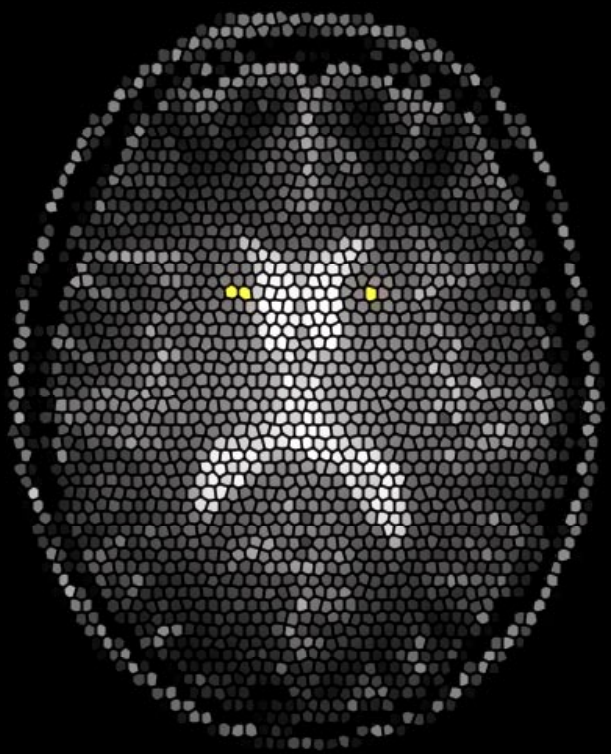
Thesis for doctoral degree (Ph.D.)
2006

Capsulotomy in anxiety disorders



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CAPSULOTOMY IN ANXIETY DISORDERS

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Stockholm 2006

Front cover: digitally manipulated axial MRI section of the brain in an OCD patient.

Published by Karolinska University Press
Box 200, SE-171 77 Stockholm, Sweden
Printed by Universitetsservice US-AB

ISBN 91-7140-769-3

ABSTRACT

Background

Anxiety disorders are common and a substantial proportion of patients do not respond to conventional treatments such as SSRIs or CBT. Capsulotomy is a neurosurgical treatment for treatment refractory patients with Obsessive-Compulsive Disorder (OCD) and other anxiety disorders. The aim of this thesis was to assess the long-term efficacy and safety of capsulotomy.

Methods and results

In Study I, 26 consecutive patients who underwent capsulotomy from 1975-1991 were followed after a mean of 13 years. Main diagnoses were Generalized Anxiety Disorder (n=13), Panic Disorder (n=8) and Social Phobia (n=5). Mean Brief Scale of Anxiety score dropped significantly from preoperative 22 to 10 at long-term. Seven patients had postoperative problems in the domains of executive functioning, apathy or disinhibition. Mean weight gain in the first postoperative year was almost 10 kg. Study II and III were substudies of Study I.

In Study II the capsulotomy lesion size and localization in the anterior-posterior plane was analyzed. We could not replicate previous findings of a common anatomical denominator in the right-sided capsule in patients responding to the treatment. In Study III, we used a self-rated personality inventory, the Karolinska Scales of Personality, to describe changes pre- to postoperatively in self-rated personality. Patients were significantly less anxiety prone at follow-up.

Study IV was a long-term follow-up of 25 consecutive OCD capsulotomies performed 1988 - 2000. Mean Y-BOCS was 34 preoperatively and dropped to 18 at long-term follow-up ($p<0.0001$). Only 2 patients achieved remission from OCD without substantial side effects. Several neurosurgical complications related to radiosurgery were reported.Two patients were severely disinhibited postoperatively. Ten patients were considered to suffer from significant problems in the area of executive functioning, apathy or disinhibition. Global functioning did not return to normal after surgery. Lesion size did not correlate significantly with efficacy or adverse effects.

Conclusions

Capsulotomy is effective in reducing symptoms in both OCD and other anxiety disorders. About every third patient experienced apathy, executive problems or disinhibition at long-term follow up, therefore we conclude that capsulotomy is not a safe procedure. We could not identify lesion characteristics that could explain the differences in outcome. We could not confirm the hypothesis of a certain right-sided lesion as a prerequisite for response to capsulotomy.

Keywords

obsessive-compulsive disorder, anxiety disorders, psychosurgery, internal capsule, prefrontal cortex, neuropsychology, personality inventory, bioethics, neurosurgery

LIST OF PUBLICATIONS

I. **Rück C**, Andréewitch S, Flyckt K, Edman, G, Nyman H, Meyerson BA, Lippitz BE, Hindmarsh T, Svanborg P, Mindus P, Åsberg M. Capsulotomy for refrac tory anxiety disorders: long-term follow-up of 26 patients. *Am J Psychiatry, 2003, 160, 513-21*

II. **Rück C**, Svanborg P, Meyerson BA. Lesion topography in capsulotomy for refractory anxiety--is the right side the right side? *Stereotact Funct Neurosurg, 2005, 83, 172-9*

III. **Rück C**, Edman G, Åsberg M, Svanborg P. Long-term Changes in Self-reported Personality following Capsulotomy in Anxiety patients. *In Press Nord J Psychiatry*

IV. **Rück C**, Karlsson A, Edman G, Ericson K, Nyman H., Meyerson B. A., Åsberg M., Svanborg P. Capsulotomy for OCD: long-term follow-up of 25 patients. *Manuscript*

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1 ABBREVIATIONS

Ac	Anterior commissure
ACC	Anterior cingulate cortex
CBT	Cognitive-behavioral therapy
CSTC	Cortico-striato-thalamo-cortical circuitry
CT	Computed Tomography
EAD	The Execution, Apathy and Disinhibition Scale
FrSBe	Frontal Systems Behavior Scale™
GAD	Generalized anxiety disorder
Gy	Gray
KSP	Karolinska Scales of Personality
MRI	Magnetic resonance imaging
NMD	Neurosurgery for mental disorders
OCD	Obsessive-compulsive disorder
OFC	Orbitofrontal cortex
PANDAS	Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections
Pc	Posterior commissure
RCT	Randomized controlled trial
SD	Standard deviation
SSRI	Selective serotonin reuptake inhibitor
WCST	Wisconsin Card Sorting Test
Y-BOCS	Yale-Brown Obsessive-Compulsive Scale

2 INTRODUCTION

2.1 WHY THIS?

It was in my fifth year in medical school that I first heard of capsulotomy. Like most people, I had a somewhat vague idea about neurosurgery for psychiatric illnesses being something evil that went on back in the days before I was born. I had also seen Milos Forman's classic film *One Flew Over the Cuckoo's Nest* and remembered that they did some nasty stuff to Jack Nicholson. After listening to the late Professor Per Mindus' lecture on OCD, I had the opportunity to sit in on a couple of his consultations. Mindus was the psychiatrist in charge of the neurosurgical treatments for psychiatric disorders. The patients with Obsessive-Compulsive Disorders immediately spellbound me. A few years later I had my first position as a junior doctor at the Psychiatric Clinic of the Karolinska Hospital and met Per Mindus again. I met one of his capsulotomy patients during my regular clinical work (who later turned out to be one of the patients in Study IV of this thesis) and contacted Prof. Mindus which was to be the start of our collaboration. I soon became aware of the controversy surrounding the treatment. In the last year of his life, this debate was also given attention in the public media. As a consequence of this, we received funding from the National Board of Health and Welfare in order to evaluate capsulotomy as a treatment for anxiety disorders.

Neurosurgery for mental disorders has always been controversial (1, 2). Capsulotomy is a neurosurgical procedure for intractable OCD and anxiety and has its historical roots in lobotomy, a treatment that for many is a symbol for medical barbarism. Capsulotomy has been used at the Karolinska Hospital since the 1950s and was introduced by the legendary neurosurgeon Lars Leksell. It has been described as an effective and safe treatment (3) for primarily OCD but also for other anxiety disorders.

When I started this research I had the notion that it was indeed a safe and effective treatment but during my work I became aware that the evidence for capsulotomy was not as solid as I had imagined. The present thesis is the result of the research that emerged from my desire to find out more about the efficacy and safety of capsulotomy as a treatment for severely ill anxiety patients.

Before we look at what capsulotomy is and the evidence for the procedure, let us recapitulate the clinical picture and neuroanatomy of the anxiety disorders.

2.2 ANXIETY DISORDERS

2.2.1 Clinical picture

Anxiety disorders are among the most prevalent psychiatric disorders (4) and often strike in childhood or early adulthood. Etymologically, anxiety has complex origins including the Latin *anxietas*, a lasting state of fearfulness*, angor*, intense fear, and the French *angoisse*, a more acute panic-like state (5). Anxiety is used both in everyday language to describe tension or anguish that is a part of normal life and to label a psychiatric symptom common not only in anxiety disorders but also in mood disorders. The anxiety disorders according to the Diagnostic and Statistical Manual of Mental disorders (DSM-IV) (6) include social phobia, panic disorder, generalized anxiety disorder, post-traumatic stress disorder, obsessive-compulsive disorder and specific phobia. Current evidence-based treatments such as SSRIs or Cognitive-Behavioral Therapy (CBT) are effective treatments for most patients (7). This thesis focuses on a neurosurgical treatment, capsulotomy, for anxiety patients that did not respond to conventional treatment, i.e. who were treatment refractory.

- **Social phobia** concerns extreme fear of being in the center of social attention, or the object for social evaluation. As a result, public speaking, social gatherings, confronting superiors, or contacts with potential sexual partners are either avoided or endured with intense fear or panic.

- **Panic disorder** includes panic attacks that are sudden surges of physiological symptoms (heart palpitation, sweating, difficulties breathing, shakiness, dizziness, etc.) and feelings (derealization, fear of losing control or dying) that come unprovoked, and then subside within some ten minutes. Often patients start worrying about further attacks, thus developing anticipatory anxiety and avoidance of situations in which he or she would be vulnerably exposed and helpless in the event of an attack.

- **Generalized Anxiety Disorder** (GAD) is characterized by constant anxiety, which is driven by excessive and more or less chronic worry about different life circumstances, e.g., economical matters, health, and work or school performance. The worry is impossible to control, and there is an inability to relax. This makes a person with GAD tense, worked up, hypervigilant, and chronically exhausted.

- **Obssessive-Compulsive Disorder** (OCD) is characterized by unwanted intrusions (obsessions) and ritualized and repetitive behavior (compulsions).

Robert Burton beautifully depicts what today would be called OCD in his “Anatomy of Melancholy” from 1632 (8): “If he be in a silent auditory, as at a sermon, he is afraid he shall speak out unawares, something undecent, unfit to be said …Another dares not go

over a bridge, come near a pool, rock, steep hill, lie in a chamber where cross-beams are, for fear he be tempted to hang, drown, precipitate himself …". Freud writes that obsessional neurosis, "is unquestionably the most interesting and rewarding subject of analytic research, but as a problem it is still unmastered [unbezwungen]"(9).

There is accumulating evidence (10) from comorbidity, family and neuroimaging studies that OCD should form its own diagnostic group (OCD spectrum disorders) with similar disorders such as Body Dysmorphic Disorder, hypochondriasis and trichotillomania.

Two clinical vignettes are presented as examples of the clinical problems this thesis tries to address.

Ms A describes herself as having been an insecure and shy child. At age 27 her insecurity around people began to increase. She soon developed severe avoidance of all social situations, including the use of public transportation. Treatments included insight-oriented psychotherapy, clomipramine, benzodiazepines, behavioral therapy and neuroleptics. By age 34 she is unable to continue her job as a nurse's assistant and is given a disability pension.

Ms. S:s OCD started in her early twenties, following the birth of her first child. Her main symptoms are contamination fears and cleaning rituals that have taken over her life. When Ms. S has to defecate, she uses 8 rolls of toilet paper and showering can last over ten hours due to extensive cleaning rituals She checks locks, the stove and electrical appliances excessively. Her Yale-Brown Obsessive-Compulsive Scale rating score is 35, indicating extreme OCD. Cognitive-behavioral and pharmacological treatment trials have been without avail.

Both patients were referred to the Karolinska Hospital for evaluation for capsulotomy. Should we recommend capsulotomy for them? What is the potiental efficacy of such a treatment and are there any adverse effects that Ms E and Ms A may experience?

