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Psychiatric Neurotherapeutics

Contemporary Surgical and Device-Based Treatments

Humana Press

Current Clinical Psychiatry

Series editor
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Current Clinical Psychiatry
ISBN 978-1-934115-50-3 ISBN 978-1-59745-495-7 (eBook)
DOI 10.1007/978-1-59745-495-7

Library of Congress Control Number: 2015956767

Printed on acid-free paper

This Humana Press imprint is published by Springer Nature
The registered company is Springer Science+Business Media LLC New York.

Preface

Treatment options for patients suffering from affective, behavioral, or cognitive disorders include psychotherapy, pharmacotherapy, and therapeutic neuromodulation. This book focuses on the latter.

Neuromodulation techniques are also commonly known under the labels of *brain stimulation*, *somatic therapies*, or more generally, *psychiatric neurotherapeutics*. They are a group of device-based technologies that target specific neural structures via surgical ablation or electromagnetic modulation, with the goal of therapeutically modifying pathological patterns of brain activity and circuit connectivity. These techniques grow from the development of a systems neuroscience paradigm that highlights the role of neural circuits and their processing strategies to understand healthy brain function, neuropsychiatric pathophysiology, and therapeutic mechanisms of action.

Neuromodulation techniques can be divided into three general groups: invasive, convulsive and noninvasive. Invasive treatments require the surgical implantation of stimulating electrodes (or the surgical disconnection of aberrant pathways via focal lesions) and include ablative limbic surgeries, deep brain stimulation (DBS), and vagus nerve stimulation (VNS). Noninvasive techniques are able to modulate brain activity transcranially, without surgical intervention, and include transcranial magnetic stimulation (TMS) as its most paradigmatic modality. convulsive treatments include Electroconvulsive therapy (ECT), the oldest of all neuromodulation therapies, and occupy a space in between the two previous

categories, as they do not require surgical intervention but need general anesthesia and the induction of a generalized seizure.

In this book, we aim to offer the reader an overview of the state of the art of therapeutic neuromodulation in Psychiatry, discussing the techniques and biophysical principles, the mechanisms of action, animal and human research, clinical indications, clinical practice, safety considerations, and future directions. The book starts with two chapters that review our understanding of major depressive disorder (MDD) (Chap. 1) and obsessive compulsive disorder (OCD) (Chap. 2), as these are the two syndromes for which most techniques are currently indicated with formal regulatory approval. We follow with a chapter that summarizes our understanding of the pathophysiology of these two conditions from neuroimaging studies, with a systems neuroscience approach and a focus on brain circuits (Chap. 3). With this background, we start discussing the oldest and most commonly used neuromodulation treatment, ECT (Chap. 4), and follow with a description of surgical psychiatric therapeutics including VNS (Chap. 5), limbic ablations (Chap. 6), and DBS (Chap. 7). Moving from more to less invasive treatments, Chap. 8 describes TMS and other noninvasive techniques. After reviewing each of these modalities in detail, the book finishes with a chapter on animal studies, presenting the basic and translational work that sustains the development of human neuroscience research and clinical applications (Chap. 9), and the last chapter on the future of Neurosurgery with a focus on functional, stereotactic, and device-based interventions in Psychiatry (Chap. 10).

The field of psychiatric neurotherapeutics is evolving very fast, incorporating new technologies, new indications, and more effective and safer uses of established techniques. These advances are possible due to paradigm-changing scientific discoveries, but also thanks to the growing clinical knowledge that emerges from academic and community clinics worldwide, as many of these treatments become standard of care. In this rapidly changing environment, this book provides a solid basis to understand the technical, neurobiological, and clinical principles of these interventions today, but it should also offer a general framework to

assimilate future developments. We hope this text will prove useful to clinicians and researchers alike and will fuel future innovations that advance this exciting field for the ultimate benefit of our patients.

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Depression: Current Conceptual Trends

1

Ziad Nahas

1.1 Introduction

Sadness is a normal reaction to life's hurdles, hinders, and disappointments. Depression is much more. Whether patients are experiencing emotional pain or feeling lifeless and empty, their symptoms engulf all aspects of their lives, interfering with their ability to be productive, to engage in meaningful relationships, and to attend to activities of daily living. Even basic body functions like eating and sleeping are disrupted and their physical health is often compromised. Feelings of hopelessness and worthlessness can be unrelenting and most affected individuals contemplate dying. Five to fifteen percent do commit suicide.

The World Health Organization (WHO) projects that depression [1, 2] will be second in medical burden only to ischemic heart disease [3]. The annual economic burden of depression in the United States was estimated at approximately $44 billion in 1990. Of the total costs, $12.4 billion was attributed to direct costs, $23.8 billion was associated with indirect costs to employers and society due to absenteeism and decreased worked productivity, and $7.5

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J.A. Camprodon et al. (eds.), *Psychiatric Neurotherapeutics*, Current Clinical Psychiatry, DOI 10.1007/978-1-59745-495-7_1

billion was associated with depression-related suicide [4]. Of all depressed individuals, only 10 % meet criteria for severe for treatment-resistant depression (TRD) [5] and account for over half the annual costs associated with treatment for depression [6]. Other studies have confirmed these estimates and shown that annual medical expenditures of TRD patients are double than non-TRD cohorts [7].

The incidence of depression is around 20 % worldwide [8]. Of the 14 million patients with depression in the United States, only 3.2 million are adequately treated following expert guidelines like ones proposed by the American Psychiatric Association [8–10]. The success rate with pharmacological treatments is not high [11], and short-term antidepressant drugs are moderately effective when compared to placebo [12]. Even after achieving a relief from depressive symptoms, 75 % will experience a recurrence of their symptoms [13]. We have shown in a meta-analysis across 2009 patients randomized to active antidepressant or placebo that the relapse rate is 23 and 51 % at 1 year [14]. In TRD patients, relapses can be as high as 50 % within 6 months despite adequate maintenance therapy. In turn, patients with repeated depressive episodes have even higher risks for relapse [15] and become more vulnerable to stress [16], and the course of their illness worsens. All this leads to longer episode durations and shorter inter-episode periods in between [17]. So how does depression develop, what is our current understanding of its pathophysiology, and how can we begin conceptualizing new treatment approaches that could confer long and sustained benefits?

1.2 Genetics of Depression

The vulnerability to depression can be inherited. Individuals with a parent or sibling that has had major depression are 1.5–3 times more likely to develop the condition than those who do not have a close relative with the condition. Bipolar disorder has a stronger genetic influence. Of those with bipolar disorder, approximately 50 % of them have a parent with a history of clinical depression. When a mother or father has bipolar disorder, their child will have a 25 % chance of developing some type of clinical depression.

If both parents have bipolar disorder, the chance of their child also developing bipolar disorder is between 50 and 75 %. Brothers and sisters of those with bipolar disorder may be 8–18 times more likely to develop bipolar disorder and 2–10 times more likely to develop major depressive disorder than others with no such siblings.

For a complex illness like depression, it is unlikely that a single gene will explain it all. So far, the large majority of genetic studies in major depression have focused on the polymorphisms relevant to monoaminergic neurotransmission. The effects though are not large. The polymorphism of the serotonin transporter promoter region (5-HTTLPR) has been linked to bipolar disorder, to suicidal behavior, and to stress vulnerability. It appears that such vulnerability is mostly associated with childhood and developmental trauma. Some studies have attempted to study the association between genes related to neurotoxic or neurotrophic processes, like brain-derived neurotrophic factor (BDNF) with limited results. Others have focused on inflammation, regulation of cortisol secretion by the hypothalamic-pituitary axis, sleep, and circadian rhythms. Whole-genome association studies are expected to yield more results, but the search remains elusive.

1.3 Stress and Depression

A stressful psychosocial event either precipitates depressive symptoms or exacerbates a preexisting depressive. The impact of external events is particularly evident in patients who have a genetic vulnerability like the serotonin transporter short allele [18]. Gender and age also modulate the impact of stress [19]. External stressors that originally led to an active episode can exert a positive sensitizing influence, ultimately leading to an autonomous progression of the illness [20, 21]. Patients can often identify what may have triggered their first or second depressive episode, but after a chronic course and repeated episodes, they cannot identify why their symptoms recurred or are surprised to how disproportionate their response to a stressful event is. Post [20] proposes a model of sensitization and kindling to explain the processes occurring in a lifetime of bipolar disorder patients. External stressors originally lead to a depressive

or manic episode and exert a positive sensitizing influence, ultimately leading to an autonomous progression of the illness. Reemergence of symptoms is clearly affected by the underlying state of the brain at the time of stress, and neurotrophic factors can play a role in limiting such progression. Presumably, a similar process occurs in recurrent unipolar depression. Such clinical phenomenon is at the heart of the emergent problem of TRD and has not been adequately studied or modeled in laboratory settings.

The repercussions of stress are determined by a host of characteristics that include its severity, chronicity, and personal relevance to the individual [16, 22, 23]. Chronic stress leads to changes in neurotransmitter neuropeptide concentrations as well as the anatomy of brain structures, which in turn alter the physiology and the adaptive responses of the neocortical regions [24] and cause increased activity in ventral limbic and paralimbic areas [25–29] (the functional neuroanatomy of depression is presented more in details further in this chapter and later in this book). Similar functional changes are associated with sadness, a core symptom of depression and a primary emotional response to loss [30]. These implicated networks receive direct and indirect signals [31] from the internal and external world through the brainstem nuclei, the hypothalamus, the insula, the cingulate, and various secondary associative areas [32]. These various regions play a regulatory role in maintaining homeostasis [33]. Stress can impair the mechanisms that protect the nervous system. It is also known to activate preprogrammed neuronal cell death. In essence, depressed patients are caught in a cycle: stress leads to fundamental alterations in brain chemistry that compromise their ability to cope with one of the initial causes of the illness—stress itself.

Direct Excitotoxicity: Stress causes neuronal damage through either an alteration of cellular energy and a decrease in brain-derived neurotrophic factor (BDNF) expression or through an increase in glutaminergic transmission that results in an increase of intracellular Ca+ and oxygen free radicals [34]. These different pathways promote neuron endangerment and are thought to contribute to the emergence of depressive states. They may also lead to hippocampal atrophy [26, 35], the disruption of activity in connected regions like the amygdala or prefrontal cortex [36], and poor feedback control of

the hypothalamic-pituitary axis (HPA) [37]. Remission may occur when a certain modulation of dysfunctional limbic-cortical interactions takes place [38]. Direct injections of BDNF in the hippocampus also reduce immobility time on the FST [39]. The cAMP response element-binding protein (CREB) is a key mediator of responses that underlie survival, memory, and plasticity of the nervous system. Chronic treatment of rodents with different classes of antidepressants, lithium [40], or electroconvulsive therapy [41] dramatically increases hippocampal levels of CREB gene transcription.

Apoptosis: In parallel, apoptosis, or programmed cell death, also appears to be linked to the pathophysiology of depression [42, 43]. Apoptosis is characterized by structural changes that ultimately lead to cell disintegration. The process is activated by a group of cysteine proteases known as caspases. Bcl-2 and related members of this family of proteins regulate the release of cytochrome *c* from mitochondria into the cytoplasm, which in turn mediates the mitochondrial pathway of apoptosis. It is tightly balanced between antiapoptotic (Bcl-2 and Bcl-xl) and proapoptotic (Bax). Interestingly, both fluoxetine [44] and moclobemide [45] have been demonstrated to upregulate Bcl-2 in purified mitochondria and isolated neural stem cells, respectively. In one of the most comprehensive studies to date, chronic mild stress model and antidepressant drugs exerted opposite effects on Bcl-2, Bcl-xl, and Bax in a region-specific manner in limbic brain regions. We have recently shown that deep brain stimulation to the infra-limbic region also modulates Bcl-2 in the hippocampus. So it appears that without the downregulation of proapototic mechanisms in brain regions and areas critical for mood regulation (like the hippocampus), antidepressants may not exert sustainable therapeutic benefits.

1.4 Emotion Regulation

Emotion regulation involves the ability to modulate the intensity and quality of responses to emotional stimuli, involving both automatic and controlled regulatory processes [46, 47]. Disruptions in

the control of emotion play a central role in mood and anxiety disorders [48–50]. A feature of depression is the inability to disengage from negative memories, feelings, and thoughts and engage the outside world with flexibility [51–53]. Negative emotions can also distract away from other cognitive demands [54–57] and make patients not able to cope with daily life needs [58]. An effective antidepressant treatment has to reduce this strong focus on negativity and allow the patients to appraise themselves and their world with a wider range of experiences.

Cognitive regulation of emotion involves directing attention to less intense aspects of an emotional stimulus or consciously altering the meaning of an emotion-eliciting stimulus [59, 60]. This "reappraisal" strategy has been shown to decrease the intensity of self-reported negative affective experience [60–62]. It is associated with increased activation in areas of the lateral and medial prefrontal cortex thought to support cognitive control (cf., [63]) and decreased activation of the amygdala, suggesting decreased emotional reactivity [61, 64–69].

1.5 Functional Neuroanatomy of Depression

Pierre Paul Broca first coined the term "limbic," using it to refer to the structures forming a loop in the middle of the brain that he posited were important in regulating emotion [70]. This circuit was further detailed by Papez [71] and elaborated within the larger concept of the triune brain [72]. Schematically, the limbic system and its connected brain stem structures are the middle of three concentric layers and unique to mammals. Alexander and colleagues [73] highlighted the interconnections between the subcortical structures and the prefrontal cortex. They described at least five important ganglia-thalamo-cortical functional working loops. Some researchers have sought to use this framework to explain how prefrontal lobe pathology might result in the symptoms of clinical depression [74].

We have made considerable progress in understanding the brain regions involved in mood dysregulation. Sadness and depressive illness are both associated with decreased activity in dorsal neocortical regions and relative increased activity in ventral limbic

and paralimbic areas [25]. In fact, increased regional cerebral blood flow and metabolism have been shown (but not always [75]) in the amygdala, orbitofrontal cortex, and medial thalamus and decrease in the dorsomedial/dorsal anterolateral PFC, subgenual ACC, and dorsal ACC relative to healthy control subjects. Failure of these subsets is hypothesized to explain the combination of clinical symptoms seen in depressed patients (i.e., mood, motor, cognitive, vegetative symptoms) [76]. These regions may be differentially affected in subtypes of depression [37]. Other important regions include the hippocampus [26], insula [32], and midbrain monoamine nuclei. Underlying structural abnormalities (reduction in volume or glia density) may also contribute to these dysfunctions [27–29]. Other factors to be considered in interpreting these results include the state of the disease, the inherited traits of the individual and genetic susceptibility [77], and the type of response to treatment. Mood, at any given time, is a continuous adaptive process. This implies that although certain localized activity changes can be identified, it is important to begin addressing the dynamic interplay within the system.

Many researchers are attempting to model mood systems based on human and animal known anatomical interconnections. Mayberg proposes that illness remission occurs when there is appropriate modulation of dysfunctional limbic-cortical interactions, an effect facilitated by various forms of treatment from antidepressant psychopharmacology that may initially regulate subcortical areas and later lead to a modulation of prefrontal regions (down-top model) [78]. The reverse may be observed with cognitive psychotherapy (top-down model).

