MA, Rosen BR (2002). Dorsal anterior cingulate cortex: a role in reward-based decision making. *Proceedings of the National Academy of Sciences of the United States of America* 99, 1, 523-528.

Cohen RA, Kaplan RF, Moser DJ, Jenkins MA, Wilkinson H (1999). Impairments of attention after cingulotomy. *Neurology* 53, 4, 819-824.

Cummings JL (1993). Frontal-subcortical circuits and human behavior. *Archives of Neurology* 50, 8, 873-880.

Cuny E, Guehl D, Burbaud P, Gross C, Dousset V, Rougier A (2002). Lack of agreement between direct magnetic resonance imaging and statistical determination of a subthalamic target: the role of electrophysiological guidance. *Journal of Neurosurgery* 97, 3, 591-597.

Davidson RJ, Irwin W (1999). The functional neuroanatomy of emotion and affective style. *Trends in Cognitive Sciences* 3, 1, 11-21.

Devinsky O, Morrell MJ, Vogt BA (1995). Contributions of anterior cingulate cortex to behaviour. *Brain* 118, Pt 1, 279-306.

Dougherty DD, Baer L, Cosgrove GR, Cassem EH, Price BH, Nierenberg AA, Jenike MA, Rauch SL (2002). Prospective long-term follow-up of 44 patients who received cingulotomy for treatment-refractory obsessive-compulsive disorder. *American Journal of Psychiatry* 159, 2, 269-275.

Eblen F, Graybiel AM (1995). Highly restricted origin of prefrontal cortical inputs to striosomes in the macaque monkey. *Journal of Neuroscience* 15, 9, 5999-6013.

Feldman RP, Alterman RL, Goodrich JT (2001). Contemporary psychosurgery and a look to the future. *Journal of Neurosurgery* 95, 6, 944-956.

Fernandez-Cordoba E, Lopez-Ibor AJ (1967). La monoclorimipramina en enfermos psiquiatricos resistentes a otros tratamientos. *Acta Luso-Esp Neurol Psiquiatr Ciene Afines* 26, 119-147.

Fiorillo CD, Tobler PN, Schultz W (2003). Discrete coding of reward probability and uncertainty by dopamine neurons. *Science* 299, 5614, 1898-1902.

Fitzgerald KD, Welsh RC, Gehring WJ, Abelson JL, Himle JA, Liberzon I, Taylor SF (2005). Error-related hyperactivity of the anterior cingulate cortex in obsessive-compulsive disorder. *Biological Psychiatry* 57, 3, 287-294.

Foa EB, Franklin ME, Kozac MJ (1998). Psychosocial treatments for obsessive-compulsive disorder. Literature review. In Swinson RP, Antony MM, Rachman S, Richter MA (Eds) *Obsessive-compulsive disorder. Theory, research, and treatment*, pp. 258-276. The Guilford Press, New-York.

Foa EB, Franklin ME, Moser J (2002). Context in the clinic: how well do cognitive-behavioral therapies and medications work in combination? *Biological Psychiatry* 52, 10, 987-997.

Fodstad H, Strandman E, Karlsson B, West KA (1982). Treatment of chronic obsessive-compulsive states with stereotactic anterior capsulotomy or cingulotomy. *Acta Neurochirurgica* 62, 1-23.

Fraix V, Houeto JL, Lagrange C, Le Pen C, Krystkowiak P, Guehl D, Ardouin C, Welter ML, Maurel F, Defebvre L, Rougier A, Benabid AL, Mesnage V, Ligier M, Blond S, Burbaud P, Bioulac B, Destee A, Cornu P, Pollak P (2006). Clinical and economic results of bilateral subthalamic nucleus stimulation in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry* 77, 4, 443-449.

Gabriels L, Cosyns P, Nuttin B, Demeulemeester H, Gybels J (2003). Deep brain stimulation for treatment-refractory obsessive-compulsive disorder: psychopathological and neuropsychological outcome in three cases. *Acta Psychiatrica Scandinavica* 107, 4, 275-282.