2.2.2 What is treatment refractory?

The inclusion criteria for surgery are described in section 4.1.2. In the studies of this thesis, patients were operated on from 1975-2000 and during this time important progress in the treatment of anxiety disorders has been made. What is considered to be treatment refractory will therefore be different across this time-span. In the 1980s clomipramine and SSRIs became standard treatments for OCD and other anxiety disorders. Before 1980 there were no randomized-controlled trials for clomipramine

(11), the first effective medication for OCD. Therefore it is unclear how the refractoriness was assessed before that time. Treatment refractoriness is considered to be a criterion for capsulotomy and has been defined as "current treatment options tried systematically for at least five years have either been without appreciable effect on the symptoms, or must be discontinued due to intolerable side effects" (12). This is also the definition that has been applied at our site. In some studies a more operationalized definition of which treatments the patient is refractory to has been applied (13). Without a more precise definition treatment refractory may be considered to be a term without much validity. Pallanti (14) therefore proposed a definition of levels of response and non-response in OCD to help define the term. Since this classification was published very recently, it was not used in our studies.

2.2.3 Neuroanatomy of OCD and anxiety

In a meta-analysis of functional neuroimaging in OCD from 2004, Whiteside et al (15) found consistent differences in between OCD patients and controls in the orbital gyrus and the head of the caudate nucleus. This is consistent with other reviews (16) claiming relative hyperactivity of OFC (orbitofrontal cortex, includes the orbital gyrus), ACC (anterior cingulate cortex) and the caudate nucleus both in resting state and in symptom provocation. There is also emerging data (17) supporting the view that different OCD symptom groups (dimensions) have distinct neural correlates. In line with those findings, OCD has been suggested (18) to be related to the emotion disgust whereas fear is a dominant emotion in the other anxiety disorders. This makes sense particularly for the washing/contamination subtype since disgust can been seen as having an evolutionary function of contamination and illness avoidance.

Another body of research that points to basal ganglia pathology in OCD are the Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) which is a recently described syndrome (19, 20) of rapid onset neuropsychiatric symptoms such as OCD or tics in primarily children infected with common streptococcal infection. PANDAS are, despite a certain controversy on the validity of the diagnosis (21), considered to be an autoimmune disease affecting the basal ganglia (22). A MRI study of children with PANDAS demonstrated enlarged caudate, putamen and globus pallidus, suggesting regional inflammatory changes in the regions that appear to be associated with OCD symptomatology (23). Generally, neuroimaging results support a proposed model of pathology within the cortico-striato-thalamo-cortical (CSTC) circuitry. To elaborate, caudate pathology has been proposed as a mechanism of CSTC dysfunction (24) This caudate malfunctioning is thought to lead to ineffective thalamic gating, which then results in hyperactivity of the OFC and ACC. Since the internal capsule, the anatomical target of capsulotomy, contains nerve fibers connecting the thalamus to parts of the prefrontal cortex it is a logical target for surgery intended to alter functioning in the CSTC circuitry. Moreover, the extended ventral striatum, including the nucleus accumbens has gained increased attention (25-27). Nucleus accumbens, situated just beneath the internal capsule, holds a key position

receiving input from e.g. the amygdala and projecting to the striatum, thalamus and the prefrontal cortex. Dopamine is the major transmittor in the nucleus accumbens (28).

Much research in neuroanatomical models of fear and anxiety focuses on the role of the amygdala. The amygdala is an almond-shaped structure located in the anterior part of the temporal lobe and is a considered to play an important role in the detection of threat and the activation of a fear response (29). The fear response will prepare for motor action, increase arousal and increase attention to fearful stimuli (30). LeDoux (31) has proposed that fear activation can operate by a fast subcortical "low road" afferent inflow to the amygdala without signals passing through the cortex, thus enabling us to respond before the feared stimulus is consciously perceived. The amygdala has connections to the prefrontal cortex and CSTC circuits affecting the inflow of information through the thalamus. The medial prefrontal cortex, including the OFC and ACC, has been proposed to exercise top-down control over the amygdala (32, 33). More specifically, panic disorder has been associated with amygdala hyperresponsitivity and impaired top-down suppression of the amygdala from the medial prefrontal cortex. In social phobia there is also some evidence of amygdala activation during symptom provocation (34).

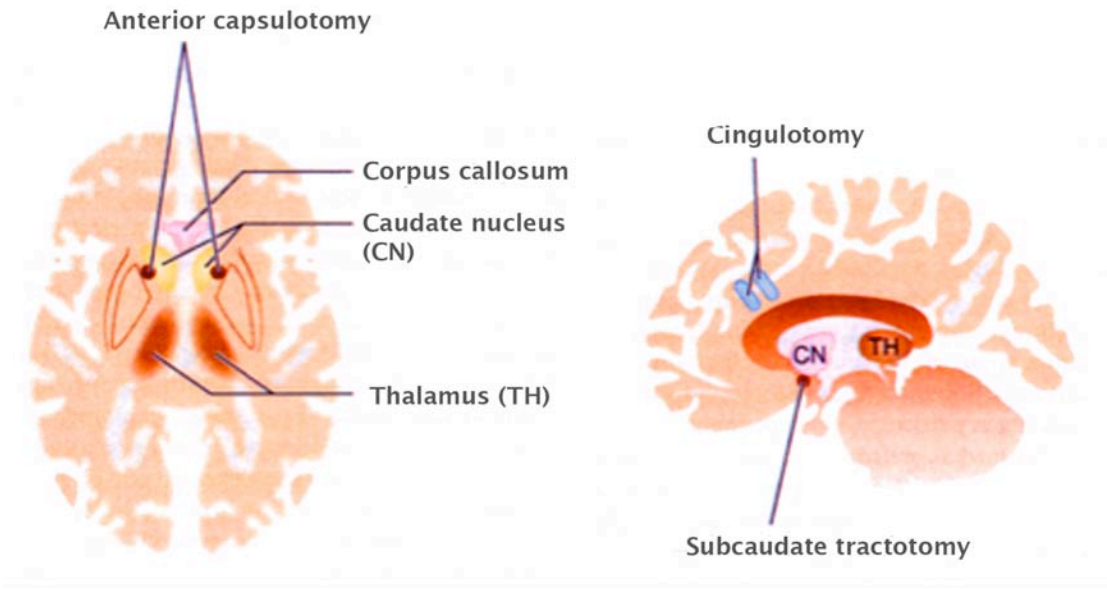


Figure 1. Anatomical structures and surgical targets for neurosurgery for mental disorders.

2.2.4 The internal capsule

The internal capsule (*capsula interna*) is a white matter tract containing several important fiber systems. The pyramidal tract (motor fibers) passes through the posterior part of the internal capsule. The anterior portion of the capsule, where capsulotomy lesions are placed, contains no motor fibers. The anterior part, crossing the striatum, contains the thalamic radiation with fibers connecting the thalamus to the prefrontal

cortex. The anterior capsule also contains the frontopontine fibers from the corticopontine tracts projecting from the prefrontal cortex to the pontine nuclei, which in turn project into the cerebellum. These fibers are intermingled with frontothalamic fibers. Smaller number of fibers from the nucleus caudatus to the nucleus lentiformis traverse the anterior limb (35). Thus, the lesions created in capsulotomy affect a number of interconnected regions, most importantly the prefrontal cortex.

2.3 NEUROSURGERY FOR MENTAL DISORDERS

2.3.1 A brief history of neurosurgery for anxiety and OCD

"Psychosurgery", now often referred to as Neurosurgery for mental disorders (NMD), is assumed to have been used in the form of trephining in ancient cultures such as the Incas. The first account of ablative NMD is from the Swiss psychiatrist Gottlieb Burckhardt who reported on the outcome of six psychotic patients undergoing cerebral cortical extirpation ("topectomy") in 1889 (36). Burckhardt reported modest outcomes and some severe complications including perioperative death. He was criticized for performing the operations and many arguments in that debate are strikingly similar to current ones. Burckhardt leaned more towards the principle of *Melius anceps remedium quam nullum* (Better an uncertain remedy than none at all) than the *Primum non nocere* (First, do no harm) of his opponents. The first 20 lobotomies were performed in 1935 by Almeida Lima and the Nobel laureate Egaz Moniz. The American neurologist Walter Freeman and colleagues quickly picked up on these news and lobotomy soon became a common treatment for mentally ill people from different diagnostic groups. The history of early psychosurgery is indeed very interesting, for reviews see e.g. Feldman et al and others (37-39).

One of the turning points in the use of lobotomy was the Swedish psychiatrist Gösta Rylander's research (40) showing gross changes in personality following frontal lobe surgery. At the 1947 meeting of the Association for Research in Nervous and Mental Disease he presented data on changes in personality after lobotomy (41, 42). He quoted relatives to patients saying "she is with me in body but her soul is in some way lost", a story that rapidly circulated (38). At the same time it is important to remember that there was evidence supporting the efficacy of lobotomy (43) and that this was at a time when there were virtually no effective treatments for the many patients filling the asylums. This could explain the enthusiasm that met new treatments such as lobotomy and psychoanalysis. Sweden is one of the countries with the most widely spread uses of lobotomy with some 4500 operations performed from 1944-1966 (44).

There has been a debate (45, 46) on whether or not lobotomy patients should be financially compensated. In 1996 the Norwegian parliament decided to pay 100,000 NOK to each patient (47), while the Swedish authorities decided not to offer any compensation.

Capsulotomy, where the bilateral lesions are produced in the anterior limb of the internal capsule, was first briefly reported by Talairach (48) in 1949. Leksell (49) further, and independently, developed the method and termed it bilateral capsulotomy. Originally, the rationale for selecting the internal capsules as targets was based on investigations by Meyer and Beck (50) in 1954 who at autopsy of patients subjected to lobotomy demonstrated that the common anatomical denominator of good outcome comprised parts of the anterior internal capsules. Other procedures such as cingulotomy, currently used for depression and OCD (13), subcaudate tractotomy (51) and limbic leucotomy (52) were developed during the same time period.

Figure 2. Gösta Rylander (1903-1979), the first professor of forensic psychiatry in Sweden. He was among the first to raise doubts on the widespread use of lobotomy.

Surgery Used on the Soul-Sick; Relief of Obsessions Is Reported

New Brain Technique Is Said to Have Aided 65% of the Mentally Ill Persons on Whom It Was Tried as Last Resort, but Some Leading Neurologists Are Highly Skeptical of It

By WILLIAM L. LAURENCE

Special to THE NEW YORK TIMES.

ATLANTIC CITY, N. J., June 6. —A new surgical technique, known as "psycho-surgery," which, it is claimed, cuts away sick parts of the human personality, and transforms wild animals into gentle creatures in the course of a few hours, will be demonstrated here tomorrow at the Comprehensive Scientific Exhibit of the American Medical Association, which is holding its eighty-eighth annual assembly here this week.

The new "surgery of the soul" has been applied to twenty mentally ill human beings, 15 per cent of whom, it is claimed, were "greatly improved," with an additional 50 per cent. "moderately improved." It is asserted the mental symptoms relieved by this new brain operation, often performed under local anaesthesia, include tension, apprehension, anxiety, depression, insomnia, suicidal ideas, delusions, hallucinations, crying spells, melancholia, obsessions, panic states, disorientation, psychalgesia (pains of psychic origin), nervous indigestion and hysterical paralysis.

When performed on wild monkeys, two of which were placed on exhibition here today, the brain operation changed the apprehensive, anxious and hostile creatures of the jungle into creatures as gentle as the organ grinder's monkey.

The new "soul surgery" was originally announced last year in a French scientific publication by Dr. Egas Moniz of Lisbon, Portugal. The results obtained by him appeared so startling that they were repeated in this country on cases in which every recognized form of treatment had been employed without improvement.

The exhibit is presented by Dr. James W. Watts, Dr. Walter Freeman and Dr. Ralph W. Barris of George Washington University Medical School. A supplementary paper will be presented by Drs. Watts and Freeman before the section on nervous and mental diseases on Wednesday. The title of the paper is "Psycho-Surgery: Effect on Certain Mental Symptoms of Surgical Interruption in the Pathways in the Frontal Lobe."

The new surgery consists in separating twelve small cores of the white matter in the brain, underlying the gray matter of the two frontal lobes, from the rest of the brain's white matter. The cores, each one centimeter in diameter, are not taken out of the brain, but are left in their places after the surgical instrument, known as the leucotome, has separated them from their original environment.

The twelve cores are separated in

Continued on Page Ten

Figure 3. From the front page of the New York Times, June 7 1937.

2.3.2 Capsulotomy

Capsulotomy is a neurosurgical procedure where lesions in the anterior part of the internal capsules (Figure 4) are produced either by heating (thermocapsulotomy) or by converging beams of gammaradiation (radiosurgery). The methods are described in detail in section 4.2.

Figure 4. Axial MRI, capsulotomy lesions bilaterally medial to the putamen.