1.6 The Anterior versus Lateral Network: Two Complementary Modes

The prefrontal cortex is divided into distinct cytoarchitectonic regions. While it is widely held that prefrontal cortex is involved in cognitive functions, the most anterior or rostral regions are believed to process higher-order abstract thinking and emotion cognitive integration. The frontopolar and lateral prefrontal cortex are thus anatomically distinct regions and part of two complementary

neuronal networks: one that attends to internal states and another that engages the individual with the outside world. Both networks are intricately tied to depressive symptoms.

The frontal pole has distinctly higher number of dendritic spines per cell and lower density of cell bodies than any other prefrontal region [79, 80]. Its rich connections are directed to the cingulate cortex including subgenual cortex or BA25 and precuneus/posterior cingulate [81], orbitofrontal cortex, and dorsolateral prefrontal cortex [80, 82], all critical regions in mood regulation. The frontal pole is an integrative center for cognitive and emotional processing with higher-level mnemonic control operations, control of emotions, memory, and motivation. The medial prefrontal cortex, which extends to the frontal pole (Brodmann Area 10), is also involved in self-reference [83], in reflective self-awareness [84], and in attributing mental states to others ("the theory of mind") [85].

The anterior/medial frontal lobe is also part of a distributed network extending caudally, known as the "default-mode" network [86]. These "resting-state" regions consist of largely medially located brain structures that decrease their activity when individuals attend to cognitively demanding, external stimuli [87].

The mid-lateral frontal regions (BA 9 and 46) maintain preferential bidirectional connections with multimodal temporal areas, on the one hand, and paralimbic areas, such as the cingulate, the retrosplenial cortex, and the rostral temporal cortex, on the other hand [88]. The dorsal regions are involved in the monitoring of information in working memory and the ventral regions are involved in active judgments on information held in posterior cortical association regions that are necessary for active retrieval and encoding of information. They play a critical role in organizing, monitoring, verification of information, attending to emotion stimuli, and reappraisal (Fig. 1.1).

1.7 The Impasse in Mood Disorder Research: The Need for a Paradigm Shift

Since the advent of the first serotonin reuptake inhibitor (SSRI) to the US market back in 1989, the diagnosis and treatment of depression have continued to become more widespread. Yet despite this

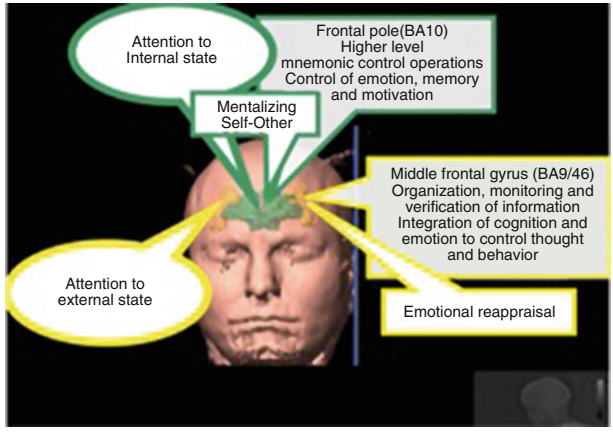

Fig. 1.1 Prefrontal cognitive and emotion integration anterior/medial (*green*) versus lateral (*yellow*) functions. Note that in this proposal, EpCS leads will be placed bilaterally and anterior and lateral prefrontal region (total four leads) to "tap into" both internal and external attention emotion regulation networks

major public health improvement, evidence suggests that treatment-resistant depression is on the rise, and with this serious disease come greater costs and higher morbidity and mortality rates [2]. Even in randomized controlled trials of nonresistant, uncomplicated major depressive disorder (MDD), only 50–60 % respond to any one medication, and of this group, only two-thirds (or 35 % of the initial group) become symptom-free. The Agency for Health Care Policy and Research original meta-analyses were later confirmed in subsequent studies in primary care settings [11]. Similarly, antidepressant drugs are found to have mild to moderate effect sizes when compared to placebo [12]. The results of the Sequenced Treatment Alternatives to Relieve Depression (STAR-D) trial demonstrate the limitations of a psychopharmacological approach to depression [89]. The STAR-D also illustrates a pattern of diminishing clinical returns: each successive pharmacological treatment failure predicted a worse prognosis of a subsequent trial. The STAR-D showed that after three successive pharmacological treatment strategies at the very best, only 67 % of all patients remit. Practicing clinicians often have to switch their patients to other treatments or combine medications. Even if some

symptom benefit can be obtained with three to four medications simultaneously, the medical risks and side effect burden can become excessive. Unfortunately, even for the few patients who reach remission, a majority relapses within few months. And whereas the original purpose of most widely used antidepressants was for acute treatment, their roles progressed to maintenance and relapse prevention as well as treating bereavement and loss [2].

Some researchers suggest that the increase in indiscriminant antidepressant use is directly associated with the increase in duration of each depressive episode and perhaps is playing a role in the chronicity of the illness [90]. This point is difficult to prove prospectively, but naturalistic studies show that depressive episodes are shorter in nonmedication users than in ones taking prescribed antidepressants (although these studies can be confounded by a different severity or types of depressive illness) [2]. Paradoxically, subjects taking antidepressant medications for longer periods may be more likely to relapse upon discontinuation [91].

Yet despite their limitations, there is little doubt that pharmacological treatments have definitively helped millions of patients. However, the concern remains that with the lack of reliable biomarkers for the different subtypes of depressive diseases, the use of the same pharmacologic interventions at all stages of acute, recovery, and maintenance treatment of depression may be associated with the emergence of TRD.

1.8 Current Paradigm and Its Limitations

At any given time, mood is a continuous state of adaptive processes. When stress becomes chronic, persistent changes in neurotransmitters and neuropeptide concentrations and the anatomy of brain structures alter the physiology and the responsiveness characteristic of the prestress homeostasis [24]. Adding an exogenous drug propels the system to a third state, where a variable degree of symptom resolution can be associated with side effects, the compliance constraints, and the potential ill effects of being in a pharmacological phase-locked state. To illustrate this point, and borrowing from chemical engineering literature, pharmacotherapy may fit under the descriptions of the process modifications used in

materials science encompassing the use of retardants, catalysts, accelerants, decelerants, or process regulators [92]. In these approaches, we add a chemical substance to a process that is not functioning in an optimal manner, and as a result, we change what was a natural process, to an artificially induced one, with a new and different homeostatic point. This implies that drug therapy does not restore the original homeostasis but introduces another state altogether. This observation is supported by numerous brain imaging studies showing localized brain activity changes with effective treatment but always different from healthy state [93].

Almost all approved antidepressant drugs increase synaptic level of monoamines, particularly norepinephrine (NE) and/or serotonin (5-HT) [94]. More recently, studies into the pathophysiology of depression, coupled with advances in neuronal and intracellular signaling, suggest that we can develop novel interventions and target recently identified brain systems implicated in depression. For example, corticotrophin-releasing factor (CRF) plays a key role in the neurobiology of stress and its relation to depression, and clinical trials involving CRF antagonists are underway. Other neuropeptide receptors are also being investigated such as NK1 and neuropeptide Y. Glutamate and gamma-aminobutyric acid (GABA) are the most common excitatory and inhibitory neurotransmitters, respectively, in the brain. The roles of these neurotransmitters in depression along with neurotrophic factors are becoming clearer, and hence they too are becoming new targets for novel interventions. Most of these newer pharmacological interventions are nonetheless in their early stages of development and have not been appraised in large-scale effectiveness studies. Moreover, all these approaches share a common denominator and constitute the prevailing paradigm in researching and treating mood disorders: exogenous pharmacologic compounds are attempting to compensate for a specific dysfunction in one domain of mood regulation and often only addressing one (of many) hypothesized deficiency. By doing so, exogenous pharmacologic agents produce an altered biosystem, different from the normal homeostasis but associated with depressive symptom resolution.

1.9 Possible Options for the Future

Developing new and effective treatments is not trivial. Nestler et al. [94] have described algorithms for identifying and validating novel treatments. One could use, for example, DNA microarray or mass spectrometry to identify genes or proteins linked in the pathophysiology of depression and later develop specific therapies. Alternatively, studies into the functional neuroanatomy of depression have revealed decreased activity in dorsal neocortical regions and relative increased activity in ventral limbic and paralimbic areas [25]. Illness remission is thought to occur when there is appropriate modulation of dysfunctional limbic-cortical interactions [38]. This can be achieved by various forms of treatment (for review [93]) including antidepressant drugs and psychotherapy. Brain stimulation therapies (BSTs) directly modulate brain function and regulate mood. Each presents with unique characteristics that define its role in the depression therapeutic landscape. Several of these will be detailed is other chapters.

Electroconvulsive therapy (ECT) remains the goal standard for acute treatment of TRD but is associated with very high relapse rates despite maintenance regimen [95] and substantial risks for cognitive impairments [96]. Ultra-brief pulse ECT and magnetic seizure therapy are promising alternatives to classic bilateral ECT. The remission rates in community settings range between 30 and 50 % and are substantially less than that in clinical trials (70–90 %). ECT is thought to enhance gamma-aminobutyric acid (GABAergic) activity in prefrontal cortex which then leads to better limbic governance [97]. We are currently testing a much more focal form of ECT, namely, focal electrically administered seizure therapy (FEAST) that potentially could induce seizure in the right orbitofrontal cortex and spare the medial temporal lobes. If early observations are confirmed, FEAST could potentially lead to a revision of ECT and its drawbacks by completely separating efficacy from cognitive side effects.

Transcranial magnetic stimulation (TMS) is a noninvasive technique whereby rapid oscillations in electrical and then magnetic energy depolarize cortical cells. Prefrontal TMS, repeated over several weeks, has clinically significant antidepressant

effects in moderate TRD [98, 99]. However, the effect sizes are variable and not always positive. Clinical and imaging data [100] imply that higher number of stimuli per session and longer treatment courses are more effective. Maintenance studies are starting to be developed.

Vagus nerve stimulation (VNS) therapy is the first BST to be US FDA approved for TRD. It involves implanting a pacemaker-like generator in the anterior chest wall and the leads around the left vagus nerve. In naturalistic follow-ups, 30–40 % of studied cohorts responded by 1 year. Two-thirds of early responders showed continued clinical benefit after 12 months and 50 % after 24 months [101]. Using real-time VNS and fMRI, we demonstrated that chronic intermittent VNS is associated with deactivations of medial prefrontal cortex [102]. These brain changes gradually occur over time and may explain the slow onset of its therapeutic action [101].

Deep brain stimulation (DBS) involves the placement of multi-contact electrodes in subcortical regions also connected to a pacemaker-like generator. DBS is routinely performed for refractory Parkinson's disease [103] and various other neurological syndromes [104]. Several successful open-label studies have been published with small samples of TRD patients using high-frequency DBS to the caudate nucleus [105], anterior thalamic nuclei [106], subgenual cingulate [107], the anterior limb of the internal capsule [108], or the nucleus accumbens [109] with up to 35 % remissions at 6-month open follow-up [107]. At present, two randomized placebo-controlled studies targeting the subgenual cingulate and the ventral capsule/ventral striatum are underway (see Chap. 7 for details).

Epidural prefrontal cortical stimulation (EpCS) involves the placement of multi-contact stimulating paddles over specific cortical regions and connected to a pacemaker-like generator. It modulates local and subcortical regions depending on stimulation intensity, frequency, and duration. The bilateral four paddle EpCS approach we pioneered in 2008 showed promising improvements in depressive symptoms and a number of behavioral measures associated with in self-awareness, internal monitoring, and regulatory executive functions. Out of five severely TRD patients, three

met criteria for remission at 7 months and 24 months follow-ups [110]. Separately from our work, an industry-sponsored study (North Star) reported on the feasibility, safety, and efficacy of *unilateral* left dorsolateral prefrontal EpCS [111]. Twelve TRD patients were randomized to active or sham single blind for 8 weeks' treatment with an adaptive open design follow-up. No significant difference across conditions was noted during the sham-controlled phase after 2 months. Active left DLPFC EpCS proceeded to have a gradual improvement from 8 to 16 weeks with 21 % ± 23 and 26 % ± 29 changes from baseline. The results also showed that the placement of their single cortical lead paddle over left DLPFC was critical for their response rate. The more anterior the paddle was, the better the response. Interestingly, we had shown a similar relationship in a larger cohort of 59 patients enrolled in an RCT with noninvasive left DLPFC TMS [112].

1.10 Final Discussion

Our field has been divided on continuing with the legacy of DSM and a more theoretically driven, biologically based, phenomenologically linked diagnostic approach to depression. With the current approach requiring five out of eight primary criteria to diagnose major depression, one can imagine the number of combinations that could exist. This likely means that we have been diagnosing and studying different disease processes under one heading. No wonder that our treatments have not been that successful.

While there may be multiple reasons to precipitate a first depression episode, whether it is a social stressor, a genetic loading, an acute medical illness, or an exposure to a toxin, it appears that over time, and with repeated relapses, patients progress to become more treatment resistant. This backdrop represents a more homogeneous group of patients where we are more likely to uncover a common underlying pathophysiology. The challenge would be to generalize it back to the predominant depressed subtypes.

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Obsessive-Compulsive Disorder

2

S. Evelyn Stewart

2.1 Clinical Features

OCD is characterized by repetitive thoughts, images, impulses, or actions that are distressing, time-consuming, or that affect function. Symptoms are very diverse and are often kept secret due to the associated shame and recognition of their "abnormality." Obsessions can focus on aggressive, religious, somatic, and/or sexually intrusive thoughts, concerns about symmetry, hoarding, pathological doubt, and/or contamination. Compulsions are also varied and include washing, counting, checking, repeating, hoarding, ordering, arranging, and the conduct of mental rituals. More often than not, patients with OCD experience multiple symptoms at any given time and change over the course of the illness. Unfortunately, proper diagnosis and treatment for OCD are frequently delayed by many years [1].