Gerfen CR (1984). The neostriatal mosaic: compartmentalization of corticostriatal input and striatonigral output systems. *Nature* 311, 5985, 461-464.

Göktepe EO, Young LB, Bridges PK (1975). A further review of the results of sterotactic subcaudate tractotomy. *British Journal of Psychiatry* 126, 270-280.

Graybiel AM, Aosaki T, Flaherty AW, Kimura M (1994). The

basal ganglia and adaptive motor control. *Science* 265, 5180, 1826-1831.
Greenberg BD, Price LH, Rauch SL, Friehs G, Noren G, Malone D, Carpenter LL, Rezai AR, Rasmussen SA (2003). Neurosurgery for intractable obsessive-compulsive disorder and depression: critical issues. *Neurosurgery Clinics of North America* 14, 2, 199-212.
Greenberg BD, Rezai AR (2003). Mechanisms and the current state of deep brain stimulation in neuropsychiatry. *CNS Spectrums* 8, 7, 522-526.
Greenberg BD, Malone DA, Friehs GM, Rezai AR, Kubu CS, Malloy PF, Salloway SP, Okun MS, Goodman WK, Rasmussen SA (2006). Three-Year Outcomes in Deep Brain Stimulation for Highly Resistant Obsessive-Compulsive Disorder. *Neuropsychopharmacology* 31, 11, 2384-2393.
Guehl D, Dehail P, de Seze MP, Cuny E, Faux P, Tison F, Barat M, Bioulac B, Burbaud P (2006). Evolution of postural stability after subthalamic nucleus stimulation in Parkinson's disease: a combined clinical and posturometric study. *Experimental Brain Research* 170, 2, 206-215.
Hassani OK, Cromwell HC, Schultz W (2001). Influence of expectation of different rewards on behavior-related neuronal activity in the striatum. *Journal of Neurophysiology* 85, 6, 2477-2489.
Herner T (1961). Treatment of mental disorders with frontal stereotactic thermo-lesions. A follow-up study of 116 cases. *Acta Psychiatrica Scandinavica* Suppl 158, 36, 1-140.
Hollerman JR, Tremblay L, Schultz W (1998). Influence of reward expectation on behavior-related neuronal activity in primate striatum. *Journal of Neurophysiology* 80, 2, 947-963.
Insel TR, Murphy DL, Cohen RM, Alterman I, Kilts C, Linnoila M (1983). Obsessive-compulsive disorder. A double-blind trial of clomipramine and clorgyline. *Archives of General Psychiatry* 40, 6, 605-612.
Jenike MA, Baer L, Ballantine T, Martuza RL, Tynes S, Giriunas I, Buttolph ML, Cassem NH (1991). Cingulotomy for refractory obsessive-compulsive disorder. A long-term follow-up of 33 patients. *Archives of General Psychiatry* 48, 6, 548-555.
Jenike MA (1998). Neurosurgical treatment of obsessive-compulsive disorder. *British Journal of Psychiatry* Suppl 35, 79-90.
Jog MS, Kubota Y, Connolly CI, Hillegaart V, Graybiel AM (1999). Building neural representations of habits. *Science* 286, 5445, 1745-1749.
Kartsounis LD, Poynton A, Bridges PK, Bartlett JR (1991). Neuropsychological correlates of stereotactic subcaudate tractotomy. A prospective study. *Brain* 114, Pt 6, 2657-2673.
Kelly D, Mitchell-Heggs N (1973). Stereotactic limbic leucotomy—a follow-up study of thirty patients. *Postgraduate Medical Journal* 49, 578, 865-882.
Kelly D, Richardson A, Mitchell-Heggs N (1973). Stereotactic limbic leucotomy: neurophysiological aspects and operative technique. *British Journal of Psychiatry* 123, 573, 133-140.
Kerns JG, Cohen JD, MacDonald AW, 3rd, Cho RY, Stenger VA, Carter CS (2004). Anterior cingulate conflict monitoring and adjustments in control. *Science* 303, 5660, 1023-1026.
Knight GC (1969). Bi-frontal stereotactic tractotomy: an atraumatic operation of value in the treatment of intractable psychoneurosis. *British Journal of Psychiatry* 115, 520, 257-266.
Koran LM, Thienemann ML, Davenport R (1996). Quality of life for patients with obsessive-compulsive disorder. *American Journal of Psychiatry* 153, 6, 783-788.
Krack P, Batir A, Van Blercom N, Chabardes S, Fraix V, Ardouin C, Koudsie A, Limousin PD, Benazzouz A, LeBas JF, Benabid AL, Pollak P (2003). Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *New England Journal of Medicine* 349, 20, 1925-1934.