2.3.2.1 Is Capsulotomy an evidence-based treatment for anxiety and OCD?

All NMD studies have been uncontrolled, as sham (placebo) operations for obvious reasons have not been applied. In systematic evaluations (such as the Cochrane Collaborations') of the evidence base of interventions, non-controlled studies are considered as having low evidence and thus capsulotomy, in principle, cannot be considered to be an evidence based treatment in the most orthodox sense. The reported efficacy in most studies is satisfactory, ranging from 40 percent of patients with permanent improvement (53) to 73 percent at least "much improved" (54). In the largest study to date, Herner in 1961 (53) reported on 116 capsulotomy patients of different diagnostic categories including 15 anxiety and 18 OCD cases. Fourteen of the OCD patients included in the study had a "regression or disappearance of symptoms". Six of the anxiety patients had regression of symptoms. Bingley (55) reported on the outcome of thermocapsulotomies in OCD patients and reported much improvement or that the patient was free from symptoms in 25 of 35 cases. Working capacity also increased and there was no evidence of adverse effects on personality or cognition. Rylander (56) reported on the outcome of both thermocapsulotomy and radiosurgery in 52 OCD and anxiety patients with favorable outcome. All patients but 3 had improved at follow-up. No permanent side effects were reported. In a congress proceeding from 1981, Burzaco reported (54) on the outcome of capsulotomy in 85 cases with OCD and

73 % were classified as “much improved or symptom free”. Lippitz (57) studied the lesion morphology in a sample of 29 OCD capsulotomy patients of whom 16 had a symptom score reduction of at least 50 %. A recent study (58) reported that 8 of 15 patients had at least a 33% OCD symptom reduction at follow-up. Thus, most of the data concerns OCD patients whereas the evidence for efficacy in other anxiety disorders is very sparse.

2.3.3 Is Capsulotomy safe?

The reported rate of adverse effects varies considerably. Herner (53) noted that in a group of 116 capsulotomy cases, frontal lobe deficit syndrome was obvious at follow-up in 30 percent. Table 1 displays the severity of the side effects in different diagnoses. Adverse effects in Herner’s sample and in a study by Kullberg (59) included fatigue, emotional blunting, emotional incontinence, indifference, low initiative, disinhibition, and impaired sense of judgment. A few studies have compared different neurosurgical methods. Kullberg (59) noted that cingulotomy produced fewer adverse effects (transient confusion and affective deficit) in the immediate postoperative phase than capsulotomy. In another study (56), conventional thermocapsulotomy was compared to Gamma Knife capsulotomy (radiosurgery) in OCD patients. The efficacy was satisfactory in both groups, but in the radiosurgery group there were no signs of postoperative confusion and disorientation, a common temporary adverse effect after thermocapsulotomy. As mentioned previously, Bingley (55) and Rylander (56) did not report any permanent adverse effects in their studies. In Mindus’ prospective one-year follow-up study of 24 thermocapsulotomies (60), favorable results were reported in general. Seven patients reported excessive fatigue postoperatively but this was not interpreted as a sign of frontal lobe syndrome. In the most recent study (58), one of 15 patients suffered from a permanent “behavior disorder” following postoperative brain edema. No other permanent side effect was reported and on neuropsychological screening no cognitive deficit was found although only 6 patients had been followed for 12 months.

2.3.4 Limitations of the previous studies

- As mentioned earlier the most important limitation of earlier studies is the lack of control treatment. The reason for this is the difficulty in designing a control treatment since it would be difficult or even impossible to perform sham (placebo) surgery.

- Given most investigators involvement in patient selection, treatment and follow-ups, there is a potential investigator bias. The patients of course also share this. Moreover, all of the mentioned studies come from highly specialized centers that might have a self-interest in the publication of favorable results.

- Many of the cited studies are published as dissertations (53, 60), book chapters or congress proceedings (54-56, 59) that may not have undergone the same peer-review as commonly is the case in scientific journals.

- Much of the evidence (53-56, 59, 60) for the efficacy of capsulotomy comes from operations performed long ago. The value of the evidence for current patient populations can be questioned since diagnostic procedures, surgical and radiological methodologies have advanced. New treatments that are added over the years will change what population of treatment refractory patients that are candidates for surgery.

- Most NMD studies to date are short-term studies and have not assessed potential adverse effects in a systematic way.

Despite that capsulotomy has been characterized as an effective and safe treatment for OCD and other anxiety disorders, there are important shortcomings in the documentation. Therefore, the conclusion is that the efficacy and safety of the procedure must be further investigated.

all *Side effects.*

Diagnosis	Schizophrenia			Depressive states			Anxiety neuroses			Obsessional neuroses			Total		
	M	F	Total	M	F	Total	M	F	Total	M	F	Total	M	F	Total
Mild	4	5	9	5	2	7	2	4	6	1	6	7	12	17	29
Moderate	—	1	1	1	2	3	—	2	2	—	2	2	1	7	8
Severe	—	2	2	5	2	7	—	—	—	1	—	1	6	4	10
Total	4	8	12	11	6	17	2	6	8	2	8	10	19	28	47

Figure 5. Side effects in Herner's capsulotomy study (53).

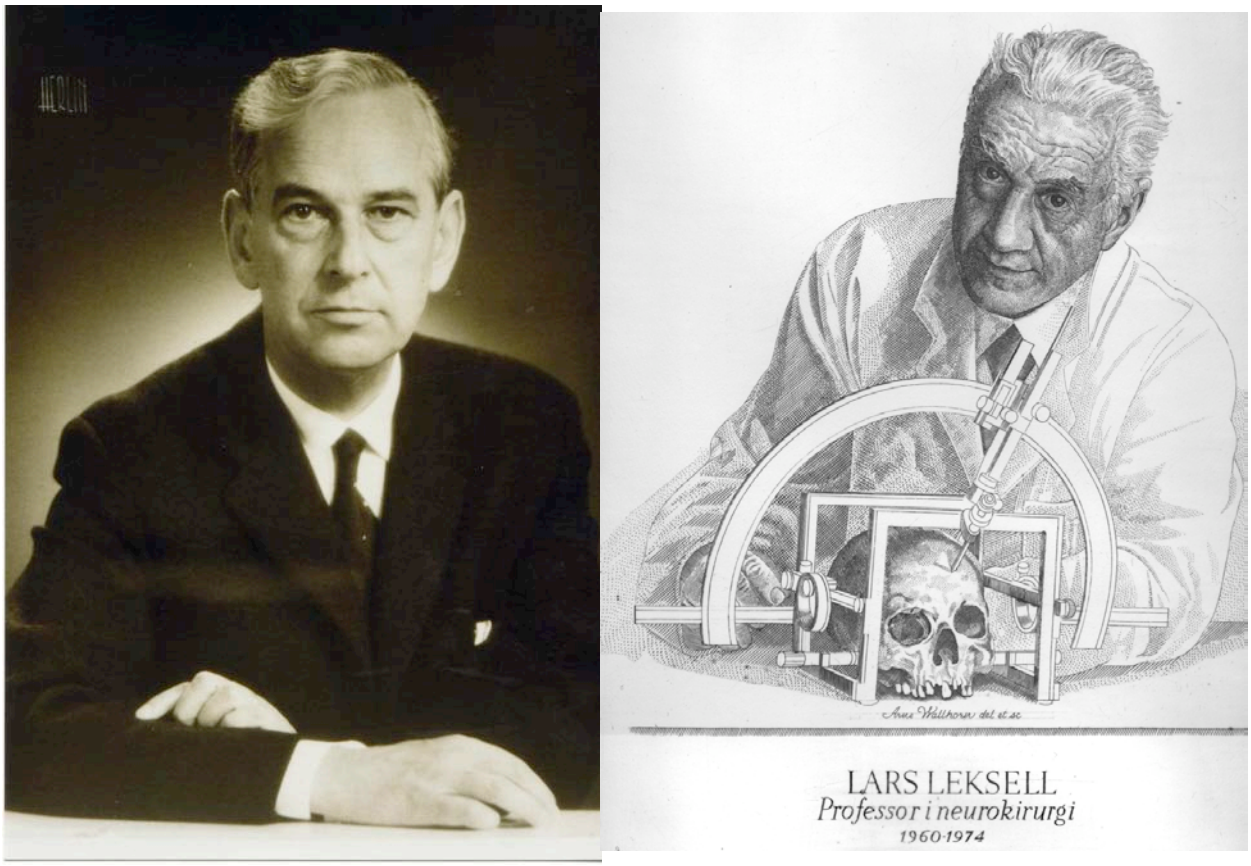


Figure 6. Portrait of Torsten Herner (1908-1996, left) and neurosurgical pioneer Lars Leksell (1907-1986, right), with one of his inventions, the stereotactic frame.

3 GENERAL AIMS

a. To assess the efficacy of capsulotomy in two consecutive samples of anxiety disorder and OCD, respectively, at one-year and long-term follow-up. Efficacy was measured as changes in symptom rating scales, ratings of impairment, improvement and global functioning.

b. To assess the long-term safety of capsulotomy samples through clinical observations, self- and family ratings of personality and frontal lobe deficit behavior and neuropsychological assessment.

c. To relate the outcome to characteristics of the neurosurgical lesion.

4 METHODS

4.1 PATIENTS

4.1.1 Patient selection

Treatment refractory patients that had undergone capsulotomy for OCD or other anxiety disorders at the Karolinska University Hospital from 1975 to 2000 were included in Study I-IV.

4.1.2 General inclusion criteria for capsulotomy

Inclusion criteria for capsulotomy (12, 61) were, in sum:

- Chronic illness (duration ≥5 years);
- The illness causes substantial suffering and considerable reduction in psychosocial functioning;
- Current available psychological and pharmacological treatment options tried systematically for at least five years without substantial effect;
- Informed consent.

4.1.3 Study I-III

All 26 (15 women and 11 men) consecutive patients with anxiety disorders other than OCD who were treated with bilateral thermocapsulotomy between 1975 and 1991 at the Karolinska University Hospital, Stockholm, Sweden, were included in Study I. Of these three were deceased, two were too somatically ill to be interviewed, one refused participation, and two patients did not show up. Thus, eighteen patients were available for long-term follow-up. Mean age at first capsulotomy was 41.4 years (range 31-54, SD 6.5). Mean age at long-term follow-up was 54.5 years (range 42-71, SD 8.3, n=18). Mean duration of illness at the time of surgery was 18.0 years (SD 9.2, range 5-40). Twelve of these 18 patients were examined with MRI at long-term follow-up. One dataset was lost, therefore 11 patients constituted the sample of Study II. Sixteen of the 18 patients that were evaluated at long-term had complete sets of the Karolinska Scales of Personality and constituted the sample in Study III.

4.1.4 Study IV

All twenty-five OCD patients subjected to capsulotomy from 1988 to 2000 at the Karolinska University Hospital in Stockholm were included in this study. Fourteen of the patients were women, 11 were men. The mean age at first capsulotomy was 41 years (SD 11.0, range 25-68) and the disorder duration at the time of surgery was 21 years (SD 8.3, range 8-40). The mean age at long-term follow-up was 52 years (SD 12.0, range 33-83). Of the 25 patients, two had died at the time of long-term follow-up.

4.2 NEUROSURGICAL METHODS

4.2.1 Thermocapsulotomy

Thermocapsulotomy is conventional stereotactic surgery where burr holes are made slightly anterior to the coronal suture and lesions are produced using an electrode with a diameter of 1.5 mm and a 10 mm bare tip with heating to 60° C during 60 seconds. In Study I-II lesions were produced with monopolar (9 operations) or bipolar (20 operations) electrodes. In the latter case, the inter-electrode distance was 6 mm. The intended height of the lesions was 18-20 mm, and for bipolar electrodes the medio-lateral extension was approximately 8 mm. Only monopolar electrodes were used in Study IV. The estimated height of the lesions in study IV, i.e. their dorso-ventral extension, was 12-20 mm. In Study IV, one patient had prior to her bilateral themocapsulotomy been subjected to trial Deep Brain Stimulation, to our knowledge the first OCD patient who had undergone such treatment. Based on data by Lippitz et al (57, 62), four patients had a unilateral right-sided thermocapsulotomy, in one case followed by a second one. Surgery was performed under local anesthesia with moderate sedation.

4.2.2 Radiosurgery

Radiosurgery, also referred to as Gamma Knife® surgery, was performed in a subgroup of patients in Study IV using different models of the Leksell Gamma Knife® unit (Elekta AB, Stockholm, Sweden, Figure 7). Lesions are produced (without opening the skull), by converging beams of gamma radiation, much like sunbeams through a looking glass. Round collimators (4 mm) were selected. Doses of 160-200 Gy were applied. Five patients received 200 Gy in 3 isocenters bilaterally. The radiobiology of these lesions has been discussed by Kihlström and collegues (63, 64) and they concluded that the larger the irradiated volume, the less predictable the resulting lesion volume. Further, three isocenters was not recommended (63). It seems that the five patients in Study IV receiving 200 Gy in three isocenters were subjected to higher doses of radiation than in hindsight would be recommended.