The *Diagnostic and Statistical Manual of Mental Disorders—Fifth Edition (DSM-5)* [2] is currently used for the diagnosis of

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J.A. Camprodon et al. (eds.), *Psychiatric Neurotherapeutics*, Current Clinical Psychiatry, DOI 10.1007/978-1-59745-495-7_2

OCD (Fig. 2.1). OCD requires the presence of either obsessions or compulsions which are significantly distressing, time-consuming, or interfering with normal routines and social or occupational functioning. Revisions from the *DSM-III-R* to create the *DSM-IV* definition for OCD included the addition of mental compulsions,

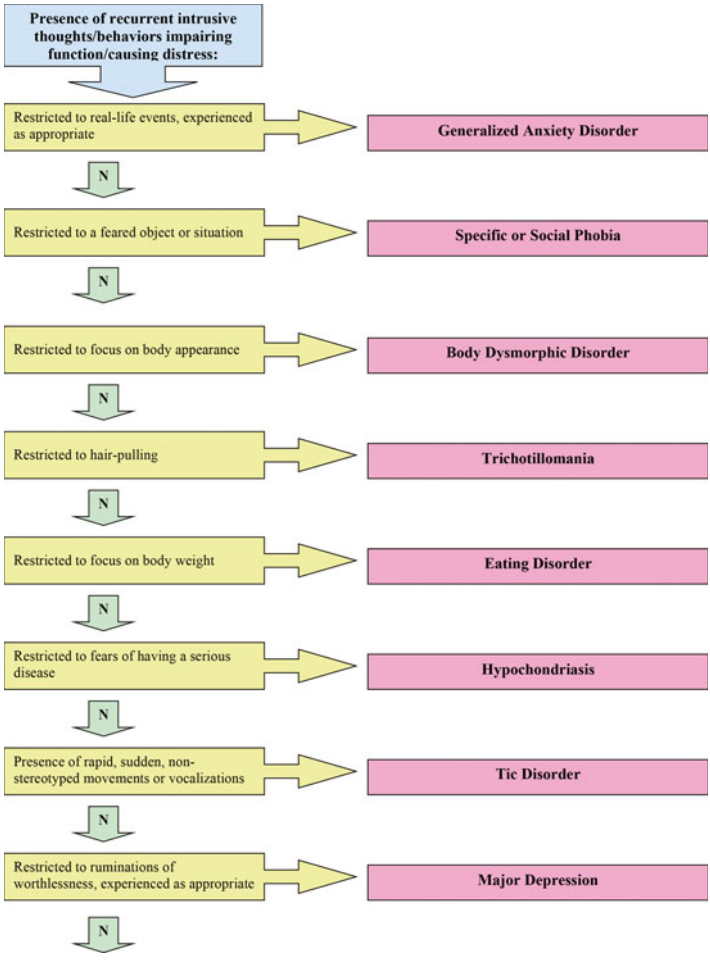

Fig. 2.1 Differential diagnosis for OCD

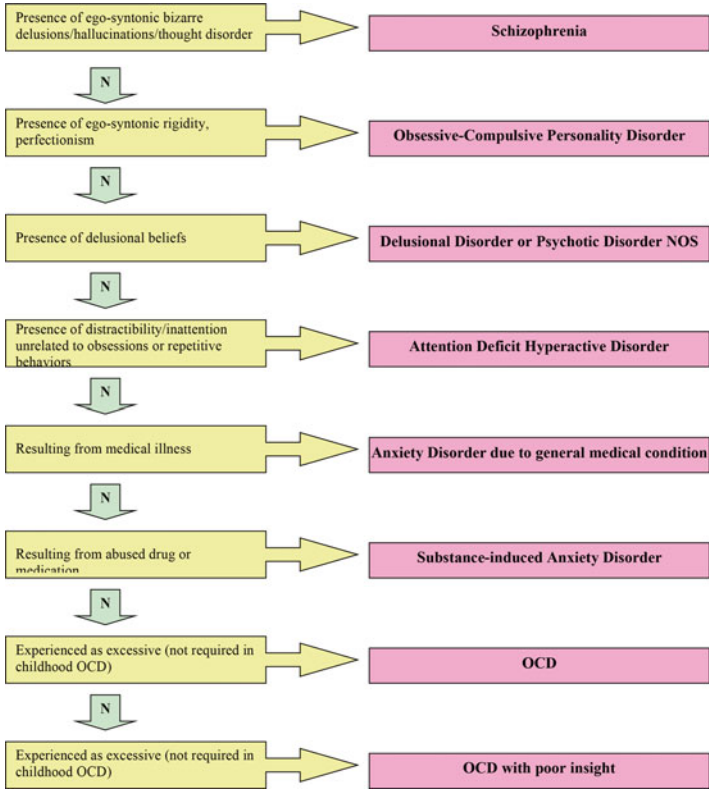

Fig. 2.1 (continued)

and exclusion if the content of the obsessions or compulsions are restricted to another Axis I disorder (e.g., concern with appearance in the presence of BDD or repeated hair pulling with TTM) or if they are due to the direct effects of a substance or general medical condition. Further revisions from the DSM-IV to DSM-5 include the addition of a "with tics" specifier, in addition to a specifier indicating "with good or fair insight", "with poor insight" or "with absent insight/delusional beliefs".

Table 2.1 DSM-5 [2] diagnostic criteria for obsessive-compulsive disorder

A. Presence of obsessions, compulsions, or both:
Obsessions are defined by (1) and (2):
1. Recurrent and persistent thoughts, urges, or images that are experienced, at some time during the disturbance, as intrusive and unwanted, and that in most individuals cause marked anxiety or distress.
2. The individual attempts to ignore or suppress such thoughts, urges, or images, or to neutralize them with some other thought or action (i.e., by performing a compulsion).
Compulsions are defined by (1) and (2):
1. Repetitive behaviors (e.g. hand washing, ordering, checking) or mental acts (e.g., praying counting, repeating words silently) that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly.
2. The behaviors or mental acts are aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situation; however, these behaviors or mental acts are not connected in a realistic way with what they are designed to neutralize or prevent, or are clearly excessive.
Note: Young children may not be able to articulate the aims of these behaviors or mental acts.
B. The obsessions or compulsions are time-consuming (e.g., take more than 1 hour per day) or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C. The obsessive-compulsive symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.
D. The disturbance is not better explained by the symptoms of another mental disorder (e.g., excessive worries, as in generalized anxiety disorder; preoccupation with appearance, as in body dysmorphic disorder; difficulty discarding or parting with possessions, as in hoarding disorder; hair pulling, as in trichotillomania [hair-pulling disorder]; skin picking, as in excoriation [skin-picking] disorder; stereotypies, as in stereotypic movement disorder; ritualized eating behavior, as in eating disorders; preoccupation with having an illness, as in illness anxiety disorder; sexual urges or fantasies, as in paraphilic disorders; impulses, as in disruptive, impulse-control, and conduct disorders; guilty ruminations, as in major depressive disorder; thought insertion or delusional preoccupations, as in schizophrenia spectrum and other psychotic disorders; or repetitive patterns of behavior, as in autism spectrum disorder).

(continued)

Table 2.1 (continued)

Specify if: **With good or fair insight:** The individual recognizes that obsessive-compulsive disorder beliefs are definitely or probably not true or that they may or may not be true. **With poor insight:** The individual thinks obsessive-compulsive disorder beliefs are probably true. **With absent insight/delusional beliefs:** The individual is completely convinced that obsessive-compulsive disorder beliefs are true.
Specify if: **Tic-related:** The individual has a current or past history of a tic disorder.

2.1.1 Prevalence

Symptoms of OCD are very common [3]. Approximately 50 % of the general population engage in some ritualized behaviors [4], and up to 80 % experience intrusive, unpleasant, or unwanted thoughts [5]. However, for most individuals, these behaviors do not cause excessive distress, occupy significant amounts of time, or impair functioning; thus, they do not represent OCD. Regarding a clinical diagnosis of OCD in adults, the 1-month prevalence rate is 0.6 % [6], and the reported 12-month prevalence ranges from 0.6 to 1.0 % for DSM-IV-defined OCD [7, 8] and from 0.8 to 2.3 % for DSM-III-R-defined OCD [9].

Measured lifetime prevalence rates for OCD appear to depend on the version of the DSM used to determine diagnoses. The estimated lifetime prevalence is 1.6 % using the *DSM-IV* [10]. Using the DSM-III, the lifetime rate was 2.5 % in the US Epidemiologic Catchment Area survey [9], and the prevalence ranged between 0.7 % (in Taiwan) and 2.5 % (in Puerto Rico and in seven other countries surveyed) [11]. These differences may be due to the fact that the *DSM-IV* better defines obsessions and compulsions and requires clinically significant distress or impairment to confirm a diagnosis [7].

2.1.2 Age of Onset

There appears to be a bimodal age of onset for OCD. Approximately one-third to one-half of adults with OCD develop the disorder in childhood [11, 12]. The National Comorbidity Survey Replication reported the median onset was 19 years (21 % of cases emerge by the age of 10 [8]), whereas the mean onset for OCD in adults occurs between the ages of 22 and 35 years [13]. Some studies report another incidence peak in mid to late adulthood [14], but others report that onset of OCD after age 50 is relatively unusual [15]. The age of OCD onset appears to be an important clinical variable. Early-onset OCD may have both a unique etiology and outcome and it may represent a developmental subtype of the disorder [16, 17]. Childhood-onset OCD is also associated with greater severity [16, 18] and with higher rates of compulsions without obsessions [16, 17]. An earlier age of onset was associated with higher persistence rates in a meta-analysis of long-term outcomes for childhood-onset OCD [19]. Comorbid rates of tic disorders [20], attention deficit hyperactivity disorder (ADHD), and anxiety disorders [21] are also higher than in adult-onset OCD.

2.1.3 Gender

The gender profile of OCD differs across age groups and populations. In clinical samples of early-onset OCD, this disorder appears to be more common in males [17, 18, 22]. However, epidemiologic studies of children and adolescents report equal rates in boys and girls [23, 24]. In contrast, a slight female predominance is reported in epidemiologic studies for adults [11, 12, 14, 25].

2.1.4 Race and Cultural Factors

The prevalence for OCD tends to be fairly consistent across countries, which suggests that race and culture are not central causal factors for OCD. However, these factors may influence the content of obsessions and compulsions. The disorder is evenly distributed

across socioeconomic strata in most studies, although there tends to be a paucity of minority subjects in epidemiologic and clinical studies in the United States [9].

2.1.5 Risk Factors

There are no clearly established environmental risk factors for OCD. However, some patients describe the onset of symptoms after a biologically or emotionally stressful event (such as a pregnancy or the death of a loved one). Streptococcal infection may be associated with an abrupt, exacerbating-remitting early-onset form of OCD, which has been termed pediatric autoimmune disorders associated with streptococcus (PANDAS) [26–28].

2.1.6 Genetic Factors

Numerous lines of evidence support the genetic basis for OCD. Twin, family aggregation, and meta-analytic studies report higher than expected rates of OCD in relatives [29–32]. The meta-analysis of five OCD family studies that included 1209 first-degree relatives [33] calculated a significantly increased risk of OCD among relatives of probands (8.2 %) versus controls (2.0 %) (OR = 4.0). In studies ascertained through children or adolescents, familial risk appears to be even higher (9.5–17 %) than that for those with later-onset OCD [34–40]. Further, a review of OCD twin studies dating back to 1929 concluded that obsessive-compulsive (OC) symptoms are heritable, with genetic influences ranging from 45 to 65 % in children and from 27 to 47 % in adults [41].

Molecular genetic studies have begun to provide evidence that specific genes play in role in the manifestation of OCD. Segregation analyses examining familial patterns of OCD transmission noted the best fit for a dominant model with at least some genes of major effect in some studies [42–44], but suggest that OCD's familial transmission is difficult to model [45]. None of the four linkage studies for OCD or OCD symptoms reported genome-wide significance [46–48], but the following regions have been suggestive for susceptibility loci: 1q, 6q, 9p, 19q, 7p, and 15q.

OCD candidate genes have been studied based upon their function and also their position in the genome. Serotonin-related genes considered in OCD include those coding for the serotonin transporter (5-HT_{T}) [49–51] and receptors 5-HT_{2A} [52], 5-HT_{2B} [53], 5-HT_{2C} [54], and 5-HT_{1B} [50] as well as the serotonin enzyme, tryptophan hydroxylase [55]. Dopamine (DA)-related genes studied in OCD include those coding for the DA transporter [56, 57]; D_2, D_3, and D_4 receptors [58]; COMT [59]; and MAO-_{A} enzymes [60, 61]. Glutamate-related genes associated with OCD include GRIK [62, 63], GRIN_{2B} [63, 64], SLC-_{1A1} [65–67], and DLGAP3 [68]. Other genes that are associated with OCD include white matter genes, OLIG_{2} [67], and MOG [69]. Few if any genes have been consistently replicated in samples to date. However, the first genome-wide association study of OCD (including approximately 2000 OCD-affected individuals) was recently completed, which reported suggestive findings for DLGAP1, which is also implicated in glutamatergic transmission [70].

2.2 Assessment

A systematic approach should be applied when assessing an individual for suspected OCD. A standard psychiatric assessment is required. In the history of present illness, the duration, severity, and associated distress of symptoms and their precipitating, exacerbating, and ameliorating factors should be elucidated. Functional consequences of these symptoms in home, work, and social environments and the level of insight, resistance, and control over symptoms should also be assessed. Family insight and accommodation of symptoms (which negatively allow their perpetuation) are other important factors to be determined. The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) and checklist should be used to record the severity and lifetime presence of specific symptoms. Frequently, OCD patients have multiple symptoms that have not necessarily been attributed to OCD. There is also a child version of this scale, the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS). Alternatively, the Obsessive-Compulsive Inventory [71] or the Obsessive-Compulsive Checklist [72] may be used. Furthermore, for assessing the impact of OCD on family

functioning, the OCD Family Functioning (OFF) Scale [73] and the Family Accommodation Scale [74] may be of value.

Following the initial assessment of suspected OCD symptoms, comorbid illnesses or disorders that better account for symptoms should be ruled out (see Fig. 2.2 for a differential diagnosis algorithm). The presence of potential comorbid OCD-related disorders (OCRDs) should be assessed, which include tics, eating, and other disorders [75]. Clinical measures used to record OCRDs include

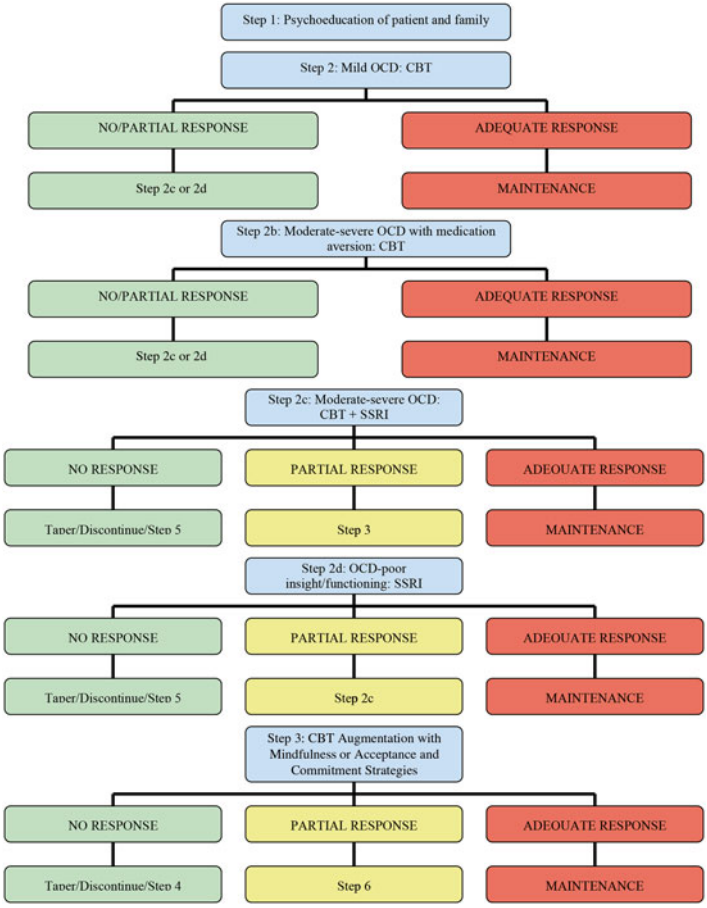

Fig. 2.2 Algorithm for the treatment of OCD

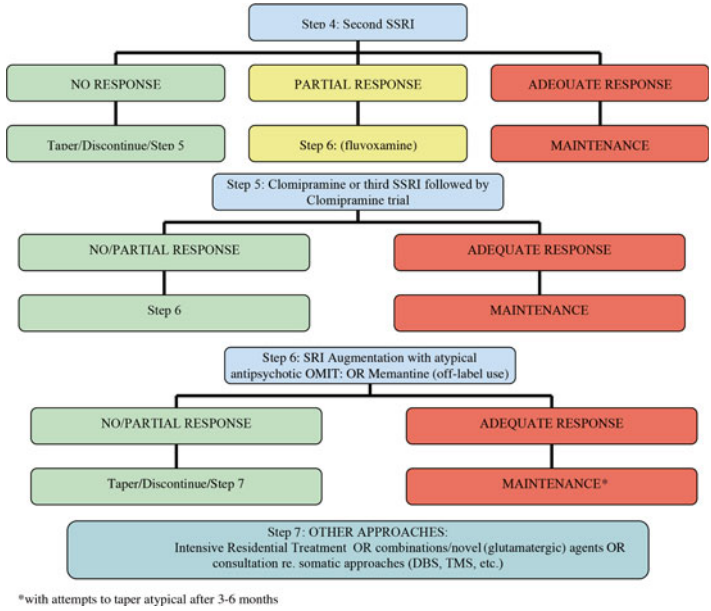

Fig. 2.2 (continued)

the Yale Global Tic Severity Scale (YGTSS) for tics and Tourette's disorder, the MGH Hairpulling Scale for TTM [76], and the Body Dysmorphic Disorder Questionnaire for BDD [77]. Other aspects to be assessed include depression and suicide risk in addition to OCD comorbidities occurring at higher than expected rates such as bipolar disorder [78] and personality and anxiety disorders (such as panic disorder, social phobia, or generalized anxiety disorder) [79, 80]. Further diagnoses (including ADHD and substance use disorders) should also be screened.