Krawczyk DC (2002). Contributions of the prefrontal cortex to the neural basis of human decision making. *Neuroscience and Biobehavioral Reviews* 26, 6, 631-664.
Kullberg G (1977). Differences in effects of capsulotomy and cingulotomy. In Sweet WH, Obrador S, Martin-Rodriguez JG (Eds) *Neurosurgical treatment in Psychiatry, Pain and Epilepsy*, pp. 301-308. University Park Press, Baltimore.
Leckman JF, Grice DE, Boardman J, Zhang H, Vitale A, Bondi C, Alsobrook J, Peterson BS, Cohen DJ, Rasmussen SA, Goodman WK, McDougle CJ, Pauls DL (1997). Symptoms of obsessive-compulsive disorder. *American Journal of Psychiatry* 154, 7, 911-917.
Lippitz BE, Mindus P, Meyerson BA, Kihlstrom L, Lindquist C (1999). Lesion topography and outcome after thermocapsulotomy or gamma knife capsulotomy for obsessive-compulsive disorder: relevance of the right hemisphere. *Neurosurgery* 44, 3, 452-458.
Malhi GS, Sachdev P (2002). Novel physical treatments for the management of neuropsychiatric disorders. *Journal of Psychosomatic Research* 53, 2, 709-719.
Mallet L, Mesnage V, Houeto JL, Pelissolo A, Yelnik J, Behar C, Gargiulo M, Welter ML, Bonnet AM, Pillon B, Cornu P, Dormont D, Pidoux B, Allilaire JF, Agid Y (2002). Compulsions, Parkinson's disease, and stimulation. *Lancet* 360, 9342, 1302-1304.
Maltby N, Tolin DF, Worhunsky P, O'Keefe TM, Kiehl KA (2005). Dysfunctional action monitoring hyperactivates frontal-striatal circuits in obsessive-compulsive disorder: an event-related fMRI study. *Neuroimage* 24, 2, 495-503.
Mashour GA, Walker EE, Martuza RL (2005). Psychosurgery: past, present, and future. *Brain Research. Brain Research Reviews* 48, 3, 409-419.
Mataix-Cols D, Rauch SL, Manzo PA, Jenike MA, Baer L (1999). Use of factor-analyzed symptom dimensions to predict outcome with serotonin reuptake inhibitors and placebo in the treatment of obsessive-compulsive disorder. *American Journal of Psychiatry* 156, 9, 1409-1416.
Mataix-Cols D, Rauch SL, Baer L, Eisen JL, Shera DM, Goodman WK, Rasmussen SA, Jenike MA (2002). Symptom stability in adult obsessive-compulsive disorder: data from a naturalistic two-year follow-up study. *American Journal of Psychiatry* 159, 2, 263-268.
Mataix-Cols D, Cullen S, Lange K, Zelaya F, Andrew C, Amaro E, Brammer MJ, Williams SC, Speckens A, Phillips ML (2003). Neural correlates of anxiety associated with obsessive-compulsive symptom dimensions in normal volunteers. *Biological Psychiatry* 53, 6, 482-493.
Mataix-Cols D, Wooderson S, Lawrence N, Brammer MJ, Speckens A, Phillips ML (2004). Distinct neural correlates of washing, checking, and hoarding symptom dimensions in obsessive-compulsive disorder. *Archives of General Psychiatry* 61, 6, 564-576.
Matsumoto K, Suzuki W, Tanaka K (2003). Neuronal correlates of goal-based motor selection in the prefrontal cortex. *Science* 301, 5630, 229-232.
Matsumoto K, Tanaka K (2004). Neuroscience. Conflict and cognitive control. *Science* 303, 5660, 969-970.
Mavissakalian M, Turner SM, Michelson L, Jacob R (1985). Tricyclic antidepressants in obsessive-compulsive disorder: anti-obsessional or antidepressant agents? II. *American Journal of Psychiatry* 142, 5, 572-576.
Meyerson BA (1998). Neurosurgical treatment of mental disorders. Introduction and indications. In Gildenberg PL, Tasker RR (Eds) *Textbook of stereotactic and functional neurosurgery*, pp. 1955–1964. McGraw-Hill, New York.
Mindus P, Jenike MA (1992). Neurosurgical treatment of malignant obsessive compulsive disorder. *Psychiatric Clinics of North America* 15, 4, 921-938.
Mindus P, Rasmussen SA, Lindquist C (1994). Neurosurgical treatment for refractory obsessive-compulsive disorder: implications for understanding frontal lobe function.