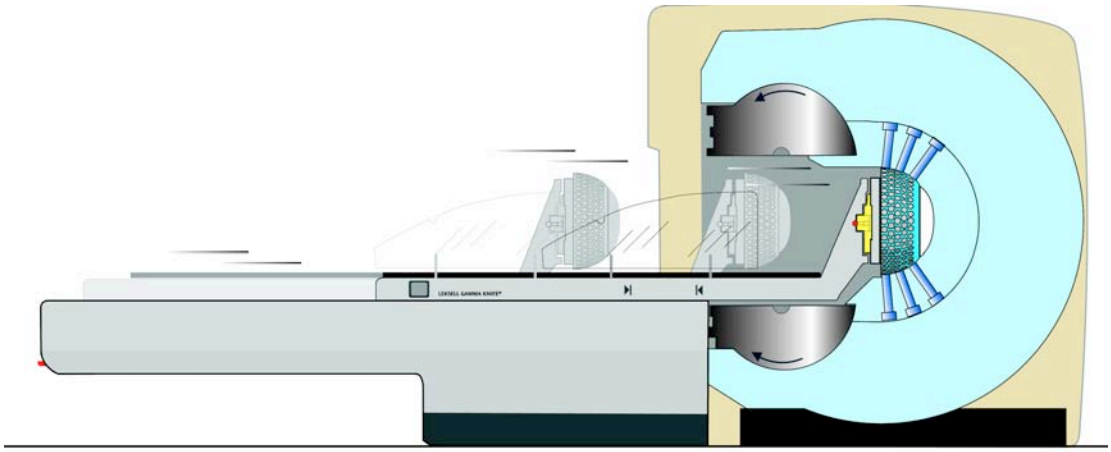


Figure 7. Section of the Leksell Gamma Knife®. Cobalt 60 (light blue) emits gamma radiation and the beams are focused through collimators to the target point in the brain. Illustration courtesy of Elekta.

4.2.3 Target localization

4.2.3.1 Study I-III

In the first patient, treated in 1975, the target coordinates were determined using pneumoencephalography. CT localization was employed in 8 operations (65), and two were performed with the aid of MRI. Different versions of the Leksell stereotactic frame with CT and MRI adaption developed during this period were used.
The original capsular target according to Leksell, determined with the aid of pneumoencephalography was located halfway on the line interconnecting the anterior commissure (Ac) and the tip of the frontal horn, i.e. 17-19 mm anterior to the Ac at the level of the Ac-Pc (posterior commissure) line. This approximately corresponds to the middle portion of the capsule at the level of the posterior part of the medial putamen border. Laterality of the targets was 18-20 mm from the midline. When CT scanning became available and integrated with stereotactic surgery it was possible for the first time to visualize the capsules and the targets were then generally placed a few mm more anterior, corresponding to the anterior part of the putamen-capsular border.

4.2.3.2 Study IV

Target localization, both for thermo- and radiosurgery capsulotomy, was performed with the aid of Magnetic Resonance Imaging (MRI) (GE 1.5 T). The Leksell stereotactic frame with MRI adaption was used. The target was placed in the anterior part of the middle portion of the anterior limb of the internal capsule approximately corresponding to the level of posterior part of the medial putamen border. Dorso-ventrally (the Z-coordinate) the target determination was first performed in an axial plane approximately corresponding to the intercommissural plane and was then adjusted in a coronal cut so that the intended lesion covered most of capsule,

particularly its basal part. For thermocapsulotomy the mediolateral angularity of the lesioning electrode trajectory was adjusted to the angle of the capsule as determined in the coronal image.

4.3 PSYCHIATRIC METHODS

4.3.1 Diagnostic methods

A semistructured interview was the most common diagnostic procedure but for 9 patients in Study IV, the Structured Clinical Interview for DSM Axis I Disorders (SCID-I) interview (66) was used.

4.3.2 Rating scales

The **Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)** (67) is a widely used scale rating the severity of OCD. It consists of 10 items rated from 0 to 4 with 5 items each for obsessions and compulsions. A positive response was defined as a $\geq 35\%$ reduction in Y-BOCS score from baseline and remission was defined as a Y-BOCS score ≤ 16 (cf. (14) for a review of response and remission criteria). The Y-BOCS was used in Study IV only. In one case the preoperative rating was missing and in 8 patients the preoperative rating was done retrospectively at the one-year follow-up.

The **Montgomery-Åsberg Depression Rating Scale (MADRS)** (68) is a widely used depression rating scale with ten items scored from 0 to 6. The **Brief Scale for Anxiety (BSA)** (69) is a rating scale for measuring anxiety symptoms consisting of eight reported and two observed items, scored on a 0-6 Likert scale.

Measures of improvement, impairment and global functioning

Global improvement was measured by the investigator-rated Physician's Global Improvement Scale (PHYGIS) and by the patient on the Patient's Global Improvement Scale (PATGIS) (70). In Study I-III an 11-point Likert scale was used. A score of 10 indicates maximal improvement. In Study IV a slightly different investigator-rated version was used, the Clinical Global Impression–Improvement scale (CGI-I), and the Clinical Global Impression–Severity scale (CGI-S) was used as a global measure of symptom severity. For the CGI-S, 1 represents "normal, not at all ill" and 7 "amongst the most extremely ill of subjects". For the CGI-I, 1 is the best possible outcome ("very much improved") and 7 the worst ("very much worse"). The Global Assessment of Functioning Scale (GAF), i.e. the axis V of the DSM-IV (6), is a composite measure of current psychological, social and occupational functioning**.** Functional impairment was evaluated with the 10-point patient-rated work, social life and family life/home responsibilities subscales of the Sheehan Disability Scale (71) (0, none; 1-3, mild; 4-6, moderate; 7-9, marked; 10, extreme).

The Frontal Systems Behavior Scale (FrSBe) (72), formerly known as the Frontal Lobe Personality Scale (FLOPS) (73) is a rating scale for the assessment of behavior problems associated with damage to the fronto-subcortical brain circuits. The FrSBe is a 46-item scale rated on a five-point Likert format. The scale comes in two forms: a patient rated and a family rated form comprising the same items. The rating is summed to a total score and to subscale scores for executive dysfunctioning (E), apathy (A) and disinhibition (D). The questionnaire asks for ratings for two time-points, premorbid (in our case preoperative) and current behavior, that is, ratings of preoperative behavior are not done preoperatively but rated retrospectively at long-term follow-up. Raw scores are transformed to T scores on the basis of gender, education and age. US norms were used in the present study. The original version was translated to Swedish and translated back to English and the backtranslation was approved by the authors of the scale. This scale was used only in Study IV. The scale has been used in research concerning neurodegenerative disorders such as Multiple Sclerosis (74), neurosurgical treatment of Parkinson's disease (75), eating disorders (76) and schizophrenia (77).

Execution, Apathy, Disinhibition Scale (EAD Scale)
For Study I a simple rating scale was constructed, the Execution, Apathy, Disinhibition Scale (EAD Scale) because rating scales such as the FrSBe (72) were then not yet available. The EAD scale was designed to measure three important functions that have been postulated to relate to frontal lobe dysfunction, namely executive dysfunction (E), apathy (A) and disinhibition (D). Severity of symptoms was rated on a four-point Likert scales (0-3) by two raters on the basis of all information available including videotapes of patient interviews and interviews with relatives. Consensus was reached for all patients before the scores were entered into the raw data matrix. Patients with a total score ≥ 3 were rated as having clinically significant dysfunction. The group of patients with EAD Scale score ≥ 3 (the EAD group) was compared to the group of patients with an EAD Scale score <3 (the non-EAD group). High interrater reliability for the EAD scale was demonstrated in Study I. In contrast to the FrSBe, this scale is clinician-rated.

4.3.3 The Karolinska Scales of Personality

The Karolinska Scales of Personality (KSP) is a self-report inventory and comprises 135 items grouped into 15 scales: *anxiety proneness* scales, i.e. Somatic Anxiety, Muscular Tension, Psychic Anxiety, Psychasthenia, and Inhibition of Aggression; *extraversion* scales, i.e. Impulsiveness, Monotony Avoidance, Detachment, Socialization, and Social Desirability; and *aggression-hostility* scales, i.e. Indirect aggression, Irritability, Verbal aggression, Suspicion, and Guilt. Most of the scales are based on the hypotheses of biologically relevant temperament dimensions. The KSP was used preoperatively, and at one-year and long-term follow-ups. In Study IV, a family rated version of the KSP was constructed by substituting all personal pronouns. This version was intended to reflect the relatives' view of the patients personality and our aim was to study differences between the patients' own scoring and that of their

relatives. The construction and the psychometric analyses of the KSP have been described in detail by Gustavsson (78). The KSP has been revised and the new version, the Swedish universities Scales of Personality (SSP) (79), has improved psychometric quality. The reason that the KSP was preferred to the SSP in Study IV was that the KSP had been used preoperatively.

4.4 NEUROPSYCHOLOGY

4.4.1 Study I

A battery of neuropsychological tests (Table 1) was used at long-term follow-up comprising tests presumably assessing pre-morbid cognitive function, executive functions and short-term working memory, respectively.

Domain	*Test*	*Function*	*Reference*
Pre-morbid level	Vocabulary MC (WAIS-R NI[1])	Verbal comprehension and semantic memory	Kaplan,(80)
	Picture completion (WAIS III[2])	Visual perception	Wechsler,(81)
Executive function	COWAT[3] (F-A-S) in writing	Initiation of word fluency	Lezak, (82)
	WCST[4]	Concept formation, shift of focus and use of feedback.	Heaton, (83)
Short-term and working memory	Digit span (WAIS-R)	Verbal short-term memory, attention and working memory.	Wechsler, (84)
	Block span (WAIS-R NI)	Spatial short-term memory, attention and working memory	Kaplan,(80)
	L-N-S[5] (WAIS III)	Verbal working memory	Wechsler, (81)

1 Wechsler Adult Intelligence Test – Revised, as a Neuropsychological Instrument; MC: Multiple choice version
2 Wechsler Adult Intelligence Test III
3 Controlled Oral Word Association Test
4 Wisconsin Card Sorting Test
5 Letter-Number-Sequencing.

Table 1. Functional domains, neuropsychological tests, cognitive functions and references.

4.4.2 Study IV

Emphasis was given to assessment of executive functions since frontal lobe dysfunction is hypothesized to play a role in OCD symptomatology (85) and because results from Study I indicated that capsulotomy may be associated with deficits in frontal lobe functioning. The chosen tests were selected for reasons of brevity and ease of use as well as for their ability to assess both subcomponents of the executive system and complex ecologically valid executive behavior. Total duration of neuropsychological testing was approximately 1.5 hours. In addition to the abovementioned tests used in Study I, the simplified six elements task from BADS (86) (Behavioral assessment of the dysexecutive syndrome) was used to assess executive functioning.The last test was

used to evaluate the capacity for social insight or the ability to represent thoughts and feelings. This choice was based on a case report by Happé (87) describing selective deficits in "theory of mind" following capsulotomy. The test consists of 16 short stories. Eight of the stories require an answer with an inference about the story characters thoughts, feelings and intentions. The eight control stories also require reasoning and inference, but the mental states of the characters are not relevant and the inference concerns for example physical causation. The first two test in Table 1 were not used in Study IV.

Using results from the neuropsychological assessment a global classification of dysexecutivity was made for each individual. Results were classified as either not showing signs of dysexecutivity (0), showing possible signs (1) and dysexecutive neuropsychological function (2). For the classification a cutoff score was identified for each of the six neuropsychological subtests of the battery. If two results were below cutoff the overall result was classified as indicative of possible dysfunction (1). If three or more results were below cutoff the performance was classified as indicative of dysexecutivity (2). As three of the tests assessed overlapping attentional and working memory aspects of executive function an adjustment was made so that Letter Number Sequencing, Digit Span and Visual Span were regarded as one sub-test. This classification was done solely on the basis on neuropsychological testing and was done independently of the clinical ratings.
Cutoff scores were:

- FAS: T-score 40
- Six Elements Task: profile score 4
- Letter-Number sequencing, Digit Span, Visual Span: cutoff WAIS scale score 7
- WCST: cutoff less than five categories (64 card version less than three)

For a subset of seven patients pre- to postoperative comparisons regarding WCST and span-tests were done.