In assessment of past psychiatric history, the duration and tolerability at the maximum dosage of every past medication trial should be recorded. The length and success of past behavior or cognitive therapies and other psychotherapies should also be established. Careful attention should be paid to determine whether actual exposure and response prevention or cognitive therapy forms of cognitive behavioral therapy (CBT) were received.

Although supportive therapy may be generally helpful in the setting of any illness, this does not reduce OCD symptoms specifically. Other factors that may impact on the treatment plan include a history of substance abuse (which may impede compliance or warrant caution with prescription of benzodiazepines and other tolerance-inducing medications). Past mood instability or a family history of bipolar disorder may indicate the risk for a switch toward mania with administration of serotonergic agents. The presence of panic attacks warrants use of caution during dosage increases, as these may trigger further attacks.

Since OCD and related disorders may have a genetic component, a thorough family psychiatric history should be elicited for the presence of OCD and Tourette disorder. Furthermore, since medication response may also have an inherited component, information regarding family history of effective treatment trials and negative medication reactions should be gathered.

A review of systems should be conducted to establish a baseline of physical symptoms. The medical history is an important component of assessment; it should include collection of information on currently prescribed, over-the-counter, naturalistic, and birth control medications, as well as drug allergies. Physical and neurological illnesses should be listed, in addition to possible symptoms that may overlap with medication side effects (i.e., insomnia or anergia). A history of thyroid problems, head injuries, or seizures should be noted, and pregnancy should be ruled out or noted. If the patient is a child with an abrupt-onset OCD, a history of streptococcal infections should be obtained, and throat cultures should be collected to guide treatment with antibiotics as necessary. This will also assist in potential diagnosis of pediatric autoimmune disorders associated with streptococcus (PANDAS), in which OCD is putatively related to autoimmune mechanisms [81, 82]. A diagnosis of Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) should also be considered (Reference - Swedo).

The final component of any psychiatric assessment is the mental status examination. A general description of patient appearance and behavior should include any external signs of OCD (e.g., red, chapped hands or repetitive, checking, or contamination-avoidance behaviors). Abnormal movements (such as tics or choreiform movements) should be noted, in addition to abnormalities of speech

(e.g., apparent pauses while performing mental rituals) and the degree of eye contact and cooperation. Mood and affect should denote the levels of potential anxiety, depression, or anger. Thought form should be assessed with respect to circumstantiality, over-inclusiveness and detail focus, and thought content with respect to overvalued ideation, delusions, and thoughts of suicide or homicide. The level of insight and degree of judgment exhibited by the patient are also important to note. The Brown Assessment of Beliefs Scale (BABS) [83] may assist with measurement of OCD-related insight.

Unfortunately, there are no laboratory findings for OCD. However, for clinicians who are considering a diagnosis of PANDAS, a positive throat culture for group A beta-hemolytic streptococcus (GABHS) is required, in addition to determination of other diagnostic criteria. Although characteristic neuroimaging findings have been reported for groups of individuals with OCD, there are no pathognomonic findings, which may be used to diagnose an individual with the disorder.

2.3 Treatment Algorithms

Treatment of OCD typically involves use of medication in combination with other modalities (such as CBT, psychoeducation, and support groups). First-line treatment options for OCD include both serotonin reuptake inhibitor (SRI) medication and CBT. SRIs include selective serotonin reuptake inhibitors (SSRIs) and the tricyclic antidepressant (TCA), clomipramine. Other TCAs with less serotonergic activity do not tend to be as effective in the treatment of OCD. Details of large controlled monotherapy SRI trials for OCD are outlined in Table 2.2. CBT approaches include exposure and response prevention (ERP) and cognitive therapy. ERP works via anxiety habituation following prolonged exposure to a feared OCD stimulus, whereas cognitive therapy works to directly modify distorted OCD beliefs [102].

The decision of whether to initiate an SSRI alone, CBT alone, or a combination depends upon individual patient variables. All three of these approaches, in addition to cognitive therapy alone [103, 104], have demonstrated effectiveness for OCD when compared to treatments such as supportive therapy. An initial trial

Table 2.2 Large ($N \geq 100$) controlled monotherapy trials in OCD

First author	Year	Trial medication (mg/day)	Sample (N)	Comparison/method (mg/day)	Measure (blinding)	Effective
Clomipramine (CMI)						
Katz [84]	1990	250	134	PBO	NIMH-OC	Yes
CCSD [85]	1991	218	281	PBO	Y-BOCS (db)	Yes
Mundo [86]	2001	300	227	Fluvoxamine (300)	Y-BOCS, NIMH-OC (db)	Both
Foa [87]	2005	≤250	122	ERP or ERP+CMI	Y-BOCS	Yes
Selective serotonin reuptake inhibitors						
Montgomery [88]	1993	Fluoxetine (20–60)	217	PBO	Y-BOCS	Yes
Tollefson [89]	1994	Fluoxetine (20–60)	355	PBO	Y-BOCS	Yes
Greist [90]	1995	Sertraline (50–200)	325	PBO	Y-BOCS, OCRS, MOC	Yes
Greist [91]	1995	Sertraline (50–200)	325	PBO	Y-BOCS	Yes
Goodman [92]	1996	Fluvoxamine (100–300)	160	PBO	Y-BOCS, OCRS	Yes

(continued)

Table 2.2 (continued)

First author	Year	Trial medication (mg/day)	Sample (N)	Comparison/method (mg/day)	Measure (blinding)	Effective
Zohar [93]	1996	Paroxetine (20–60)	406	Clomipramine (50–250) or PBO	Y-BOCS, NIMH	Yes, except PBO
Kronig [94]	1999	Sertraline (165)	167	PBO	Y-BOCS	Yes
Koran [95]	2002	Sertraline (50–200)	223	PBO	Clinical	Yes
Denys [96]	2003	Paroxetine (60)	151	Venlafaxine (300)	Y-BOCS	Paroxetine > venlafaxine
Hollander [97]	2003	Fluvoxamine (100–300)	253	PBO	Y-BOCS	Yes
Hollander [98]	2003	Paroxetine (20–60)	105	Switch to PBO	Y-BOCS	40 and 60 mg only
Hollander [98]	2003	Paroxetine (20–60)	348	PBO	Y-BOCS	Yes
Kamijima [99]	2003	Paroxetine (50)	191	PBO	Y-BOCS	Yes
Sousa [100]	2006	Sertraline (100)	56	CBGT	Y-BOCS	Yes, both
Stein [101]	2007	Escitalopram (10–20)	466	PBO or Paroxetine	Y-BOCS	Yes

SRI serotonin reuptake inhibitor, *SNRI* serotonin-norepinephrine reuptake inhibitor, *db* double-blind, *PBO* placebo, *Y-BOCS* Yale-Brown Obsessive-Compulsive Scale, *OCRS* Obsessive-Compulsive Rating Scale, *NIMH-OC* NIMH Obsessive-Compulsive Scale, MOC Maudsley Obsessive-Compulsive Scale, *CCSD* The Clomipramine Collaborative Study Group 1991, *CBGT* Cognitive Behavioral Group Therapy

of CBT alone may be preferable for those who are opposed to taking medications, or who are very young, pregnant, nursing, or medically ill, and for those with mild illness in which potential medication side effects outweigh benefits. For those without access to a CBT-trained clinician and/or with poor motivation or insight, an initial trial with a SSRI alone may be optimal. Furthermore, comorbid depression, psychosis, or other anxiety disorders that may interfere with CBT are factors that suggest that medication should be included in the initial management approach.

A suggested management approach in the treatment of OCD is outlined in Fig. 2.2. It is advisable to initiate SRI treatment with an SSRI rather than clomipramine, given the side effects associated with TCAs. If the initial SSRI is not effective, one to two other SSRI trials should be attempted prior to use of clomipramine. In an effort to minimize clomipramine metabolite side-effects, in addition to required dose for clomipramine, combination with fluvoxamine should be considered. Selecting fluvoxamine for the 2nd or 3rd SSRI trial will ensure maximal clomipramine metabolic inhibition (via CP4501A2 enzyme inhibition). Following poor response to fluvoxamine, clomipramine may be added with dose increases as suited by EKG and serum level results. The selection of a specific SSRI is open to clinical judgment, as head-to-head trials and meta-analyses of SSRIs in children and adults with OCD have not found significant differences. Factors that may be helpful in making this selection include a family history of a positive response or an adverse reaction to a specific SSRI, potential interactions with other medications, and side effect profiles. In a recent Cochrane Database Systematic Review, data from 17 studies including 3097 subjects were examined and SSRIs were found to be similarly more effective than placebo in treating OCD [105]. However, there were significant differences in side effects reported for the individual SSRIs.

To determine the effectiveness of a medication, a 10- to 12-week trial at the highest tolerated dose within the advised dose range is strongly advised. For treatment of OCD, doses are typically higher than are those required for depression (Table 2.3). Further, the reduction of OCD symptoms occurs more commonly than full remission. In clinical trials, "response" is typically defined by a $\geq$25 % or $\geq$35 % decrease in Y-BOCS-defined OCD severity. And

Table 2.3 Therapeutics box: OCD medications, dosages, and side effects

Drug generic name	Drug trade name	Starting dose (mg/day)	Target dose (mg/day)	Adverse effects
First-line agents				
SSRIs				
Citalopram*	Celexa	20	40	Common: insomnia, anxiety, GI upset, sexual, dizziness, sedation Rare: rash, headache *QT prolongation reported at doses higher than 40 mg daily
Escitalopram	Lexapro	10	20	
Fluoxetine	Prozac	20	80	
Fluvoxamine	Luvox	50	300 (75–100 with clomipramine)	
Paroxetine	Paxil	20	60	
Sertraline	Zoloft	50	200	
Tricyclics				
Clomipramine	Anafranil	25	250 (50–100 with fluvoxamine)	Common: anticholinergic s/e, dizziness, sexual, weight gain, tremor Rare: EKG changes, seizures**
Adjunctive/second-line agents				
Buspirone	Buspar	10 (divided bid)	10–45 (divided bid)	Common: dizziness, headache, nausea Rare: sedation, rash
Benzodiazepines				
Clonazepam	Klonopin	0.25–0.5 (od or divided bid)	0.5–3 (od or divided bid)	Common: sedation, tolerance Rare: impaired cognition, disinhibition Ataxia
Lorazepam	Ativan	0.5 (divided bid-tid)	0.5–4 (divided bid-tid)	

(continued)

Table 2.3 (continued)

Drug generic name	Drug trade name	Starting dose (mg/day)	Target dose (mg/day)	Adverse effects
Atypical antipsychotics				
Risperidone	Risperdal	1 (od or divided bid)	0.5–6	Common: weight gain, dizziness, sedation, constipation, sexual Rare: hyperglycemia, elevated prolactin, extrapyramidal symptoms
Olanzapine	Zyprexa	5	5–20 (od or divided bid)	
Quetiapine	Seroquel	50 (divided bid)	500 (divided bid)	
Aripiprazole	Abilify	10	10–30	
Ziprasidone	Geodon	40 (divided bid)	40–160 (divided bid)	
Typical antipsychotics				
Haloperidol	Haldol	0.5	0.5–10	Common: sedation, extrapyramidal symptoms, sexual, anticholinergic s/e Rare: EKG changes, tardive dyskinesia, neuroleptic malignant syndrome
Pimozide	Orap	1	1–3	

**serum monitoring of clomipramine and d,m-clomipramine is required in addition to EKG monitoring following dose adjustments

approximately 40–60 % of patients respond to SRIs with a 20–40 % reduction of OCD symptoms [106, 107].

Before initiating a medication trial, it is necessary to consider the need for baseline laboratory and clinical evaluations, depending on the specific agent to be used. For example, this may include

measurement of weight, abdominal circumference (and height for children), blood pressure sitting and standing, a lipid profile, liver and kidney enzymes, and an electrocardiogram (EKG). A list of physical complaints should also be made prior to the medication trial in order to differentiate these from adverse effects. It is also necessary to rule out previous allergic/negative reactions to the agent and to consider potential interactions with other medications in the current regimen. Between each step in the treatment plan (see Fig. 2.2), assessment of adherence/compliance and adverse effects with the medication regime should be conducted.

Second-line medication strategies include SRI augmentation or replacement monotherapy. Details of moderate-sized controlled trials supporting these approaches are given in Table 2.4. Clonazepam, buspirone, and venlafaxine are rarely used as replacement monotherapy in OCD treatment. SRI-augmenting agents reported to be potentially effective for OCD include atypical antipsychotics and clonazepam. Suggested dosages and common and rare adverse effects of the best-studied second-line agents are found in Table 2.3. However, it should be noted that distinct adverse-effect profiles also exist for certain medications within classes (e.g., ziprasidone and potential QT prolongation on the EKG). In addition, high doses are not required for augmenting agents.

Most recently, glutamate-related medications including memantine and riluzole have shown early promise as OCD-augmenting agents [120–122]. D-cycloserine has also been found to improve rate of improvement with CBT for OCD [123, 124]. For severe refractory cases, intensive residential treatment [125, 126] or surgical and device-based treatments such as deep brain stimulation could be considered.

Once an effective medication and dose are identified in the treatment of OCD, this should be maintained for at least one year prior to its discontinuation. Unfortunately, the subsequent relapse rate following medication discontinuation is very high. In discontinuation studies of responders, these rates range between 24 and 89 % after 6 months of follow-up [95, 98, 127, 128]. For the individuals who have also received previous CBT, however, relapse rates are lower (12 % versus 45 % for clomipramine responders at 12 weeks post-discontinuation) [87].