Journal of Neuropsychiatry and Clinical Neurosciences 6, 4, 467-477.

Mindus P, Edman G, Andreewitch S (1999). A prospective, long-term study of personality traits in patients with intractable obsessional illness treated by capsulotomy. *Acta Psychiatrica Scandinavica* 99, 1, 40-50.

Mitchell-Heggs N, Kelly D, Richardson A (1976). Stereotactic limbic leucotomy a follow-up at 16 months. *British Journal of Psychiatry* 128, 226-240.

Montoya A, Weiss AP, Price BH, Cassem EH, Dougherty DD, Nierenberg AA, Rauch SL, Cosgrove GR (2002). Magnetic resonance imaging-guided stereotactic limbic leukotomy for treatment of intractable psychiatric disease. *Neurosurgery* 50, 5, 1043-1049.

Niki H, Watanabe M (1979). Prefrontal and cingulate unit activity during timing behavior in the monkey. *Brain Research* 171, 2, 213-224.

Nuttin B, Cosyns P, Demeulemeester H, Gybels J, Meyerson B (1999). Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. *Lancet* 354, 9189, 1526.

Nyman H, Mindus P (1995). Neuropsychological correlates of intractable anxiety disorder before and after capsulotomy. *Acta Psychiatrica Scandinavica* 91, 1, 23-31.

O'Doherty J, Dayan P, Schultz J, Deichmann R, Friston K, Dolan RJ (2004). Dissociable roles of ventral and dorsal striatum in instrumental conditioning. *Science* 304, 5669, 452-454.

Phillips ML, Drevets WC, Rauch SL, Lane R (2003). Neurobiology of emotion perception I: The neural basis of normal emotion perception. *Biological Psychiatry* 54, 5, 504-514.

Ramnani N, Owen AM (2004). Anterior prefrontal cortex: insights into function from anatomy and neuroimaging. *Nature Reviews. Neuroscience* 5, 3, 184-194.

Rasmussen SA, Tsuang MT (1986). Clinical characteristics and family history in DSM-III obsessive-compulsive disorder. *American Journal of Psychiatry* 143, 3, 317-322.

Rasmussen SA, Eisen JL (1990). Epidemiology of obsessive compulsive disorder *Journal of Clinical Psychiatry* Suppl 51, 10-13.

Rasmussen SA, Eisen JL (1992). The epidemiology and differential diagnosis of obsessive compulsive disorder. *Journal of Clinical Psychiatry* Suppl 53, 4-10.

Roesch MR, Olson CR (2004). Neuronal activity related to reward value and motivation in primate frontal cortex. *Science* 304, 5668, 307-310.

Rosenkilde CE, Bauer RH, Fuster JM (1981). Single cell activity in ventral prefrontal cortex of behaving monkeys. *Brain Research* 209, 2, 375-394.

Rück C, Andreewitch S, Flyckt K, Edman G, Nyman H, Meyerson BA, Lippitz BE, Hindmarsh T, Svanborg P, Mindus P, Asberg M (2003). Capsulotomy for refractory anxiety disorders: long-term follow-up of 26 patients. *American Journal of Psychiatry* 160, 3, 513-521.