4.5 NEURORADIOLOGY

4.5.1 Study I–II

The imaging study at long-term follow-up was performed with MRI (1.5 T GE Signa scanner) that included standard imaging sequences (T1-, proton density-, and T2-weightings). Slice thickness was 4 mm and interslice gap was 2 mm. A well-demarcated hyperintense signal change within the anterior limb of the internal capsule on proton-weighted sequences was defined as the lesion. The site and extension of the lesions were determined according to the same protocol as used in the study by Lippitz et al (57). Images were reformatted on the MRI console with an equal angulation parallel to the anterior commissure- posterior commissure (Ac-Pc) line as individually

defined in all cases. For quantitative interindividual comparison of lesion localization, the following anatomical landmarks on the *z* plane were selected: the anterior commissure, the foramen of Monro, and the internal cerebral vein (Figure 9). The lesion extent within the internal capsule in the *x* and *y* planes was measured in axial slices on a superimposed ruler in relation to the adjoining putamen. The part of the anterior limb of the internal capsule at the anterio-lateral edge of the putamen was assigned to constitute the 0 coordinate, and the capsular part adjacent to the posterio-medial putaminal edge was defined as the 100 coordinate. In every reformatted MRI slice, the start and end points of the lesion were measured on the virtual ruler. The values were expressed in percent relative to this virtual ruler, allowing inter-individual comparison. The lesion's site and extension were compared with the right-sided lesions reported (57) as being the common topographic denominator of responders: coordinate 42–64 at the level of the foramen of Monro and coordinate 40–50, 4 mm above on the plane defined by the internal cerebral vein. These data were also used to measure correlations between lesion extension and outcome. The total lesion area was defined as the summed lesioned area determined in the three axial planes.

4.5.2 Study IV

The imaging study at long-term follow-up was, similarly to Study I-II performed with MRI (1.5 T GE Signa scanner) that included standard imaging sequences (T1-, proton density-, and T2-weighted images). Slice thickness was 5 mm and interslice gap was 2 mm. At the last follow-up a detailed MRI study was performed including axial and coronal 3D thin-slice imaging, FLAIR, as well as isotropic and anisotropic diffusion sequences. The rapid technical evolution of imaging techniques now allows for more elaborate studies than were available at the time when the follow-up study was started. Methods such as tractography could therefore not be applied to the anisotropic diffusion studies.

4.6 STATISTICAL CONSIDERATIONS

Since sample sizes were small and most variables were non-continuous, generally non-parametric methods were used. The limited power that was a consequence of the small sample sizes is discussed further in section 6.5.2.

5 RESULTS

5.1 STUDY I: CAPSULOTOMY FOR REFRACTORY ANXIETY DISORDERS: LONG-TERM FOLLOW-UP OF 26 PATIENTS

Aims
To assess the long-term efficacy and safety of capsulotomy in 26 consecutive patients with non-obsessional anxiety disorders by clinical symptoms ratings and cognitive tests.

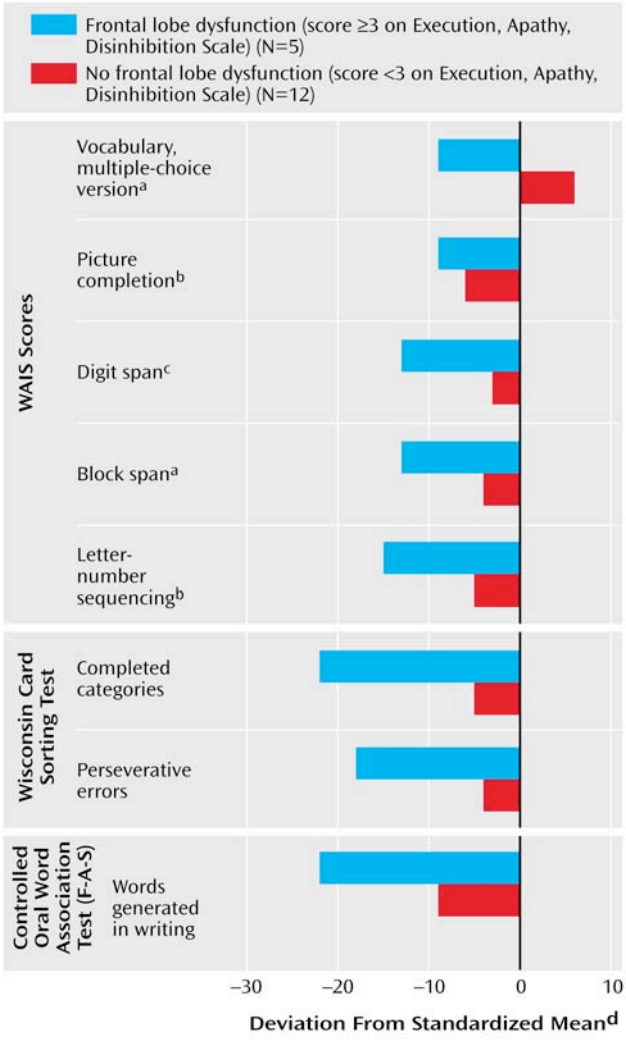
Sample
Twenty-six patients who had undergone bilateral thermocapsulotomy were followed up after a mean of 13 years. Main diagnoses were Generalized Anxiety Disorder (n=13), Panic Disorder (n=8) and Social Phobia (n=5). Seventeen of 23 patients alive at long-term follow-up were followed-up in person and relatives were interviewed. Of the eight patients lost to long-term follow-up, three had died (of suicide, chronic alcoholism, and cardiovascular disease, respectively), two were too somatically ill to be interviewed, one refused participation, and two patients did not show up.

Efficacy
Mean preoperative Brief Scale of Anxiety score was 22.0 (SD 5.6), one year postoperatively it was 4.6 (SD 4.2), and at long-term follow-up it was significantly ($p<0.001$) lower than at baseline, 9.9 (SD 5.8). There were no significant between-diagnoses differences. Using a definition of a ≥50 percent reduction in BSA score, 23 out of 25 were rated as responders at the one-year follow-up. At long-term follow-up the responder rate was 12/18.
The mean preoperative MADRS score was 17.6 (SD 7.4), indicating mild to moderate depression (88). At one year postoperatively the MADRS score had decreased to 6.8 (SD 7.0), and at long-term follow-up to 8.0 (SD 6.8). The changes were significant ($p< 0.001$ and $p< 0.01$, respectively).

Safety
Seven patients had EAD scores ≥3, indicative of dysfunction in circuitry involving the prefrontal lobe. Examples of poor execution were inability to perform simple household tasks such as taking out the garbage, and showing poor judgment. Examples of apathy included neglect of hygiene and clothing, lack of initiative, passivity, and fatigue. Disinhibition included behavior such as foul language and indecent exposure. Two cases of postoperative seizures were recorded. Mean weight gain in the first postoperative year was almost 10 kg. The results of the neuropsychological assessment are presented in Figure 8.

Conclusions

Thermocapsulotomy is an effective treatment for selected cases of non-obsessive anxiety but may carry a significant risk of adverse effects, indicating impairment of frontal lobe functioning. Our results underscore the importance of assessments of adverse effects carried out face-to-face.



[a] WAIS-R as a Neuropsychological Instrument
[b] WAIS-III
[c] WAIS-R
[d] Mean=50, SD=10.

Figure 8. Performace on neuropsychological tests at long-term follow-up.

5.2 STUDY II: LESION TOPOGRAPHY IN CAPSULOTOMY FOR REFRACTORY ANXIETY–IS THE RIGHT SIDE THE RIGHT SIDE?

Aims

A previous report (57) on bilateral capsulotomy in Obsessive-Compulsive Disorder showed common topographic features of lesions in the right-sided internal capsule in all patients responding to the treatment. The aims of the present study were to test if the same region was involved in anxiety patients responding to surgery and to examine whether lesion area and site correlated with adverse effects and effect on target symptoms.

Sample

In this substudy to Study I, the MRI examinations of 11 patients with treatment-refractory anxiety disorders other than OCD treated with bilateral thermocapsulotomy in 1975-1991 were analyzed.

Results

None of the eight responders had lesions that corresponded to the earlier reported right-sided anatomical denominator. Four patients out of 11 were rated as having significant clinical symptoms indicating frontal lobe dysfunction. The total sum of the lesion area determined in each of the three anatomic levels did not correlate with the degree of anxiety reduction or ratings of executive dysfunctioning, apathy and disinhibition. However, if three of the eleven patients were excluded as being outliers, the lesion area may be suggested to be related to the rating of executive dysfunction, apathy and disinhibition (Figure 10).

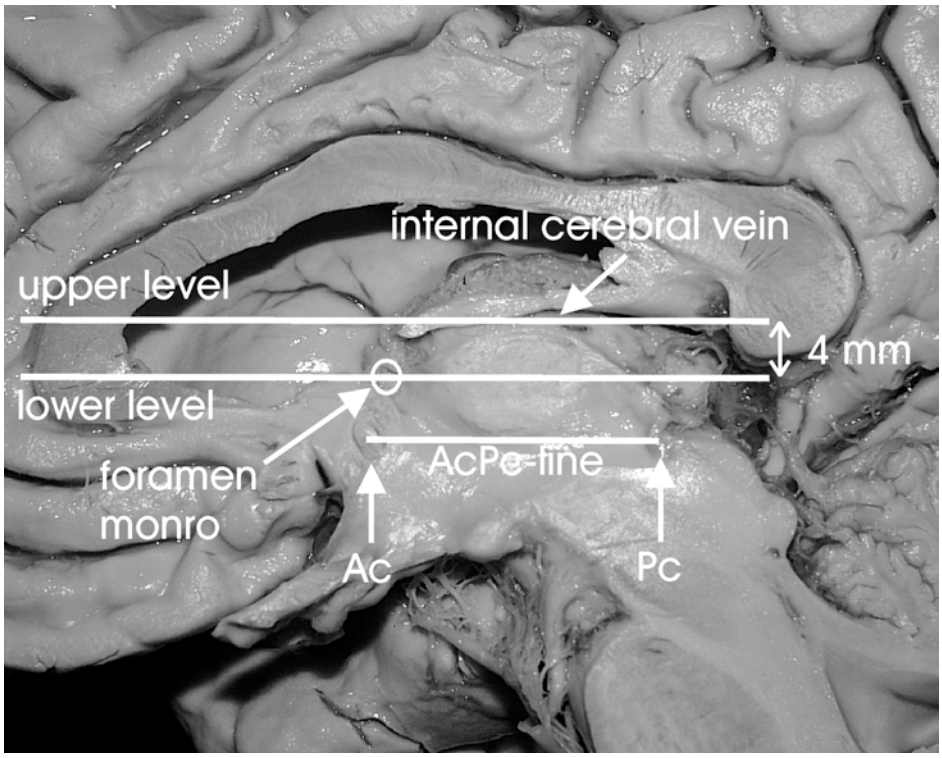


Figure 9. Sagittal brain section demonstrating the anatomical landmarks and the three axial planes used for the quantitative MRI analysis. Ac: Anterior commissure. Pc: Posterior commissure.

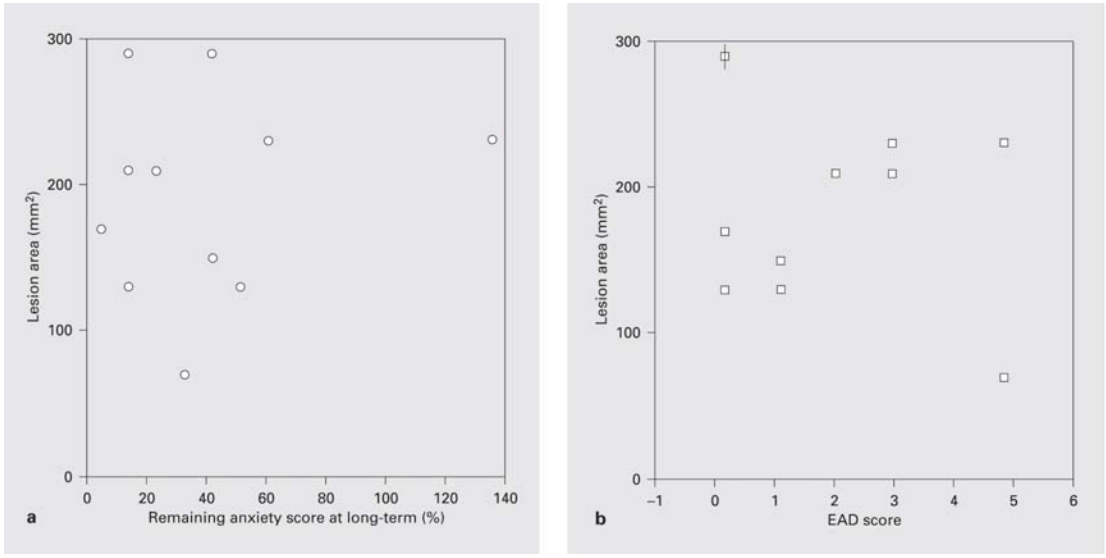


Figure 10. Relationship between lesion area and anxiety reduction (a) and adverse effects (EAD score) (b). In both figures the Y-axis represents the summed lesion area in the three anatomical planes. In Figure 4b the dot marked with a vertical line in the uppermost part of the graph represents two patients.