Table 2.4 Moderate-sized ($N \geq 30$) augmentation/refractory sample trials in OCD

First author	Year	Baseline medication (mg/day)	Augmenting agent (mg/day)	Comparison agent (mg/day)	Sample	Effective
Adjunctive						
McDougle [108]	1994	Fluvoxamine (300)	Haloperidol (10)	PBO	34	Yes
Pallanti [109]	2004	Citalopram (20–80)	Mirtazapine (15–30)	PBO	49	Earlier response
SRI-refractory cases						
McDougle [110]	1993	Fluvoxamine (300)	Buspirone (60)	PBO	33	No
McDougle [108]	1994	SRI with comorbid Tic d/o	Haloperidol (10)	PBO	34	Yes
McDougle [111]	2000	SRI	Risperidone (2.2)	PBO	70	Yes
Denys [112]	2004	SRI	Quetiapine (300)	PBO	40	Yes
Denys [113]	2004	Venlafaxine (300) or paroxetine (60)	Venlafaxine (300) or paroxetine (60)	None	43	Yes, Paxil > Venlafaxine
Crockett [114]	2004	Sertraline	Clonazepam	PBO	37	No
Shapira [115]	2004	Fluvoxamine (40)	Olanzapine (6.1)	PBO	42	Yes, both
Bogan [116]	2005	SSRI	Quetiapine (116)	None	30	Yes, but uncontrolled
Erzegovesi [117]	2005	Fluvoxamine (300)	Risperidone (0.5)	PBO	45	Yes
Carey [118]	2005	SRI	Quetiapine (169)	PBO	41	Yes, both
Arias Horcajadas [119]	2006	SRI	Risperidone (3.8)	None	31	Yes, but uncontrolled

SRI serotonin reuptake inhibitor, *rct* randomized controlled trial, *db* double-blind, *sb* single-blind, *PBO* placebo, *n/a* not available, *Y-BOCS* Yale-Brown Obsessive-Compulsive Scale was used in all studies

2.3.1 Prognosis

OCD usually has a gradual onset, although acute onset occurs in some cases (e.g., PANS). The long-term course of OCD has been studied in both children and adults and in clinical and population samples. In a landmark follow-up study, 144 adult inpatients with OCD, aged 19–52 years, were reevaluated after a mean of 47 years [129]. Nearly half (48 %) reported clinical recovery (no clinically relevant symptoms for ≥5 years), but only 20 % reported full remission (no symptoms for ≥5 years). At follow-up, 80 % had clinical (52 %) or subclinical (without distress or interference) (28 %) symptoms, 9 % had no improvement, and 8 % reported a deteriorating course. Forty-six percent of those in remission at the first evaluation remained in remission for at least 30 years. In an Italian 10-year follow-up study, 27 % had an episodic course (≥6 months of full symptom remission), and 73 % had a chronic course (with a stable or fluctuating symptoms or with deterioration) [78]. Finally, in a US study of 200 outpatients with OCD, 85 % had a waxing and waning course, 10 % had a deteriorating course, and 2 % had an episodic course with full remissions of ≥6 months [130]. In the single long-term outcome study of a community sample, 22 adults with OCD [131] were followed up after a mean of 13 years. At follow-up, only 5 % met DSM-IV diagnostic criteria, 86 % had no symptoms, and 9 % had symptoms and moderate distress.

A meta-analysis by Stewart and co-workers [19] was conducted on 22 long-term outcome studies for childhood OCD ($N = 521$ subjects), with follow-up periods ranging between 1 and 15.6 years. Pooled mean persistence rates were 41 % for *full* OCD and 60 % for *full* or *subthreshold* OCD. Earlier age of OCD onset, increased OCD duration, and inpatient versus outpatient status predicted greater persistence at follow-up. Hence, OCD appears to be a chronic illness with a waxing and waning course. Although with proper treatment, most individuals with OCD experience at least mild to moderate improvement throughout their illness course.

2.4 Clinician/Consumer Resources

International Obsessive-Compulsive Foundation
Tel: 617-973-5801
https://iocdf.org/
Anxiety BC
Tel: 604-525-7566
http://www.anxietybc.com/

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Neuroimaging and Neurocircuitry of Obsessive-Compulsive Disorder and Major Depressive Disorder

3

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3.1 Introduction

Major depressive disorder (MDD) and obsessive-compulsive disorder (OCD) are two of the most common and disabling psychiatric disorders [1]. Mood disorders and OCD (and related disorders) are classified in separate diagnostic categories, but there is a high

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J.A. Camprodon et al. (eds.), *Psychiatric Neurotherapeutics*, Current Clinical Psychiatry, DOI 10.1007/978-1-59745-495-7_3

rate of comorbidity between the two illnesses. Indeed, about two-thirds of patients with OCD develop depression [2], and an estimated 1/6 patients with MDD have some form of pathological obsessions and/or compulsions [3]. In addition, similar pharmacological treatments such as selective serotonin reuptake inhibitors have been shown to be effective in both MDD and OCD.

Although precise causal pathophysiological mechanisms are still elusive, modern neuroscience has made great strides in determining the brain neurocircuits underlying these two disorders [4, 5]. Unsurprisingly given the frequent comorbidity and commonalities in terms of treatment response, neuroimaging studies have revealed significant overlap between OCD and MDD. Mainly, both disorders involve dysfunction in neuronal networks composed of prefrontal cortical areas, limbic regions, and their related connections to specific areas of the basal ganglia. This chapter summarizes current data on the neurocircuitry of OCD and MDD and describes how this relates to neuromodulation treatments.

3.2 Obsessive-Compulsive Disorder

Obsessive-compulsive disorder (OCD) is a heterogeneous clinical entity characterized by recurrent distressing intrusive thoughts, images, and impulses, in addition to compulsive behavioral or mental rituals [1]. Obsessions are a source of anxiety, which usually drives the performance of compensatory compulsive rituals. It is currently classified within OCD and Related Disorders in DSM-5 and has both clinical and neurobiological connections with a spectrum of disorders including body dysmorphic disorder, hair pulling disorder, skin picking disorder, hoarding disorder, and tic disorders [6]. OCD remains entirely a clinical diagnosis, but it has been the subject of intensive neurobiological research. Although we are far from a complete understanding of the neurophysiological processes leading to OCD phenomenology, the underlying neurocircuitry has been reasonably reliably identified using both functional and structural neuroimaging methods [4, 7, 8]. Among major psychiatric disorders, OCD has been one of the most successful areas of neurocircuitry research.

3.2.1 Background

Brain structures that have been most consistently linked to OCD include the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), striatum, and thalamus [4, 8, 9]. At the neural circuit level, a convergence of neuroscience research points to cortico-striato-thalamo-cortical (CSTC) pathways as the common pathways underlying OCD. In this chapter, we will initially outline the classical anatomy of CSTC circuitry as it pertains to OCD. We will further detail the putative role of each components of this circuit, touching upon more recent theories expanding our understanding of CSTC pathways and future areas of research.

Imaging modalities used to delimitate OCD circuitry are diverse and have evolved over the years. Although structural data does support the involvement of the above-described brain areas, functional imaging modalities have really been key to develop a better understanding of OCD in living humans [7]. Initial studies compared regional brain function in subjects compared to healthy controls. Subsequently, studies have compared affected subjects pre- and post- treatment. More recent approaches entail symptom provocation and specific cognitive-affective paradigms. A complete review of all available data is out of the scope of this chapter, but most significant and consistent findings will be reviewed.

3.2.2 Functional Anatomy

The prefrontal cortex (PFC) mediates a variety of cognitive functions including response inhibition, planning, organizing, controlling, and verifying operations. Consequently, prefrontal dysfunction is associated with disinhibition, disorganization, inflexibility, perseveration, and stereotypy [10]. The PFC comprises several functional subterritories. The dorsolateral prefrontal cortex (dlPFC) plays a role in learning and memory as well as planning and other complex cognitive (i.e., executive) functions. The ventral PFC can be subdivided into two functional domains. The posteromedial orbitofrontal cortex (pmOFC) is a component of the paralimbic system and plays a role in affective and motivational functions [11]. The anterior and lateral orbitofrontal cortices

(alOFC) represent the structural and functional intermediaries between the lateral prefrontal and paralimbic prefrontal zones. For instance, the alOFC seems to play a role in response inhibition and regulation of behavior based on social context as well as other affectively tinged cognitive operations [11, 12].

The "paralimbic" system is the name given to a contiguous belt of cortex that forms the functional conduit between other cortical areas and the limbic system proper. The constituents of the paralimbic belt include the pmOFC as well as the cingulate, anterior temporal, parahippocampal, and insular cortices [11]. This system is believed to integrate abstract representations of the outside world with inner emotional states, so that appropriate meaning and priority can be assigned to information as it is processed. Convergent data from recent human neuroimaging studies, together with previous animal and human research, suggest that the paralimbic system plays a critical role in mediating intense emotional states or arousal; in particular, this system has been implicated in anxiety [13–15]. Furthermore, it has long been appreciated that paralimbic elements serve to modulate autonomic responses, including heart rate and blood pressure, which represent the somatic manifestations of intense affects or heightened arousal [11].

The striatum comprises the caudate nucleus, putamen, and nucleus accumbens (also called the ventral striatum). Historically, the basal ganglia, including the striatum, were thought to play a circumscribed role, limited to the modulation of motor functions. More recently, a much more complicated scheme has been adopted which recognizes the role of striatum in cognitive and affective functions as well [16–18].

3.2.3 Cortico-Striato-Thalamo-Cortical Pathways

In a series of classic articles, Alexander and colleagues introduced and reviewed the organization of multiple, parallel, segregated CSTC circuits [19, 20]. Briefly, each CSTC circuit involves projections from a variety of cortical zones to specific corresponding subterritories of the striatum, which in turn send projections via other intermediate basal ganglia targets to ramify within the thalamus.

These circuits are ultimately closed via reciprocal projections from thalamus back to the same prefrontal cortical regions from which the corticostriatal projections originated. Although initially described as segregated circuits, recent evidence has demonstrated significant interactions of the different loops within the striatum and thalamus [4, 21].

Parallel, segregated, CSTC circuits differ from one another on the basis of their distinct projection zones within cortex, striatum, and thalamus and thus the particular type of functions each subserves. The three most salient CSTC circuits thought to be implicated in OCD are as follows: (1) projections from the ACC and ventromedial PFC (vmPFC) via the nucleus accumbens form the affective circuit which is mainly involved in affective and motivational functions; (2) projections from the alOFC via ventrolateral caudate/putamen nucleus constitute the ventral cognitive circuit which is thought to mediate context-related operations and response inhibition; and (3) projections from the dlPFC via the dorsolateral caudate nucleus constitute the dorsal cognitive circuit which is thought to mediate working memory and other executive functions. These circuits are illustrated in Fig. 3.1 [4].

Within the ventral cognitive circuit resides the corticothalamic (CT) branch, which runs from the OFC to the thalamus through the anterior limb of the internal capsule. The CT pathway is excitatory and bidirectional, purportedly mediating consciously initiated output (corticothalamic) and consciously accessible input (thalamocortical) streams. A second pathway, the cortico-striato-thalamic (CST) branch, runs from the OFC/PFC to the thalamus through the ventral striatum. It is inhibitory and counterbalances the CT pathway [13, 22, 23]. Purportedly, the function of the striatum in this context is to process information automatically and without conscious representation. Hence, the normal striatum function within these circuits, via exerting a balance of suppression and/or enhancement at the level of the thalamus, is to (A) filter out extraneous input, (B) ensure refined output, and (C) mediate stereotyped, rule-based processes without necessitating the allocation of conscious resources [16, 24–26]. In this way, the striatum regulates the content and facilitates the quality of information processing within the explicit (i.e., conscious) domain by fine-tuning input

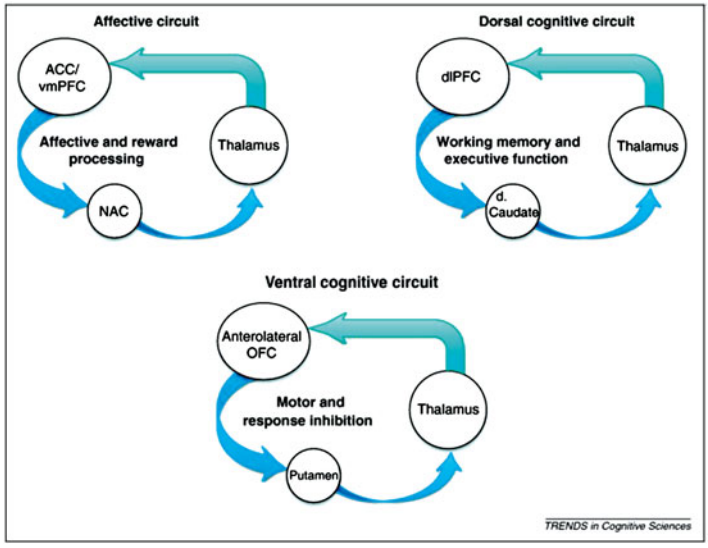

Fig. 3.1 Schematic diagram illustrating the three most relevant cortico-striato-thalamo-cortical circuits. *Abbreviations*: *dlPFC* dorsolateral prefrontal cortex, *NAC* nucleus accumbens, *OFC* orbitofrontal cortex, d. caudate, dorsal caudate. *Reproduced from Milad M, Rauch S. 2012. Obsessive-compulsive disorder: beyond segregated corticostriatal pathways. Trends Cogn Sci. 16:43–51*

and output. In addition, the striatum enhances the efficiency of the brain by carrying out some nonconscious functions, thereby reducing the computational load on conscious processing systems. One interesting hypothesis is that OCD symptoms could arise when the CST pathways fails to adequately inhibit the CT pathway [8].

The "direct" and "indirect" cortico-striato-thalamic pathways represent a third level of complexity. Each cortico-striato-thalamic collateral consists of both a "direct" and "indirect" pathway [20, 27, 28]. These two systems operate in parallel, with opposing ultimate influences at the level of the thalamus. The direct system is so-named because it involves direct projections from striatum to the globus pallidus interna, with a net excitatory influence on the thalamus. Conversely, the indirect system involves indirect projections from striatum via the globus pallidus externa to the globus pallidus interna and has a net inhibitory effect at the level of the thalamus.

3.2.4 The Corticostriatal Hypothesis of OCD

For the past two decades, neurobiological models of OCD have emphasized the role of the PFC and the striatum [9, 25, 26, 29–33]. The scheme of corticostriatal circuitry fits well with emerging data implicating the elements of those circuits. Convergent results from neuroimaging studies in subjects with OCD have implicated hyperactivity at rest of the OFC, ACC, and the caudate nucleus in the pathophysiology of OCD, abnormalities that are attenuated with effective treatments [34–36]. Neuropsychological studies are also consistent with subtle deficits involving fronto-striatal functions [25, 37]. Of note, neurosurgical procedures that interrupt these circuits (e.g., anterior cingulotomy, capsulotomy, subcaudate tractotomy) appear to reduce OCD symptoms [8, 36], and ventral capsule/ventral striatum (VC/VS) deep brain stimulation has shown potential for treatment-refractory OCD [38]. Furthermore, other diseases characterized by documented striatal pathology often exhibit OCD symptoms or related clinical manifestations [30, 33, 39].