Salkovskis PM (1985). Obsessional-compulsive problems: a cognitive-behavioural analysis. *Behaviour Research and Therapy* 23, 5, 571-583.

Salkovskis PM (1999). Understanding and treating obsessive-compulsive disorder. *Behaviour Research and Therapy* 37, Suppl 1, S29-52.

Saxena S, Brody AL, Schwartz JM, Baxter LR (1998). Neuroimaging and frontal-subcortical circuitry in obsessive-compulsive disorder. *British Journal of Psychiatry* Suppl 35, 26-37.

Saxena S, Brody AL, Maidment KM, Smith EC, Zohrabi N, Katz E, Baker SK, Baxter LR, Jr. (2004). Cerebral glucose metabolism in obsessive-compulsive hoarding. *American Journal of Psychiatry* 161, 6, 1038-1048.

Schultz W (2000). Multiple reward signals in the brain. *Nature Reviews. Neuroscience* 1, 3, 199-207.

Schwartz JM (1998). Neuroanatomical aspects of cognitive-behavioural therapy response in obsessive-compulsive disorder. An evolving perspective on brain and behaviour. *British Journal of Psychiatry* Suppl 35, 38-44.

Schwartz JM (1999). A role of volition and attention in the generation of new brain circuitry. Toward a neurobiology of mental force. *Journal of Consciousness Studies* 6, 115-142.

Shidara M, Richmond BJ (2002). Anterior cingulate: single neuronal signals related to degree of reward expectancy. *Science* 296, 5573, 1709-1711.

Shima K, Tanji J (1998). Role for cingulate motor area cells in voluntary movement selection based on reward. *Science* 282, 5392, 1335-1338.

Skoog G, Skoog I (1999). A 40-year follow-up of patients with obsessive-compulsive disorder *Archives of General Psychiatry* 56, 2, 121-127.

Ström-Olsen R, Carlisle S (1971). Bi-frontal stereotactic tractotomy. A follow-up study of its effects on 210 patients. *British Journal of Psychiatry* 118, 543, 141-154.

Sturm V, Lenartz D, Koulousakis A, Treuer H, Herholz K, Klein JC, Klosterkotter J (2003). The nucleus accumbens: a target for deep brain stimulation in obsessive-compulsive- and anxiety-disorders. *Journal of Chemical Neuroanatomy* 26, 4, 293-299.

Summerfeldt LJ, Richter MA, Antony MM, Swinson RP (1999). Symptom structure in obsessive-compulsive disorder: a confirmatory factor-analytic study. *Behaviour Research and Therapy* 37, 4, 297-311.

Thoren P, Asberg M, Cronholm B, Jornestedt L, Traskman L (1980). Clomipramine treatment of obsessive-compulsive disorder. I. A controlled clinical trial. *Archives of General Psychiatry* 37, 11, 1281-1285.

Thorpe SJ, Rolls ET, Maddison S (1983). The orbitofrontal cortex: neuronal activity in the behaving monkey. *Experimental Brain Research* 49, 1, 93-115.

Tobler PN, Fiorillo CD, Schultz W (2005). Adaptive coding of reward value by dopamine neurons. *Science* 307, 5715, 1642-1645.

Tolin DF, Abramowitz JS, Brigidi BD, Foa EB (2003). Intolerance of uncertainty in obsessive-compulsive disorder. *Journal of Anxiety Disorders* 17, 2, 233-242.

Tremblay L, Hollerman JR, Schultz W (1998). Modifications of reward expectation-related neuronal activity during learning in primate striatum. *Journal of Neurophysiology* 80, 2, 964-977.

Tremblay L, Schultz W (1999). Relative reward preference in primate orbitofrontal cortex. *Nature* 398, 6729, 704-708.

Whitty CW, Duffield JE, Tow PM, Cairns H (1952). Anterior cingulectomy in the treatment of mental disease. *Lancet* 1, 10, 475-481.