5.3 STUDY III: LONG-TERM CHANGES IN SELF-REPORTED PERSONALITY FOLLOWING CAPSULOTOMY IN ANXIETY PATIENTS

Aims
To describe changes in self-reported personality in anxiety patients undergoing capsulotomy.

Sample
Twenty-six consecutive patients with anxiety disorders other than OCD who were treated with thermocapsulotomy between 1975 and 1991 at the Karolinska University Hospital were included in Study I. Eighteen patients were available for long-term follow-up. Sixteen of the 18 patients had complete Karolinska Scales of Personality (KSP) sets (preoperatively, at one-year and at long-term follow-up) and constituted the sample of the present study.

Results
Patients were significantly less anxiety prone at long-term follow-up as evidenced by the reduction in somatic anxiety ($p<0.05$) and muscular tension ($p<0.05$) on the KSP. Four patients suffered from adverse effects indicating frontal lobe dysfunction. There was no significant correlation between the reduction in BSA score and the KSP change from preoperatively to long-term in any of the KSP scales.

Conclusion
In line with previous studies, high anxiety proneness normalizes after capsulotomy in anxiety patients. The adverse effects, described in Study I on the same group of patients was not reflected in the KSP. Thus, the conclusion based on previous KSP findings that the incidence of adverse personality changes following capsulotomy is low and does not increase with time is challenged by the present study.

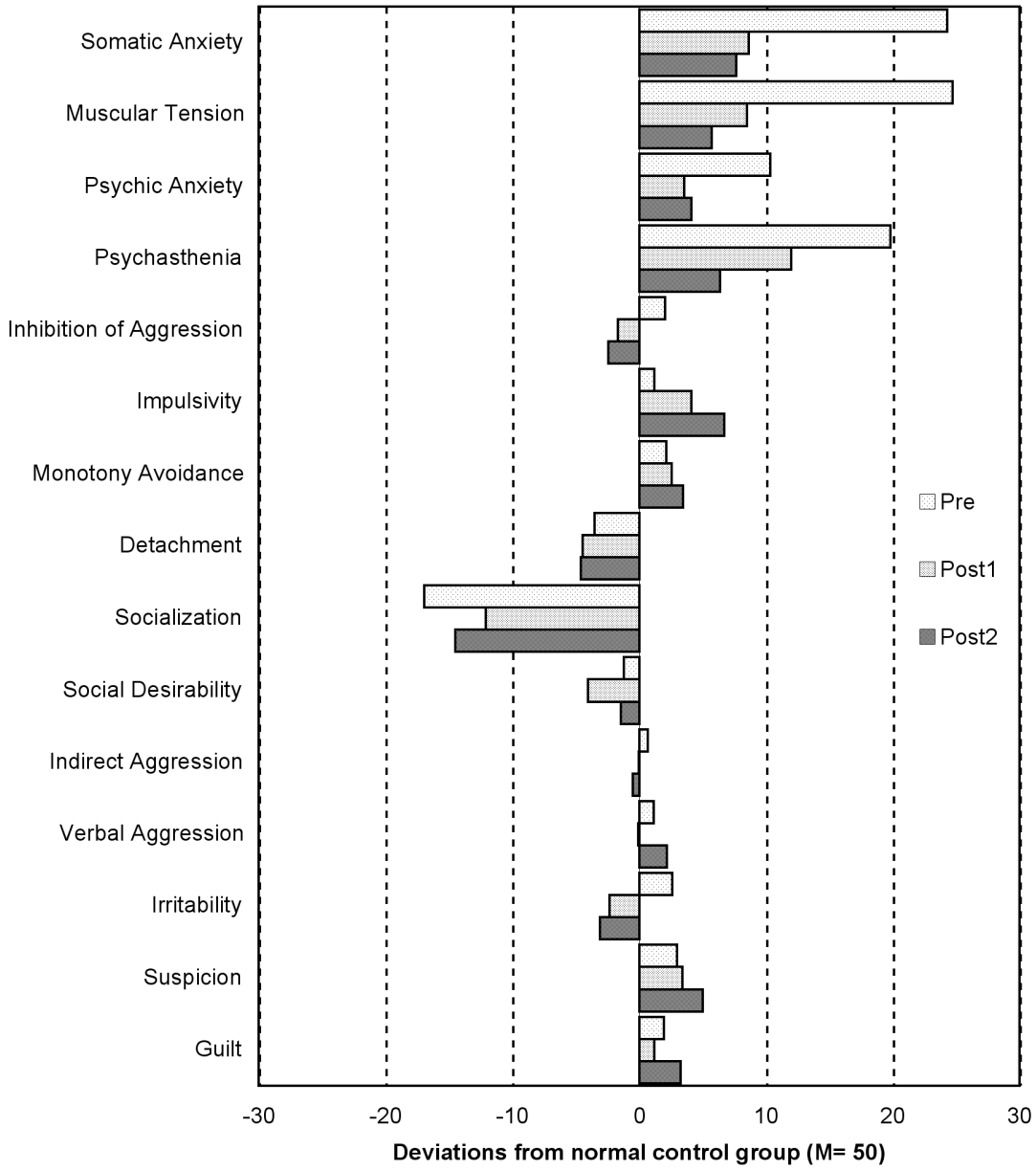


Figure 11. Mean scores in personality scales from the Karolinska Scales of Personality in non-OCD anxiety patients before capsulotomy (Pre), one year after the surgery (Post1), and at long-term follow-up (Post2). The scores are expressed as differences from the mean T-score of a control group of 200 men and 200 women (mean= 50 and SD= 10).

5.4 STUDY IV: CAPSULOTOMY FOR OCD: LONG-TERM FOLLOW-UP OF 25 PATIENTS

Aims
To assess if capsulotomy is effective in reducing obsessive-compulsive symptoms and safe. Further to investigate if there are differences in the outcome related to surgical method.

Sample
25 consecutive OCD patients undergoing thermo or radiosurgical capsulotomy. No drop out to long-term follow-up except for two deceased (one of homicide and one of suicide).

Results
Mean Y-BOCS was 34 preoperatively and dropped to 18 at long-term follow-up ($p<0.0001$). Twelve patients responded (≥35 % Y-BOCS reduction) and eight were in remission (Y-BOCS<16) at long-term follow-up. The scores of depression and anxiety ratings were also significantly lower at long-term follow-up (Figure 12). Only 2 patients achieved remission from OCD without substantial side effects. Several neurosurgical complications related to radiosurgery were reported. A mean weight gain of 6 kg was reported in the first postoperative year ($p<0.001$). Two patients were severely disinhibited postoperatively. Ten patients were considered to suffer from significant problems in the area of executive functioning, apathy or disinhibition.

Fourteen patients were classified as dysexecutive at long-term follow up based on neuropsychological testing. In all these cases dysfunctioning was manifested in at least three tests. In seven patients a comparison of pre- and postoperative tests indicated a worse performance postoperatively in tests of executive functions. Of the ten patients that were rated as showing clinically significant signs of executive dysfunctioning, apathy or disinhibition, eight also were classified as neuropsychologically impaired.

In a preliminary analysis of the lesion size in 21 patients, the mean size of right sided lesion was 2494 mm^3 (SD 4731, range 463-22756) and of the left sided lesion 3981 mm^3 (SD 6035, range 460-25170). Lesion size did not correlate significantly with efficacy (percentage of Y-BOCS reduction, $r=0.17$) or total EAD score ($r=-0.29$) (Figure 13).

Conclusions
Capsulotomy is effective in reducing OCD symptoms but carries a significant risk of substantial side effects.

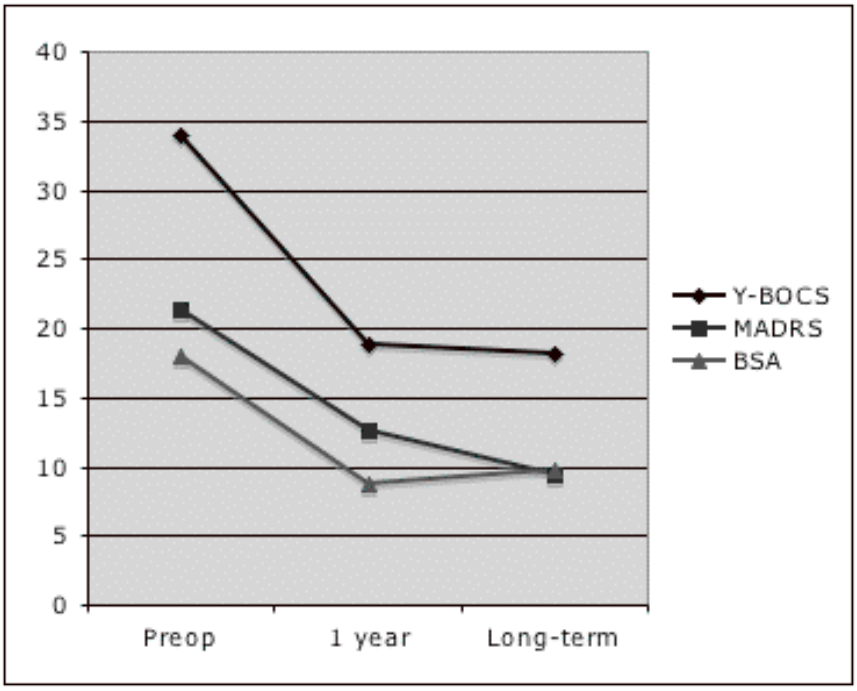


Figure 12. Symptom rating mean scores preoperatively, at 1-year and long-term follow-up.

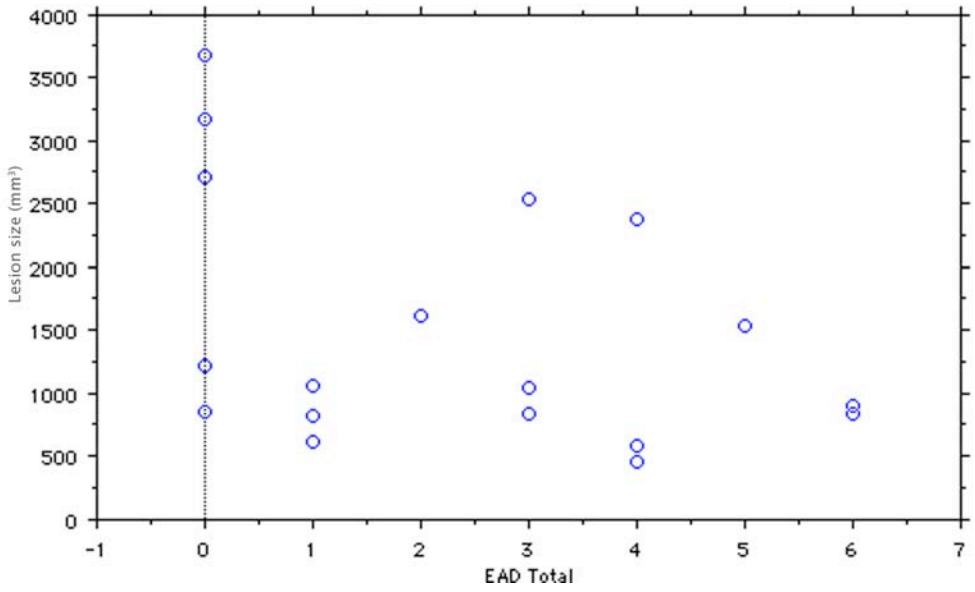


Figure 13. Right sided lesion size (Y-axis) and EAD total score (X-axis). The patient (id 20) with the largest lesion (22756 mm^3) was excluded from the display.

6 DISCUSSION

The aim of this thesis was to evaluate the long-term safety and efficacy of capsulotomy in anxiety disorders (Study I-III) and OCD (Study IV).

6.1 IS CAPSULOTOMY EFFECTIVE IN TREATING ANXIETY AND OCD?

6.1.1 The efficacy

In our two long-term follow-up studies of anxiety and OCD patients who had undergone capsulotomy, symptom reduction at both one-year and long-term follow-ups was significant. The symptom improvement must be considered impressive given the severity and chronicity of the patients' illness. The magnitude of the improvement is in line with standard treatments for anxiety disorders such as SSRIs and CBT (89, 90) and with previous capsulotomy studies (53, 56, 58).