Across the years, various heuristic models of a corticostriatal hypothesis underlying symptoms of OCD have been proposed. Although there were several early versions of this model, each posited an overdriven corticothalamic reverberating circuit. Modell et al. (1989) proposed that a hyperactive caudate nucleus might be the cause of net excitation of the thalamus [32]. Baxter et al. (1990) hypothesized that the apparent hyperactivity in caudate represented insufficient compensation for intrinsic striatal dysfunction, such that inhibition of the thalamus via the cortico-striato-thalamic collateral was inadequate [29]. As researchers came to appreciate the ramifications of the direct and indirect systems within the cortico-striato-thalamic collateral branch, the models evolved. It was proposed that an appropriate balance between the direct and indirect systems enabled optimal modulation of thalamic activity, whereas in OCD, a shift toward dominance of the direct system could result in excitation or disinhibition at the thalamus, thereby overdriving the corticothalamic branch [30, 40].

Finally, Baxter and colleagues articulated a “striatal topography model” of OCD and related disorders, suggesting that different corticostriatal circuits might mediate different symptoms and therefore define a spectrum of different disease entities [29, 41, 42].

Originally, they proposed that ventromedial caudate/accumbens involvement might mediate obsessions, dorsolateral caudate dysfunction might mediate compulsions, and that putamen involvement might mediate the tics of Tourette syndrome (TS). Subsequently, based on results of symptom provocation studies, we have proposed that the paralimbic system (including pmOFC) mediates affective manifestations including the anxiety of OCD and the urges of TS, while the ventral cognitive circuit comprising alOFC and ventrolateral caudate mediates obsessional symptoms [42].

3.2.5 Structural Imaging in OCD

Structural imaging modalities have significantly evolved over time and now include studies of cortical thickness and white matter tractography. Older region-of-interest analyses have often revealed reduced OFC volume in OCD, but a recent meta-analysis did not find such evidence of structural changes [43]. Regarding the volume of the striatum in OCD, some studies have found increased gray matter volume, while region-of-interest approaches have sometimes yielded lower volume. So far, the most consistent anatomical finding has been the reduction in volume of the dorsal ACC (dACC) in patients with OCD [44]. Diffusion tensor imaging studies have also inconsistently suggested abnormalities in a variety of white matter tracts, such as the cingulum bundle, the anterior limb of the internal capsule, and corpus callosum [45, 46].

3.2.6 Recent Developments in OCD Neurocircuitry

Milad and Rauch (2012) have reviewed recent data on the neurocircuitry of OCD, and these authors suggested that the field should move beyond the above-described concept of segregated CSTC pathways [4]. In fact, anatomical evidence now suggests that corticostriatal loops are more integrated than initially described [21]. The CSTC model also does not factor the role of the amygdala and hippocampus, two structures that are closely linked to the physiology of anxiety.

Another recent development has been the observation that different subparts of the OFC probably mediate different functions. More specifically, the lateral OFC (lOFC) predominantly mediates negative valence processing, while the medial OFC (mOFC) is more involved in mediating positive valence [47]. This distinction is noteworthy in view of the findings from functional imaging studies of hyperactivity in the lOFC in OCD, in conjunction with hypoactivity in the mOFC [48, 49]. The lOFC hyperactivity has been linked to response to selective serotonin reuptake inhibitors (the less hyperactivity the better the response) [50], while symptom severity is inversely correlated with mOFC function [49, 51]. Indeed, the activity of the mOFC and the vmPFC correlate with the magnitude of fear extinction in healthy humans [52], suggesting that subjects with OCD may fail to activate the vmPFC/mOFC during exposure to OCD triggering stimuli.

The dACC has also been implicated in the pathophysiology of OCD in functional neuroimaging studies. This region is involved in detecting cognitive conflicts, in addition to error monitoring and detection (e.g., stroop test, go/no-go) [53, 54]. Functional imaging revealed increased dACC activation during perceived errors or incongruent conditions, compared to correct or congruent conditions [55]. In OCD increased "effective connectivity" (functional correlation) was reported between the hemodynamic responses of the dACC and those of the DLPFC, potentially supporting the hypothesis that an "overactive error control system" and adverse decision-making process underlie the pathophysiology of this disorder [56]. Such results conceivably may reflect either exaggerated responses to perceived incongruity or error or greater uncertainty of perceived correctness. The dACC also has a role in fear learning and fear expression [57]. Since surgical lesions of the anterior cingulum bundle improve OCD [58–60] and decreased dACC activation is seen with successful SSRI treatment [61], this strongly supports a crucial role for this structure in the physiology of OCD.

Finally, the amygdala also has been implicated in the pathophysiology of OCD. This nuclear complex plays critical roles in evaluating the significance of and organizing the behavioral response to experiential stimuli that are novel or emotionally salient because they are associated with aversive or rewarding

outcomes. This structure thus plays a central role in mediating fear and anxiety responses. In OCD, stimuli which specifically trigger obsessions/compulsions lead to increased amygdala blood flow, while other salient stimuli that are unrelated to obsessions/compulsions lead to less activation compared to healthy controls [62, 63]. However, these results have not been consistently reproduced in other studies [64]. Nevertheless, while further investigation is needed, neurocircuitry models of OCD must consider the role of the amygdala in the maladaptive fear learning that putatively underlies the exaggerated salience of phobic stimuli in OCD.

3.2.7 Conclusions

Although much work remains to be done, OCD neurocircuitry research has been one of the most successful areas of the psychiatric neuroimaging field. The main brain structures showing abnormalities in OCD—i.e., the OFC, ACC, striatum, thalamus, and amygdala—have been consistently identified, and we now have a better understanding of their interactions at the circuit level. This research has been inspired by historical studies of CSTC loops and now integrates more recent developments showing a high level of interactions between these circuits, in addition to the use of new paradigms such as the neurobiology of fear extinction [4]. This research has already helped guide novel neurotherapeutics treatments of OCD, such as the development of ventral capsule/ventral striatum deep brain stimulation which modulates connections between the PFC (including the OFC) and related subcortical structures (including striatum and mediodorsal thalamus) [38]. Hopefully, neuroimaging research will lead to the discovery of biomarkers that could be clinically helpful to better target specific treatments to individual patients in the future.

3.3 Major Depressive Disorder

Major depressive disorder (MDD) is the leading cause of years of life lived with disability for all age groups [65], however until recently little was known about the underlying neural underpinnings.

Despite the absence of consistent gross brain pathology associated with MDD and the lack of clear animal models for spontaneous recurrent depression, the development of neuroimaging technologies have allowed a better in vivo characterization of the anatomy, physiology, and neurochemistry of mood disorders in humans.

3.3.1 Background

Early studies identified the amygdala, hippocampus, and other parts of what was termed the "limbic" system as central parts of the emotional brain. Detailed connection data on this system began to be obtained in the 1970s and 1980s, as more effective neuroanatomical techniques based on axonal transport became available. In the last 15 years these methods have been applied extensively to the limbic system and prefrontal cortex of monkeys, and much more specific circuits have been defined [5, 66, 67]. In this chapter, we will review the neuroanatomy of neural circuits involved in mood disorders, synthetizing findings from nonhuman primates, neuroimaging studies in humans, and *postmortem* methodologies.

3.3.2 The Neural Substrates of Mood Disorders

There is considerable evidence that the medial prefrontal cortex (mPFC) and the amygdala are centrally involved in mood disorders [68–70]. These regions are part of a wider circuit that connects the amygdala and the medial network with other cortical areas in the anterior and medial temporal cortex, the posterior cingulate cortex, as well as with subcortical structures in the ventral striatum, pallidum, medial thalamus, hypothalamus, periaqueductal gray (PAG) matter, and other parts of the brainstem (Fig. 3.2) [5].

Distinct from the medial prefrontal network, but adjacent and closely related to it, is a network of areas in the central orbital cortex. Unlike the medial network, the orbital network has connections with several sensory-related cortical areas and appears to play a critical role in assessing objects and anticipating reward [71]. Depressed subjects show abnormalities in both networks during fMRI studies involving reward and emotional processing tasks,

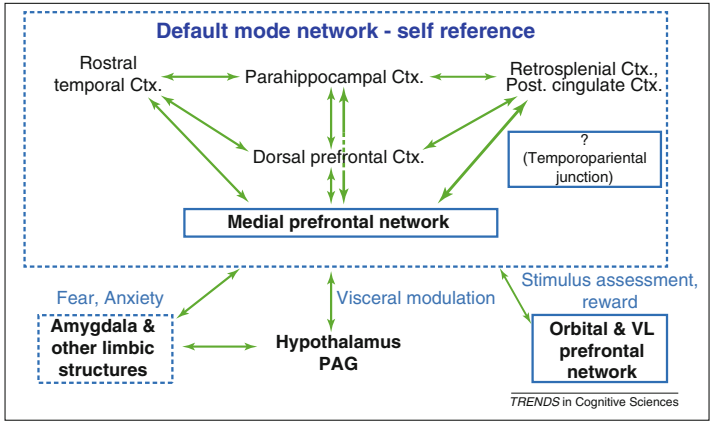

Fig. 3.2 Schematic diagram illustrating connections between the medial prefrontal network and other cortical areas as well as with the amygdala, hypothalamus, and periaqueductal gray (PAG). *Reproduced from Price JL, Drevets WC. 2012. Neural circuits underlying the pathophysiology of mood disorders. Trends in Cognitive Sciences. 16:61–71*

although the medial network has been more specifically related to mood disorders [72]. Abnormalities in structure and function evident within these networks potentially impair cognitive processes such as reward learning and autobiographical memory and may dysregulate visceral, behavioral, and cognitive responses to emotional stimuli and stress [73], potentially accounting for the clinical phenotype of MDD. In the following sections we will review individual components of this neurocircuitry in more detail.

3.3.3 Limbic Structures

The amygdala has reciprocal anatomical connections to the medial prefrontal network and, to a lesser extent, the orbital network, as well as to related insular and temporal cortical areas, the mediodorsal thalamic nucleus, and the ventromedial striatum [74]. Outputs to hypothalamic and brainstem areas involved directly in visceral

control arise mainly from the central and medial nuclei [74]. These projections terminate in the medial and lateral hypothalamus, but also in the PAG, parabrachial nuclei, and autonomic nuclei in the caudal medulla. As such, they can modulate autonomic and endocrine mechanisms affecting a wide variety of visceral functions [75].

The strongest connections of the large, celled basal amygdaloid nucleus are with the medial prefrontal cortex and anterior and ventral to the genu of the corpus callosum. In addition, there are substantial amygdaloid projections to the medial, caudal, and lateral edges of the orbital cortex (leaving the central orbital cortex relatively free). There are also interactions with the rostroventral insula, temporal pole, inferior temporal cortex, entorhinal and perirhinal cortex, hippocampus [76], and the posterior cingulate cortex [77].

Within the striatum, the major targets of amygdala projections are the nucleus accumbens and the adjacent medial caudate nucleus and ventral putamen [78]. These striatal areas in turn project to the ventral and rostral pallidum, which itself sends GABAergic axons to the mediodorsal thalamic nucleus [79]. Of note, the pre- and subgenual prefrontal cortices are connected to overlapping areas of the ventromedial part of the striatum [80, 81] as well as of the mediodorsal thalamic nucleus [79, 82]. These neuroanatomical data form part of the larger organization of overlapping and interconnected medial prefrontal cortico-striato-pallido-thalamic and amygdalo-striato-pallido-thalamic loops.

3.3.4 Prefrontal Cortex

3.3.4.1 Orbital and Medial Prefrontal Cortex

Axonal tracing experiments in macaque monkeys have defined the cortical and sub-cortical circuits related to the medial prefrontal cortex and amygdala. Based on local cortico-cortical connections, two connectional systems or networks were recognized within the orbital and medial prefrontal cortex (OMPFC), which have been referred to as the "orbital" and "medial prefrontal networks." The areas within each network are preferentially interconnected with other areas within the same network, but also have common connections with other parts of the cerebral cortex [67].

3.3.4.2 Orbital Prefrontal Network

The orbital network consists of areas in the central and caudal part of the orbital cortex and the adjacent anterior agranular insular cortex. It does not include areas along the medial edge of the orbital cortex and some areas in the caudolateral orbital cortex. In addition to the local cortico-cortical interactions between the areas of this network, it is characterized by specific connections with several areas that can be classified as sensory-related cortex [83, 84]. The only sensory modality that apparently lacks an input to the orbital network is audition. In addition, many neurons appear to code for the presence or expectation of reward [85] and for the relative value of stimuli [86]. These anatomical observations appear consistent with evidence from electrophysiological, functional imaging, and lesion analysis studies indicating that the orbital network functions both as a system for integration of multimodal stimuli and as a system for assessment of the value of those stimuli, underlying the capacity to use predicted reward or aversion value as a guide to behavior [87].

3.3.4.3 Medial Prefrontal Network

The medial prefrontal network is probably still more significant for mood disorders. The most prominent limbic connections are with areas of the medial network [66, 88]. It consists of areas on the ventromedial surface of the frontal cortex, anterior and ventral to the genu, areas along the medial edge of the orbital cortex, and a small caudolateral orbital region at the rostral end of the insula [67]. As with the orbital network, the areas of the medial network are preferentially interconnected with each other, but the network is also characterized by outputs to visceral control areas in the hypothalamus and PAG. The subgenual anterior cingulate cortex (SgACC) provides the heaviest projection, which terminates in both the medial and lateral hypothalamus and in both dorsolateral and ventrolateral columns of the PAG [71]. While the orbital network is to some extent a sensory-related system, the medial network is more an output system that can modulate visceral function in relation to emotions.

In addition, the medial network is connected to a very specific set of other cortical regions, particularly the rostral part of the

superior temporal gyrus and dorsal bank of the superior temporal sulcus, the anterior and posterior cingulate cortex, and the entorhinal and parahippocampal cortex. This cortico-cortical circuit is different from and in some ways complementary to the circuit related to the orbital network. None of the areas related to the medial network are directly related to a sensory modality. Instead, they together resemble the "default mode network" which has been identified in resting fMRI studies and thought to be involved in self-referential processes and potentially depressive symptoms [89, 90].

3.3.4.4 Lateral Prefrontal Cortex

The lateral prefrontal cortex (lPFC) is subdivided in three areas: the dorsolateral PFC (dlPFC), the ventrolateral PFC (vlPFC), and the caudolateral PFC (clPFC) [68, 91]. Each region is preferentially connected to other local areas in the same region, and each is connected to a specific set of areas in other parts of the cortex [83]. The dlPFC is interconnected with the medial prefrontal network and shares most of its other connections. As with the medial network, there are outputs from dorsal areas to the hypothalamus and PAG, so this system can also modulate visceral functions. Further, the system connects to the same set of other cortical areas as the medial network, including the rostral superior temporal gyrus, the anterior and posterior cingulate cortex, and the entorhinal and parahippocampal cortex. The vlPFC interacts with the orbital prefrontal network and its connections are very similar. The major difference with the orbital network is that there do not appear to be olfactory or taste inputs to the ventral system. The clPFC is distinct from the other systems in that it does not relate to either the medial or orbital networks.