6.1.2 Why isn't global functioning improved?

The global function as measured by the GAF does not show any substantial improvement in Study IV. A return to a normal functioning with for instance employment was hardly ever seen. In Study III, GAF had only been rated at long-term follow-up but was in line with the results of Study IV. Another study (58) found a strikingly similar postoperative GAF score. The long duration of illness in almost all patients should be taken into account. It may be extremely difficult to return to work from disability pension even if symptoms subside. It may also be that the long duration of illness had induced dysfunctional behavioral patterns not specific to illness that linger after symptom relief. However, in Study IV, the *self-rated* social disability rated with the Sheehan Disability Scale showed marked improvement.

My personal impression that includes insights from home visits and talking to the patient's relatives is that there was impairment in general functioning at long-term that was not explained by neither anxiety nor obsessive-compulsive or depressive symptoms but rather related to drive and motivation. Autism spectrum disorders such Asperger's syndrom have a high comorbidity with OCD (91). Undetected comorbidity with these disorders could in some cases be an explanation for the low global functioning at long-term follow-up. Another speculation would be that the remaining dysfunction is a remainder of OCD, much like negative symptoms in schizophrenia that the surgical intervention does not alleviate.

6.1.3 Which surgical method is the most effective?

Most patients included in this thesis were subjected to conventional thermosurgery. In Study IV, 9 patients underwent radiosurgery. Within the radiosurgery group there was considerable variation in the surgical method, that is, five patients received

exceptionally high doses of radiation and of these three cases the patients developed an adverse radiation reaction. Therefore, our radiosurgery sample is not comparable to those studies where other doses have been used. In the capsulotomy series performed at Brown University, Rhode Island, 180 Gy at two isocenters bilaterally is used (Georg Norén, personal communication), a dose considerably lower than what some of our patients received. We could not find any significant difference between radiosurgery and thermosurgery but given the small sample sizes and the variation within the group it is not possible to draw any general conclusion about the differential efficacy of the methods.

The mean Y-BOCS reduction from baseline to long-term follow-up was 47% in Study IV. In a recent long-term follow-up of cingulotomy (13), the corresponding figure was 29%. Kullberg reported a case series including both cingulotomy and capsulotomy cases and the efficacy of capsulotomy was higher (59). However, without a randomized head-to-head comparison between capsulotomy and cingulotomy, it is not possible to draw a firm conclusion on the differential efficacy of the methods.

We could not find any correlation between lesion size and symptom reduction in either of our studies. The two patients in Study IV that had the largest lesions, (Id 17 and 20) had a Y-BOCS score of 15 and 27 at long-term follow-up, indicating that even very large lesions can sometimes fail to relieve the patient from OCD.

6.1.4 Effect over time

After the first postoperative year there was generally no further improvement in neither of the samples. A report by Kihström et al (63) showed that the tissue reaction volume after radiosurgery may still be increasing after 3 years, suggesting that there may be late effects of the treatment. This was not observed in Study IV since the radiosurgery patients that responded did so already at the one-year follow-up. Our conclusion therefore is that, in contrast to an earlier report (92), improvement is generally maintained over time.

6.1.5 Are there differences across diagnoses?

Due to the small number of patients in each diagnostic group, any comparison between groups will be severely underpowered. Given this very important limitation, we found no difference between diagnoses. In the OCD patients of Study IV it could be speculated that the effect on the OCD symptomatology is not a direct effect on OCD but rather secondary to anxiety reduction, that makes obsessive intrusions less prone to evoke a behavioral response. The fact that capsulotomy is used for both depression, anxiety disorders and OCD may be an indication that the effect is not that specific. This efficacy across diagnostic boundaries is something that NMD shares with other, more common treatments such as the SSRIs.

6.1.6 What would the outcome have been without surgery?

In their unique 40-year follow-up, Skoog & Skoog (93) followed the course of OCD patients, originally assessed in the 1950s. Most of the patients improved over time and recovery was common. A similar pattern of recovery was seen in the Zurich study by Angst et al (94). Mataix-Cols and collegues (95) studied the temporal stability of individual OCD symptoms over 2 years and concluded that most patients maintained the symptoms and if symptoms changed they remained within the same symptom dimension. It is important to take into consideration the possibility that patients may improve even without treatment. On the other hand, patients, almost without exception, said at long-term follow-up that they would choose surgery again, indicative of their own estimation of their poor prognosis. The preoperative clinical impression in our studies, given the chronic state of the patients with illness duration of 20 years and more, was that no remission was in sight without treatment.

Due to the severity of the illness and the associated risk of suicide some have argued that patients would risk suicide if they were denied surgery. There has been some controversy as to whether anxiety disorders are independently associated with suicide risk or if the risk rather is associated with comorbid mood disorder. It has now been demonstrated that anxiety disorders are an independent risk factor for suicidal ideation and attempts (96). Anxiety patients have also been shown to be at greater risk for suicide than the normal population (97-99), but probably less at risk than depressed patients. In our studies the rate of patients that had made suicide attempts was similar before and after surgery. Two patients committed suicide postoperatively. Therefore, our studies do not provide support for a vital indication for surgery.

6.2 IS CAPSULOTOMY SAFE?

The majority of the patients did not experience any side effects. At the same time, we encountered more adverse effects of capsulotomy in our two samples than expected from the literature (55, 56, 60). Seventeen of totally 51 patients (33%) had executive problems, apathy or disinhibition. Not only were these adverse effects common, they also severely impacted functioning. The most common side effect was apathy and executive dysfunctioning whereas only a few patients developed disinhibition. Other complications were weight gain, epilepsy and urinary incontinence. Similar types and frequencies of adverse effects were seen in both anxiety and OCD patients. Adverse radiation reactions were obviously only seen in the OCD sample since radiosurgery was only applied in Study IV. We thus have to conclude that capsulotomy is not a safe procedure.

6.2.1 Is radiosurgery safer than conventional surgery?

Radiosurgery is non-invasive surgery, probably coming across as more “modern” than conventional surgery but is not safer per se. It is not meaningful to discuss the differences between surgical methods without taking lesion size into account. In both

the radiosurgery and the thermocapsulotomy group there was considerable variation within the surgical method, i.e. size of the intended thermolesion or radiation dose, leading to expected differences in lesion sizes. Radiosurgery may be a safer procedure at other radiation doses than those we used or with refined accuracy in lesion placement. Nevertheless, it is important to notice that large lesions does not explain why certain individuals had adverse effects and others not. Some patients were surprisingly intact after very large lesions whereas other had severe side effects after normal or even small lesions.

6.2.2 Why do some patients develop side effects and others not?

There is a large variation in how patients reacted to the lesioning in our samples of totally 51 patients. To be able to avoid future complications, it is essential to understand why some patients suffered from severe side effects while others were unaffected. The analysis of the characteristics of the surgical lesion has not yet been fruitful in explaining this. A further analysis of lesion localization is in preparation, which hopefully can provide the necessary answers. The side effects were seen across diagnosis and surgical method. Preoperative neuropsychological examination was only available in a few patients, therefore we do not know for certain if some patients may have been more vulnerable due to pre-existing cognitive problems.

6.2.3 Some comments on the assessment of side effects

6.2.3.1 KSP - normalization of personality?

In a study by Mindus and colleagues (100), 19 patients were studied before capsulotomy for OCD and at 1- and 8-year follow-up. The main finding was changes towards normalization on all 15 KSP scales at 1-year follow-up and significant reductions in anxiety proneness at the 8-year follow-up. Significant reductions in aggression-hostility, indirect aggression and guilt were observed at 8-year follow-up. The authors conclude, "adverse personality changes are not to be expected even many years after the operation". This normalization of self-reported personality after capsulotomy has been used (3, 60) as an argument for the safety of capsulotomy. However, the results have been challenged (2) as the validity of self-reported personality inventories in measuring adverse frontal events has not been proven. One of our main findings was that adverse effects on personality were clinically obvious despite "improvement" on the KSP on a group level. The type of personality changes, that were most incapacitating, namely those indicative of impaired frontal lobe functioning, are not within the scope of the KSP. Furthermore, the lack of insight which characterized some of our patients is likely to impair the validity of a self-assessment instrument such as the KSP. In our analysis of family and self-rated KSP in Study IV, there were large variations across different scales in the KSP in the correlation between family and self-rating. There was a good agreement on many scales including the anxiety related scales but poor correlation between the raters on scales such as the Psychastenia, Irritation and Socialization scales.

6.2.3.2 Face-to-face examinations

When Gösta Rylander did his research on patients with frontal lobe damage (40), he based his results on a thorough examination, including an astonishingly advanced neuropsychological assessment, but also on observations made during visits in the patients' homes. He even hired one lobotomy patient as a cook, although she "had difficulties in using new recipes and made ridiculous mistakes"(42). Rylander's personal observations added something to his testing and his characterization that a patient had "lost his soul" became despite its subjectiveness a very important argument against the indiscriminate use of lobotomy by Walter Freeman and others (38). In the spirit of Rylanders work, I would like to emphasize the importance of multimodal face-to-face evaluations that can take aspects of the patient's mental state into account that e.g. telephone follow-ups will miss.

6.2.3.3 Relatives – a window into our patients' world

For our studies, it turned out to be important that we interviewed the patients' relatives. The case report 1 in Study I is an example. When I asked this man, who now was considerably better in his anxiety disorder, what he did during the day he told me that he read books and watched TV. When I asked his wife the same question she told me "Oh, he reads the same book every day since 10 years!" It turned out to be a book for kids about cats.

6.2.3.4 Neuropsychological testing

In Study I only postoperative testing was available and results showed subnormal results, especially in the patients that displayed clinical signs of executive disfunction and apathy. Fourteen patients in Study IV were classified as dysexecutive at long-term follow up based on neuropsychological testing. Our sample was characterized by more pronounced neuropsychological deficits than in most OCD samples reported (101, 102). Interestingly, symptom severity in OCD has not been shown to be correlated to neuropsychological functioning (101) and there might therefore be other, unknown characteristics of our sample that explain the severity of the neuropsychological impairment. Executive dysfunction has not consistently been observed in OCD patients compared to normal controls (101, 102).

The possibility of pre- and postoperative comparisons was limited since only a minority of the patients in Study IV and none in Study I were adequately assessed before the operation. A comparison in seven patients indicated a worse performance postoperatively in tests of executive functions. Nyman et al (103, 104) have reported neuropsychological test results in both capsulotomy patients and patients on waiting list for capsulotomy. Our findings were in line with the previous findings regarding postoperative performance in capsulotomy (103-105). In the pre- vs. postoperative comparison in the small study of Nyman et al (104) a subgroup had more perseverative errors in the WCST. In Study IV, the reduction of OCD symptoms was not

accompanied by an improvement in executive performance. Similar lack of correspondence between neuropsychological functions and symptom improvement has been observed with other forms of treatment (106).

6.2.4 Other studies did not report safety problems

Most other capsulotomy studies (55-58, 60, 107) did not report the same side effect frequency. We can only speculate why that may be. It may be that our patients had some, for us unknown feature that made them especially vulnerable to develop side effects and thus, that the same safety problems are not to be encountered in other case series. However, it is not evident that our patients are different from other samples. It may also be speculated that there was something in the surgical method that was used at our site that resulted in differences in lesions from others sites. Unfortunately, there is a lack of published reports on the outcome from other sites, therefore this question cannot be resolved at this time. It may be that the multimodal face-to-face follow-up that we used was more sensitive to identify adverse effects that others have missed. A systematic evaluation of potential safety problems appears essential in studies of neurosurgery for mental disorders.

6.3 INTO THE GARDEN OF GOOD AND EVIL: ETHICAL CONSIDERATIONS

6.3.1 Burckhardt's dilemma

The possibility of symptom relief and adverse effects takes us back to the first "psychosurgeon" Gottlieb Burckhardt who already in 1891 was caught between the *Melius anceps remedium quam nullum* (Better an uncertain remedy than none at all) and the more cautious *Primum non nocere* (First, do no harm). Clearly, there is no easy answer since withholding even a potentially dangerous treatment comes with the price of missing the possible benefit of the treatment. To make things harder, patients with the most pronounced change in personality (i.e. disinhibition) stated that they had never been better and one patient even claimed to have found her true self.

6.3.2 Who decides?

If the disinhibited patient, whose behavior clearly makes her relatives suffer, claims that she does not have any symptoms and is feeling well, who is to decide on the general outcome of her treatment? Autonomy is a widely cherished ideal and in its most restricted meaning it is about self-determination. Living an autonomous life is to live according to our own wishes, desires and according to our own ideas of a good life. In that sense, patients that have become disinhibited after surgery can still be considered to be autonomous, probably even more so than before surgery. This conceptualization of autonomy does not contain in itself any idea of what an ideal or moral life is, since self-determination per se does not imply good, or for that matter evil. A pedophile could be conceptualized as very autonomous. To make autonomy

useful in this context, the capacity to make decisions and understand their consequences for others must be taken into account. For a more educated discussion on what autonomy is and is not, cf. (108). Personally, I agree with John Donne who in 1624 (109) captured the essence of this issue:

> No man is an island, entire of itself
> every man is a piece of the continent, a part of the main

6.3.3 Informed consent

In the past, psychosurgery occasionally has been used as an involuntary treatment. Today we regard this as an abuse, even if the outcome in a specific patient was beneficial. Nowadays, patients give their informed consent to neurosurgical procedures such as capsulotomy. Nevertheless, we cannot simply assume that patients are capable to consent just because they are willing to undergo the treatment (110). Having the capacity to consent must include basic mental skills and therefore a child or a mentally retarded patient would not be considered eligible for surgery. Informed consent obviously requires that the patient has obtained correct information about the possible risks and benefits of a procedure. Autonomy is a prerequisite for free choice (110, 111). Consenting to capsulotomy is making a choice, and in this particular case a choice that irreversibly alters brain functioning. Now, consider a severely ill OCD patient that has tried all available treatment to no avail, is she free to choose when considering capsulotomy, that is, has she the choice of different options? Or is the desperate patient impaired in her capacity to give an informed consent? This is a common problem in many other medical conditions, such as cancer or chronic pain, where the patient's choice is limited by his or her illness. Another complication is that, if *who we are* is changed after a treatment, even if it's for the better, how is the patient then able to evaluate this change? Even if we can't answer these difficult questions, in clinical practice, these are the questions that we should be aware of when discussing the treatment with patients.

6.3.4 Compassion and the unusual ones

Severe and treatment refractory illness often calls for desperate measures. Pharmacological treatment options are more regulated than medical devices and surgery since extensive legislation is limiting its use. There is a risk that compassionate use of methods for unusual patients is not followed by proper evaluation. I would argue that it is especially important in severe illness and in unusual treatments such as capsulotomy to ensure that scientific evidence is gathered. The desperate situation of the patients and our own compassion cannot let us make an exception from this rule. To conclude, all centers performing neurosurgery for mental disorders must include their patients in studies that can contribute to a more solid evidence base for the methods.

The paucity of published reports in recent years, indicate that more could be done to gather further evidence.

6.4 NEUROANATOMICAL CONSIDERATIONS

6.4.1 Are the side effects related to a certain type of lesion?

In Study II we tried to find correlates of the anterior-posterior lesion location and the outcome without success. In neither Study II nor IV we could find firm evidence for a relationship between lesion size and side effects. It is our hope that further analysis of the MRI data on both the axial and the coronal planes in Study IV can bring some light into the optimal lesion placement. There were large differences between the patients' side effects pointing towards an effect on different parts of the prefrontal cortex. Interindividual variation in the wiring of the internal capsule could also contribute to the differences in vulnerability.

6.4.2 Was the right side the right side?

Previous research (57) indicated that a certain right-sided capsulotomy lesion was a prerequisite for treatment response in OCD. This hypothesis did not prove to be correct, at least not in non-OCD anxiety, and given the variability in lesion placement as evidenced by Study II the validity of the previous findings is unclear. As for the OCD patients of Study IV, we await further analysis of the lesion site. Four patients in Study IV underwent unilateral right-sided thermocapsulotomy but the results failed to impress since the one of the four who was in remission at long-term follow-up instead was incapacitated by somatoform symptoms, living in a nursing home.

6.4.3 Next stop: ventral striatum?

Based on a possible role of the nucleus accumbens in OCD and the clinical impression that ventrally placed capsulotomy lesions are more effective, Sturm et al (28) stimulated four patients with Deep Brain Stimulation (DBS) in the right-sided nucleus accumbens with promising results. Despite interesting theoretical reasons and a clinical impression, there is no published evidence on where in the dorso-ventral plane of the anterior capsule the surgeon should place the lesions. The only way to gain empirical evidence is to systematically study the lesions and the outcome and we aim to contribute to that with a future analysis of the lesions in the coronal plane in Study IV.

6.5 LIMITATIONS

6.5.1 Evaluation bias

The studies were not randomized-controlled trials, a fundamental weakness shared with all other NMD studies to date. Some of the other potential biases encountered in some earlier (cf page 10) studies were avoided since the principal author was not involved in preoperative treatment of the patients and he did not select patients for surgery. Another strength of these studies is that data loss was limited and that face-to-face interviews with patients and their relatives were performed.

6.5.2 Power

The relatively small sample sizes yield a low power to detect small and medium sized differences. This is an inherent problem in studies of infrequent treatments. Fortunately, we found very significant improvements in our primary outcome measures and the power issue does not weaken these findings.

6.5.3 Regression towards the mean

The regression towards the mean effect (112) is the phenomenon that a variable that is extreme on its first measurement will tend to be closer to the center of distribution for a later measurement. This is particularly important in non-randomized medical trials that use inclusion criteria such as a high symptom score. Waxing and waning of symptoms will also contribute to this effect. In our studies we only included patients with severe symptomatology, therefore the reduction at later follow-ups may to some extent be attributable to the regression towards the mean effect.

6.5.4 Rating scales

Most of the Swedish versions of the rating scales had not been validated and the EAD scale was constructed for Study IV and its psychometric properties are not known.

6.5.5 Preoperative data incomplete

Some important preoperative data, e.g. neuropsychological testing, in missing to a various extent in the studies. This was an inevitable consequence of the long-term follow-up study design but nevertheless limits the conclusivity of the neuropsychological results.

6.5.6 Causality

The long follow-up period will for each patients include many life events, in some cases comorbid disorders and other events that will affect the outcome at long-term follow-up. A temporal relationship between the surgical intervention and the state of the patient should therefore not be confused with a causal relationship.

7 MS. A AND MS. S: WHAT HAPPENED?

Ms. A

Feeling increasingly desperate, she took the initiative to be evaluated for capsulotomy, which was performed at age 40. At the two-month follow-up most avoidance behavior had dissipated and she needed no medication. Within a year she was back at her old job and reported that her social anxiety “was a closed chapter”. At long-term follow up, at age 52, she reports leading a life without limitations and states, “without the operation I wouldn’t be alive today”. Her anxiety symptoms were gone and there were no adverse effects of the procedure.

Ms S

At age 50, after evaluation and approval for capsulotomy, she became, to our knowledge the world’s first OCD patient to undergo Deep Brain Stimulation. The treatment was unsuccessful, electrodes were extracted and she went on to have a bilateral thermocapsulotomy. After initial improvement her OCD worsened and was was back to baseline severity at long-term follow-up. She gained almost 20 kg in her first postoperative year and has persistent urinary incontinence. Intensive trials both with pharmacological and psychological treatment have had modest effects. Her relatives describe her as apathetic and displaying lack of initiative. Ms S makes no effort to resist the obsessive intrusions. Neuropsychological evaluation confirms a decline in executive functioning.

8 GENERAL CONCLUSIONS

a. Capsulotomy is effective in reducing symptoms in both OCD and other anxiety disorders. Global functioning did not return to normal after surgery but the evidence suggests that most patients will remain incapacitated. Self-rated anxiety proneness and depressive symptoms decreases after surgery.
b. About every third patient experienced apathy, executive problems or disinhibition at long-term follow up. Other adverse effects reported included epileptic seizures, urinary incontinence and weight gain. Capsulotomy is not a safe procedure.
c. We could not identify lesion characteristics that could explain the differences in outcome. We could not confirm the hypothesis of a certain right-sided lesion as a prerequisite for treatment response.
d. Interviews with the patients' relatives are crucial to correctly identify potential adverse effects of surgery.
e. In the light of its potential adverse effects and the limited evidence of the procedure, capsulotomy clearly needs to be studied more extensively. Until such studies are at hand, NMD procedures should only be performed within study protocols and are preferably regarded as experimental treatments.

8.1 WHAT NOW? FUTURE DIRECTIONS

Since OCD is the main indication for NMD, this will likely be the focus of future research in this field. As evidenced by the studies of this thesis, capsulotomy is followed by unacceptably high risks of adverse effects. These adverse effects are often permanent. There is yet no evidence on how ablative NMD can be made safe. A method that is reversible would therefore be preferable. One such method is Deep Brain Stimulation, were electrically stimulated electrodes are implanted in the brain. There are several centers currently implanting DBS devices in OCD patients and the question of optimal lesion placement is central to the development in this field. We hope that further analysis of the lesion topography in Study IV, especially in the dorso-ventral direction, can elucidate this issue regarding both the positive and negative effects. Certainly, DBS is to be preferred over ablative NMD from a safety standpoint even though only very limited information is at hand on the safety of DBS in OCD. Further research should also explore non-surgical treatment options such as intensive CBT programs, something that was unavailable preoperatively to the patients of this thesis. Neurosurgery also provides a unique opportunity to study brain and behavior. Hopefully, more sophisticated techniques and hypotheses in the future can derive insights from these treatments that can eventually be helpful to the patients.

9 ACKNOWLEDGEMENTS

First of all, I want to express my sincere gratitude to the patients and their relatives for letting me (and all the rating scales) into their lives.

My thanks also to:

Late Professor Per Mindus, who was my first supervisor and sadly passed away only a year after I got to know him. Per was spectacular in many ways. Thanks for believing in me.

My principal supervisor Professor emerita Marie Åsberg who took me on as a scientific orphan after Per Mindus died. Thank you for your intellectual clarity and for teaching me the value of independence and endurance.

My assistant supervisor Pär Svanborg who always has been a rock to hold on to in times of scientific confusion, always honest, friendly and always helping out. His introduction to opera has been very appreciated many late nights when using song in the battle against distraction from this work.

My second assistant supervisor Associate Professor Gunnar Edman for providing expertise in statistics and, most of the times, solid advice on movies.

Former head of the Psykiatricentrum Peter Nordström and current head of Psykiatri Nordväst, Maj-Britt Larsson-Gladh for proving fertile soil for innovation and research.

Professor emeritus Björn Meyerson for all the time and effort put into this project. Working with Björn in his old-school room, with some classical music playing gently on the radio, has always been a pleasure.

Friend and co-author Sergej Andréewitch with whom I have travelled around the world many times, always a pleasure, even if he sleeps on the flights when I, out of restlessness, have the urge to speak.

Psychologists Andreas Karlsson, Karin Flyckt and Håkan Nyman for neuropsychological expertice.

Professor of Neuroradiology Kaj Ericson for helping me navigating the shores of the basal forebrain.

Chairperson Martin Ingvar and the Department of Clinical Neuroscience, for providing research opportunities.

Secretaries Lisbeth Eriksson, Marita Signarsson, Marianne Youssefi, Yvonne Sedlenieks and research nurse Monica Hellberg for good-humored help with paperwork.

Everyone at the Anxiety Disorders Program (Sergej Andréewitch, Jan Bergström, Annelie Holmström, Brjánn Ljótsson, Lena Lindberg and Yvonne Sedlenieks) for being my closest allies in the war on anxiety disorders.

Peter Csatlós, Maria Wiklander, Hanna Sahlin-Berg, Per Lundström, Lena Lindberg, Eva Andersson and Marianne Ask of the Borderline unit, you're great!

I am most grateful to all the colleagues at the Psychiatric Clinic; particularly Associate Professor Nils Lindefors, who without being directly involved in this project, has pushed me in the right direction. My former clinical supervisor Gabriella Oxenstierna for being so serious about what it's all about; the patients. Björn Mårtensson, who always is there for good advice. All the residents and all the staff for creating an intellectual hothouse. Kaj Forslund who asked me, back in medical school, what speciality I wanted to go into and when I answered psychiatry he said "I thought so". When a psychiatrist says that it can mean at least two things.

To the ones funding this research: the National Board of Health and Welfare, the Swedish Research Council, Stiftelsen Bror Gadelius Minnesfond, Psykiatrifonden, Pfizer, Lundbeckstiftelsen, Organons stiftelse and funds from the Karolinska Institutet.

Professor Arne Öhman who, for reasons unknown to me, seems to think that I know something. Markus Heilig for speed. Professor Alexander Bystritsky, Jamie Feusner and Arie Winograd of the UCLA for being the midwives of our anxiety disorders program. David Mataix-Cols for inspiration.

When I was a hyperactive and restless boy, my father used to say to me: "Zuerst in die Schule, dann in den Zirkus". I haven't decided on what circus to join yet, but anyway, my appreciation to my parents and to my brother Andreas and my sister Birgitta for everything. My brother also for kindness and help with everything from cooking to cover design.

To my dear friends Ulrik Sartipy, Wouk Stannervik, Johan Person, Tobias Lekberg and Mini Ruiz whom I met in the first week of medical school. For all the fun we had!

Brainiacs Erik Lindeman, Predrag Petrovic and Kalle Malmberg for creativity and for the ability to search and research.

Finally, to myself. From her to eternity.

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