3.3.5 Cortico-Striato-Thalamo-Cortical Pathways

Like other cortical areas, the PFC also has specific connections with the striatum and thalamus. Several circuits can be delineated. The first are the reciprocal thalamocortical connections that relay subcortical input to the cortex through principal thalamic nuclei. Closely related to these are the previously described CSTC loops,

which also involve the principal nuclei. The orbital network areas connect to a relatively central region that spans the internal capsule and includes parts of both the caudate nucleus and the putamen (Fig. 3.1, ventral cognitive circuit) [92]. The medial network areas project to the nucleus accumbens and the adjacent medial edge of the caudate nucleus bordering the lateral ventricle (Fig. 3.1, affective circuit). These striatal regions, in turn, project to the ventral pallidum, which projects to the portion of mediodorsal thalamic nucleus that is connected to the medial network areas [73].

3.3.6 Clinical Evidence from Studies of Mood Disorders

3.3.6.1 Limbic System

Multiple functional imaging studies have demonstrated both resting and task-based amygdalar abnormalities in depression. Resting glucose metabolic abnormalities appear to be selective for depressive subgroups, including increased left amygdala metabolism specifically in bipolar depression, familial pure depressive disease, or melancholic subtype (see [93] for a review). In contrast, task-based hemodynamic responses of the amygdala show a pattern of abnormalities reflecting negative emotional processing biases that appear more generalizable across depressed samples. It has been shown that subjects with depression have an exaggerated hemodynamic response of the amygdala to sad words and sad faces, but a blunted response to happy faces [94, 95]. This response appears to be trait-like, and interestingly antidepressants have been demonstrated to shift emotional biases toward the positive direction in both healthy and MDD samples [95]. These studies on MDD support the idea that a pathological negative processing bias occurs automatically, is below conscious awareness, and is mediated at least in part by the amygdala.

3.3.6.2 Prefrontal Cortex

The medial PFC, especially the SgACC, is involved in the experience and/or regulation of dysphoric emotions in depression and normal sadness reactions [96, 97]. In nondepressed subjects,

hemodynamic activity increases in the SgACC during sadness induction, exposure to traumatic reminders, and extinction of fear conditioned stimuli (see [68] for a review). In addition, the pregenual ACC (PgACC) and vmPFC situated anterior to the SgACC have been implicated in reward processing in healthy subjects and conversely anhedonia in depressed subjects (see [98] for a review). Moreover, in the supragenual ACC, depressed subjects show attenuated BOLD responses versus controls while recalling autobiographical memories [99]. This is associated with lower subjective arousal ratings experienced during memory recall, a function that is impaired in subjects with MDD. More dorsal regions of the PgACC show physiological responses to diverse types of stimuli with emotional valence or stimuli associated with autonomic arousal [100–102]. Higher activity in the PgACC holds positive prognostic significance in MDD, as depressives who improve during antidepressant treatment show abnormally elevated metabolism or hemodynamic responses to emotional stimuli in the PgACC prior to treatment relative to treatment-nonresponsive cases or healthy controls [103, 104]. Regions where metabolism correlates positively with depression severity include the SgACC and ventromedial frontal polar cortex [105, 106]. In contrast, the vlPFC, lateral orbital regions, and the lateral frontal polar cortex show inverse correlations with depression severity, which suggests that they play an adaptive or compensatory role in depression [93].

Within the medial prefrontal cortex, a relatively consistent abnormality reported in early-onset MDD has been a reduction in gray matter in SgACC [93, 107, 108]. The co-occurrence of increased glucose metabolism and decreased gray matter within the same regions in mood disorders has been demonstrated most consistently by comparing neuroimaging data from depressed patients before versus after treatment and from remitted patients scanned before versus during depressive relapse [93]. Functional imaging studies of mood disorders that have taken into account the partial volume effect of reduced gray matter generally revealed that metabolism is increased in the SgACC in the depressed phase and decreases to normative levels with antidepressant treatment (see [93], for a review). This finding is consistent with evidence that SgACC metabolism decreases during symptom remission

induced by a variety of antidepressant treatments, including electroconvulsive therapy and deep brain stimulation [69]. Indeed, the subcallosal ACC (including the SgACC) is one of the most promising deep brain stimulation targets for treatment-resistant major depression [109, 110].

Another crucial aspect to understand the neurobiology of the depression comes from fMRI studies showing that activity in the mPFC correlates with visceral activation in response to emotional [111] and nonemotional stimuli [112]. Humans with lesions of the vmPFC exhibit severe deficits in visceral responses to emotionally salient stimuli [113]. There seems to be an inability to link cortical analysis of a stimulus or situation to the appropriate visceral response. Such a deficit is hypothesized to lead to maladaptive social functioning, including poor decision-making and difficulty in controlling impulsive behavior, on the basis of aberrant "somatic markers" provided by the visceral activation (or the neural signal that produces visceral activation) that normally assists unconscious cognitive processes in controlling behavior [113]. From a mood disorder perspective, it is conceivable that overactivation of this visceromotor system (e.g., due to excessive activity in the mPFC or SgACC) may contribute to the chronic sense of "unease" commonly experienced by patients with depression.

Although the medial PFC appears to play a prominent role in the pathophysiology of MDD, various studies have demonstrated abnormalities in other prefrontal areas. As an example, depressed subjects show exaggerated behavioral sensitivity to negative feedback versus controls during probabilistic reversal learning [114]. The finding was associated with blunted BOLD activity in the dorsomedial and ventrolateral PFC during reversal shifting, in addition to an absence of the normative deactivation of the amygdala in response to negative feedback [114]. Therefore, disrupted top-down control by the PFC over the amygdala thus may result in the abnormal response to negative feedback consistently observed in MDD [115].

3.3.6.3 Other Subcortical Structures

The neurophysiological activity of subcortical structures that shares extensive connections with the medial prefrontal network has been shown to correlate with depressive symptoms. Per example, the

elevation of glucose metabolism in the nucleus accumbens area seen under catecholamine depletion correlates positively with the corresponding increment in anhedonia ratings [105]. In addition, fMRI studies have demonstrated that blunted ventral striatal responses to rewarding stimuli is associated with higher ratings of anhedonia in both healthy [98] and depressed subjects and that hemodynamic responses of the ventral striatum to rewarding stimuli are decreased in subjects with depression compared to controls (see [116], for a review).

3.3.7 Conclusions

The description of MDD neurocircuitry is not yet complete and there are many important details that have yet to be worked out. However, important foci such as the mPFC, the SgACC, and the amygdala have been identified, and their contributions to larger brain networks are now better understood. Given the complexity of this system, there are likely to be multiple factors causing different phenotypical aspects of heterogeneous mood disorders. Despite these limitations, the progress made in the past 15–20 years has been impressive and has helped to guide surgical and device-based therapeutic trials for MDD.

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Electroconvulsive Therapy

4

Cristina Cusin

Electroconvulsive therapy (ECT) was the first device-based treatment to become available for psychiatric disorders in the 1940s and consists of the application of an electric stimulus to the surface of the head, with the aim of inducing a seizure.

ECT is currently used in clinical practice; however, an accurate estimate of the number of patients undergoing ECT in the USA is lacking. A survey of psychiatric practices in the late 1980s found that an estimated 100,000 people received ECT annually, with wide variation among metropolitan areas.

4.1 Indications

ECT is considered the gold standard for *treatment-resistant depression* (*TRD*) or depression that has not responded to two or more adequate pharmacologic trials with antidepressants (ADs). Current guidelines from the American Psychiatric Association (APA) [1] recommend ECT when there is need for a rapid response because

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J.A. Camprodon et al. (eds.), *Psychiatric Neurotherapeutics*, Current Clinical Psychiatry, DOI 10.1007/978-1-59745-495-7_4

of the severity of a psychiatric condition, when there is a history of poor treatment response or a history of good response to ECT, or if there are intolerable adverse effects from medications. In the past decade, the significant superiority of ECT above ADs in the treatment of unipolar depression has been confirmed in several studies and meta-analyses that using rigorous methodology reported a very large standardized effect size close to 1.0 [2, 3]. According to STAR-D data for patients with TRD, whose depression does not remit after two adequate treatments in the current episode, the likelihood of recovery with each subsequent medication treatment decreases by half to approximately 15 % [4].

The clinical efficacy of ECT in this population is well established and substantially exceeds that of any other form of antidepressant treatment, with a 60–90 % rate of response [2]. A recent US Federal Drug Administration (FDA) systematic review in a meta-analysis of efficacy of ECT vs. sham indicated an overall 7.1-point advantage for ECT over sham treatment; however, this included small studies and studies with significant methodologic issues. The two largest sham-controlled trials reported an improvement difference of 12 and 23 points on the Hamilton Depression Rating Scale, respectively [5, 6]. From a recent Agency for Healthcare Research and Quality (AHRQ) Comparative Effectiveness Review [7], the group of patients treated with ECT had a larger mean decrease in depression severity compared to the sham group and greater response rate compared to the group treated with antidepressants. Finally, in a large, multicenter clinical effectiveness study in the community setting that included 398 patients with various diagnoses, the overall response rate was 64 % [8].

Regarding *bipolar depression*, the evidence for the efficacy of electroconvulsive therapy in bipolar depression is not as extensive as that for unipolar depression. However, retrospective observational double-blind sham-controlled studies including both unipolar and bipolar depression concur to support the similar efficacy of ECT [9–13]. In a recent multicenter trial from the Consortium for Research in ECT (CORE) group, comparing the three commonly used electrode placements in 230 patients with unipolar and bipolar depression, Kellner et al. [14] reported remission rates of 55–64 % after a mean of six treatment sessions.

The presence of *suicide risk* (suicidal thoughts and/or acts) is a major reason to consider ECT earlier in the course of treatment. Although retrospective data, including registry and cohort studies, report mixed results for the effectiveness of ECT on suicidal behaviors, those retrospective data are likely to be affected by selection bias, with most severely ill patients being more likely to receive ECT. In the CORE study, expressed suicide intent was shown to be relieved within 1 week or 3 ECT sessions in 38 % of patients, within 2 weeks in 61 %, and in 81 % by the end of the treatment [15].

In *bipolar mania and mixed state*, ECT is generally used in patients who are intolerant of, or refractory to, lithium and other antimanic agents, with remission rates that are comparable to those seen in depression [16]. According to APA guidelines, in severe cases where the patient is at significant risk of harming self or others, requiring physical restraint or large doses of sedatives, or when the symptoms are life threatening owing to exhaustion, ECT should be considered earlier.

ECT has a peculiar role in the treatment of *catatonia*, a syndrome characterized by stupor, mutism, rigidity, refusal to eat or drink, automatic obedience, excitement or hypokinesis, or repetitive movements. ECT is used as second-line management of catatonia after high-dose benzodiazepine trials. Several studies, mostly case reports and case series, have reported a beneficial impact of ECT on catatonia with response rates from 60 to 100 %, without difference in response rate relative to the underlying disorder [17–20]. From a recent review including a total of 211 cases of children and adolescents with catatonia [21], ECT seems to be a safe and effective treatment, producing a marked improvement in 87 % of cases.

Regarding the use of ECT in *schizophrenia*, a recent review [22] identified 31 clinical studies, seven of which compared ECT plus antipsychotics against sham ECT plus antipsychotics in patients with schizophrenia. Overall, patients treated with ECT showed greater global improvement and fewer relapses during the acute phase compared with the sham group. As general indication, ECT combined with antipsychotic medications may be an option for patients with schizophrenia who are treatment resistant or have a limited response to drug therapy alone and when a rapid global improvement is necessary.

Other indications for ECT may include refractory Parkinson's disease, particularly those cases with "on-off" syndrome (e.g., severe, unpredictable motor fluctuations), neuroleptic malignant syndrome, and intractable seizure disorders. ECT is considered a first-line treatment when medical or psychiatric factors require a rapid and robust clinical response, during pregnancy, when there is a clear history of favorable response to ECT, or when the patient prefers ECT to medications.

4.2 Predictors of Response

Older age (above 65) and depression severity have historically been considered predictors of good outcome, together with the presence of melancholic features, psychotic features, and psychomotor retardation. However, in a large multicenter trial, DSM criteria of melancholic features failed to identify depressed patients more likely to respond to ECT [23, 24]. In patients suffering from depressive disorder with psychotic features, higher remission rates have been reported after an acute course of bilateral ECT compared with nonpsychotic depressed patients (95 % vs. 83 %, respectively) [25].

Among the predictors of non-remission for an acute ECT trial are chronicity of depression, longer episode duration, and very high level of medication resistance [26, 27], while bipolar subtype, presence of manic symptoms during depression, low level of severity of depressive symptoms, and protracted duration of the episode were associated with lack of response in a sample of patients with affective disorders [28].

4.3 Contraindications

There are no absolute contraindications to ECT. Preoperative workup for general anesthesia usually includes a detailed clinical history, a physical examination, a review of laboratory data, and an electrocardiogram.

Some medical conditions may increase the risks of adverse events related to ECT, for example, recent myocardial infarction is

a risk factor for adverse cardiac events, and both severity of the ischemia and time lapse since the event should be factored in the decision-making process. Other conditions that require particular attention are uncompensated congestive heart failure, severe valvulopathy, or unstable angina. Brain lesions with increased intracranial pressure, history of recent stroke, severe pulmonary conditions, or tumors of the oral or nasal cavity that may lead to difficulty in airway management are all cases in which the risks and benefits of ECT should be carefully evaluated. Patients should be instructed not to eat or drink anything for at least 8 h prior to each treatment, as it is usually recommended prior to general anesthesia.

4.4 Adverse Effects

Common adverse effects of ECT are usually temporary and include arrhythmias, headaches (up to 45 % of patients report headaches of various severity), muscle aches (most frequent after the first treatment), minor dental and tongue injuries, and nausea (up to 23 %) [29, 30]. These effects may be the result of the seizure, the anesthesia, or some combination of the two, are not medically serious, and can be treated prophylactically with analgesic and antiemetic drugs.

Serious medical complications, such as myocardial infarction, stroke, or death, are exceedingly rare, with an estimated ECT-related mortality rate of less than 1 death per 73,440 treatments [31].

The cognitive side effects produced by ECT have been the subject of intense investigation [32, 33]. Immediately after the induction of the ECT seizure and upon emergence from anesthesia, patients experience a usually brief period of cognitive impairment with compromised orientation, attention, and memory that usually lasts minutes to hours [34]. ECT may cause different forms of amnesia, both anterograde (inability to recall newly learned information, usually short-lived) and retrograde (the forgetting of information learned before treatment). Following termination of ECT, the anterograde amnesia usually resolves, while persistent deficits are usually greater for events that occurred at the time of the ECT series [33]. A recent meta-analysis showed that cognitive abnormalities associated with ECT are mainly limited to the first 3 days

posttreatment, and after 15 days, anterograde memory, processing speed, working memory, and other aspects of executive function were improved beyond baseline levels [35].

Prospective studies comparing ECT patients with controls have not observed anterograde amnesia to persist more than 4 weeks [36]. On the other hand, there is very limited data from longitudinal studies regarding new onset or persistence of anterograde amnestic symptoms [37]. Data regarding long-term or irreversible cognitive deficits in ECT-treated patients is limited to anecdotal reports. Retrograde amnesia following ECT is often a primary reason limiting treatment. It has to be underlined that depression itself is associated with memory disturbances, some of which may persist during the remitted phase of the illness.

A major limitation of studies assessing the iatrogenic cognitive side effects from ECT stems from the instruments used to measure memory performance. Autobiographical memory is usually measured through a test-retest procedure and quantified in terms of percentage of coherent responses over time, while the scoring system is based on percentage consistency with performance at baseline. By their construction, these instruments based on consistency cannot capture any improvement, as follow-up performance is always inferior to baseline performance. In addition, such instruments cannot reliably determine if a possible retrograde amnesia is persistent over time. Lisanby and colleagues [38] showed that patients develop a more pronounced retrograde amnesia for recent impersonal events than for recent personal events, which may suggest a differential effect of ECT on different types of retrospective memories.

The technique utilized in delivering ECT has a profound impact on the nature and magnitude of acute cognitive side effects with bilateral electrode placement, higher electrical dosage relative to seizure threshold, shorter treatment intervals, and higher dosage of anesthetic for induction being independently associated with more severe side effects [38, 39]. Moreover, patients vary considerably in their predisposition to develop adverse effects, with patients manifesting global cognitive impairment before treatment and those experiencing prolonged disorientation in the acute postictal period being the most vulnerable to persistent retrograde amnesia for autobiographical

information [40]. In those patients who experience deficits in attention and concentration due to the underlying condition, ECT usually produces a significant improvement [41].

4.5 Maintenance ECT

ECT is considered highly effective for acute treatment of a major depressive episode; however, there is evidence for a very high rate of relapse after discontinuation. Relapse rates as high as 64–84 % have been reported in controlled studies, predominantly occurring within the first 6 months after a successful treatment course [42]. Very few studies have investigated with rigorous methodology the prophylactic effect of medications or maintenance ECT. In one of those studies from the CORE group, the investigators randomly assigned 84 patients with major depression, who had achieved remission with ECT, to receive continuation treatment with placebo, nortriptyline, or a combination of nortriptyline and lithium. During a 24-week follow-up period, 84 % of placebo-treated patients and 60 % of patients treated with nortriptyline relapsed. The combination of nortriptyline and lithium was able to reduce the relapse rate to 39 % [42]. Most clinicians are convinced that relapse rates can be further reduced by adapting treatment schedules to symptom emergence in each patient, as was shown in a Swedish naturalistic cohort study [43].

Another recent review [44] identified six prospective naturalistic studies and two randomized controlled trials on maintenance ECT. In an NIMH-sponsored controlled trial, 201 patients who were considered ECT responders were randomized to receive 6 months of continuation ECT (C-ECT) given at a predetermined fixed schedule and no medications or continuation pharmacotherapy (C-PHARM) with combination of lithium and nortriptyline. Overall, the relapse rate at 6 months was very high and did not differ statistically between the two arms (37.1 % for C-ECT and 31.6 % for C-PHARM, respectively) [45]. Typically, a maintenance ECT course for depression lasts from 2 to 6 months, with longer courses of treatment indicated for patients with more severe, recurrent, and treatment-resistant forms of depression. In these cases, ECT should be administered at the minimum frequency necessary

to prevent relapse. The APA Task Force calls for reevaluation of the necessity of treatment at least every 6 months, taking into consideration both beneficial and adverse effects. Relapses during C-ECT usually respond rapidly to further ECT treatments and to increases in treatment frequency [46].

4.6 Mechanisms of Action of ECT

During the past seven decades of ECT history, numerous theories regarding its mechanism of action have been suggested [47–49]. An early model of the underlying pathophysiology of ECT and its suggested mechanism of action was the "anticonvulsive hypothesis" with an increased depletion of γ-aminobutyric-acid (GABA) in the cortical network. A compensatory increase in the function of inhibitory neurotransmission (i.e., GABA) in the brain circuit was supposed to be responsible for ECT's antidepressant and anticonvulsive properties [50]. This hypothesis is supported by reports of a significant increase in occipital cortex-GABA concentrations measured by using proton magnetic resonance spectroscopy (MRS) after a course of ECT treatment of depressive disorder [51].

The monoamine neurotransmitter systems, such as norepinephrine, serotonin, and dopamine, have been discussed as possible mediators for treatment response in ECT. In fact a number of studies suggest that changes in dopamine levels and dopamine receptors in the brain are associated with treatment efficacy in ECT [52, 53]. Also endocrine alterations have been suggested as possible mechanism underlying ECT effects, and this hypothesis has been supported by evidence that ECT induces endocrine responses in humans, such as elevated prolactin, adrenocorticotropin, AVP, and NPY [54–56]. Moreover, ECT produces an acute surge in plasma catecholamines, growth hormone, and oxytocin. So far, none of these acute biochemical changes have been associated with clinical efficacy of ECT.

The neurotrophic theory suggests that ECT, like other antidepressants, may have a positive effect by inducing neurogenesis and increasing neurotrophic signaling in the brain [57]. Madsen et al.

[58] reported a strong increase in rat hippocampal neurogenesis after electroconvulsive seizures, showing that both a single seizure and a series of seizures induced neurogenesis in the dentate gyrus of the hippocampus in a dose-response-related manner.

Functional imaging has shown significant changes in cerebral glucose metabolism in bilateral anterior and posterior frontal areas and decreases in cerebral blood flow (CBF) in cingulate and left dorsolateral frontal cortex elicited by the seizures [59].

However, the postictal (i.e., post-seizure) state is characterized by decreases in CBF and CMR, indicating functional suppression [60]. Further neuroimaging research is needed to further investigate the effects of ECT on regional brain function.

4.7 Clinical Application of ECT

4.7.1 ECT Technique

Since its introduction in 1938, the technique of ECT has changed considerably. Before ECT, a general anesthetic is administered to the patient together with a short-acting muscle-paralyzing agent in order to prevent injuries. Hyperventilation is generally obtained via bag valve mask prior to the administration of the stimulus, and the patient's vital signs are closely monitored throughout the procedure.

Studies comparing the effects of different anesthetics (etomidate, propofol, and thiopental) showed that all three had similar efficacy and cardiovascular effects [61]. Ketamine has been investigated in one retrospective study [62] that compared seizure duration, EEG, and cognitive side effects between ketamine and methohexital during ECT and reported ketamine possibly being associated with longer duration of seizure and faster posttreatment reorientation.

The most commonly used muscle-relaxing agent is succinylcholine. In case of patients with history of prolonged immobility, such as catatonia or neuromuscular disease, the use of non-depolarizing agent (such as rocuronium or cisatracurium) is recommended. The technical properties of administrating

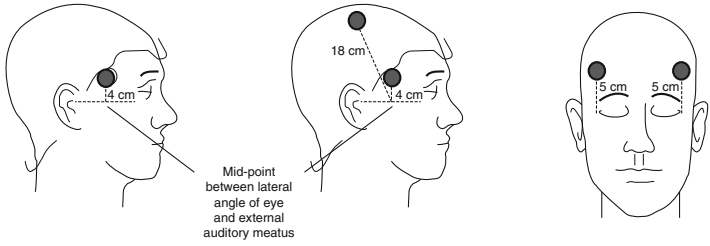

Fig. 4.1 Common ECT electrode positions. *Left*: bilateral stimulation; *center*: right unilateral stimulation; *right*: bifrontal stimulation

ECT, in particular the electric stimulus and electrode placement, can profoundly affect treatment outcomes and side effect profiles.

The parameters of the electric stimulus can vary widely (pulse width from 0.25 to 1 ms, frequency from 10 to 140 Hz, duration of the stimulus 0.5–8 s) and are titrated according to seizure threshold (or "ST," the minimum amount of energy that induces a seizure in an individual patient), clinical efficacy, and the side effects for each individual. The sites of application of the stimulus can be bilateral (BL), right unilateral (RUL), or bifrontal (Fig. 4.1). The EEG recorded during the seizure usually presents patterned sequences consisting of high-voltage sharp waves and spikes, followed by rhythmic slow waves that in most cases end abruptly.

Regarding the schedule of administration, there is no consensus worldwide on this issue, with two treatments per week recommended in some countries (e.g., the UK), while ECT is usually given three times per week in the USA and Australia. A few studies compared different schedules of administration [63, 64]. Overall, their findings suggest that twice-weekly ECT resulted in fewer treatments overall, with better cognitive outcomes, though likely a slower speed of response and longer duration of the treatment course (in weeks).

An optimal approach may be one that tailors the frequency of ECT treatments to the degree of clinical urgency and the type of

ECT, i.e., twice-weekly treatments for forms of ECT associated with high efficacy but greater cognitive side effects (e.g., bilateral ECT) [65].

For decades it was common belief that the induction of a generalized seizure with a duration of approximately 30 s provided the necessary and sufficient conditions for ECT's antidepressant effects [66]. However, the notion that clinical efficacy is correlated with the induction of a seizure was no longer valid after a well-designed randomized, double-masked trial comparing three dosages of right unilateral ECT (RUL) (at 1.5, 2.5, or 6× ST) and a high dosage of BL ECT (2.5× ST). This study demonstrated how the response rate differs significantly between "low-dose" versus "high-dose" ECT, in particular for unilateral therapy, while high dosage RUL (6× ST) and BL ECT did not differ in any efficacy measure [32]. As a result, RUL ECT at 6× the seizure threshold has become the standard practice in most ECT centers, and it seems associated with lower incidence of cognitive side effects, while BL ECT is preferred in cases where a rapid response is necessary, or in the case of no response to RUL ECT.

Further developments of ECT technique with the goal of minimizing cognitive adverse effects are the administration of an ultrabrief pulses [67, 68] and the application of bifrontal stimulation (for a review, see reference [69]).

4.7.2 Interaction with Medications

The practice of stopping antidepressant medications prior to ECT was derived from studies in the 1960s and 1970s in patients who were not resistant to medications. Limited data are available on the combination of medications and ECT. One study suggested that adding imipramine to ECT resulted in superior efficacy compared with adding paroxetine; however, during continuation treatment, relapse rates were reduced in patients receiving paroxetine relative to imipramine or placebo [70].

In a 2009 well-designed prospective, randomized, triple-masked, placebo-controlled study, the efficacy of ECT was substantially increased by the addition of an antidepressant medication,

but such medications may differ in whether they reduce or increase cognitive adverse effects [71].

Some authors in the past have cautioned strongly against the combination of lithium and ECT, because of a higher risk of neurological complications and cognitive side effects. However, hundreds of patients are described as without increase in complications, memory impairment, or recovery times [72], and controlled studies are lacking.

Seizure duration is unaffected by the most antidepressants, while the combination of antipsychotics and ECT is well tolerated and may in fact be beneficial due to their synergistic seizure threshold-lowering effects [73, 74]. There have been several studies indicating the safety of the combination of ECT and risperidone [75] and ECT-clozapine combination in patients nonresponsive to pharmacotherapy [76].

Currently, there is no published prospective randomized double-blind controlled trial about combination of antidepressant therapy as augmentation for ECT in depression. A careful consideration of pros and cons must be undertaken with antiepileptic agents because they may inhibit seizure activity.

4.7.3 Informed Consent

A written informed consent is a necessary part of ECT procedure in the USA and Canada. For the consent to be deemed valid, it must include the information about benefits and risks of the treatment, the information about alternatives to ECT, the risks and benefits of receiving no treatment, and an assessment of the patient's decision-making capacity.

The patient is then given the opportunity to accept or reject the treatment. The form states how many treatments are recommended and also makes the patient aware that the treatment may be revoked at anytime during a course of ECT. The report advises psychiatrists to involve patients in discussion, possibly with the aid of leaflets or videos, both before and during a course of ECT.

4.7.4 New Directions

Over the past three decades, ECT technique has evolved with modification of parameters like ultrabrief pulse ECT, nondominant hemispheric stimulation of the brain, and pulsed square-wave stimulation, in the search for optimal efficacy of the stimulus.

New research is studying the effects of a unidirectional ECT stimuli, with current flowing in one direction and new stimulation techniques, such as "focal electrically administered seizure therapy" (FEAST) [77] and magnetic seizure therapy (MST). MST is a form of convulsive therapy in which seizures are induced through a magnetic rather than electrical impulse, using transcranial magnetic stimulation technology [78].

4.8 Summary

Treatment-resistant depression has been associated with poor clinical outcomes, impaired long-term social functioning, high rates of medical comorbidity, and high rate of mortality from both suicide and medical illness. ECT therapy can be successfully integrated in the algorithm for management of treatment-resistant depression, bipolar disorder, schizophrenia, and catatonia, with specific indications for severe or acute psychiatric condition, a history of poor treatment response or a good response to ECT, or if there are intolerable adverse side effects from medications. There are no absolute contraindications for ECT, and this treatment is usually well tolerated. The cognitive side effects are of major concern for patients and clinicians alike, but in the majority of cases, they are of short duration and resolve within weeks. The mechanisms of action of ECT are still unknown, and numerous theories regarding its mechanism of action have been suggested; however, further research is necessary.

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Vagus Nerve Stimulation (VNS) 5

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5.1 Introduction

Depression is a common, recurrent, and chronic disorder and as such is one of the leading contributors to disability globally [1]. Persistent and severe depression is also strongly linked to suicide which remains a leading cause of death for adolescents and young adults in the USA [2]. Despite the disability burden and the intimate links between depression and suicide, our current treatments including psychotropic

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J.A. Camprodon et al. (eds.), *Psychiatric Neurotherapeutics*, Current Clinical Psychiatry, DOI 10.1007/978-1-59745-495-7_5

medications, psychotherapy, and electroconvulsive therapy (ECT) fail to elicit adequate response in 20–40 % of cases [3]. The less than optimal outcomes observed in the state-of-the-art STAR-D clinical effectiveness trial sponsored by the NIMH highlighted these limitations [4]. Although ECT is highly effective as an acute treatment, it has a high relapse rate (50 % at 1 year) [5].

In response to this need for additional treatment options for the severely depressed patient, a new therapeutic field known as "neuromodulation" has gradually emerged. Vagus nerve stimulation (VNS) is an implantable neuromodulation device, which has established efficacy in medication-resistant epilepsy. It was approved by the US Food and Drug Administration (FDA) as an adjunctive treatment for severe, recurrent unipolar and bipolar depression in 2005 and has been investigated as a therapy for other disorders including anxiety, migraines, and Alzheimer's disease [6, 7].

The purpose of this chapter is to review the history and development of VNS, its efficacy and safety profile, and its current role in clinical practice as a treatment option for patients who suffer from severe depression.

5.2 History and Evidence

VNS was approved for treatment-resistant epilepsy in Europe in 1994 and in the United States (USA) in 1997 [7]. Anecdotal clinical observations of mood improvement in epilepsy patients after VNS implantation suggested a role for VNS therapy in depression and prompted further clinical investigation [6, 8, 9].

5.2.1 Mood Changes in Epilepsy Studies

An initial pilot prospective study of the effects of VNS on mood in epilepsy patients treated either with VNS or antiepileptic drugs showed mood improvement in the VNS group at 3 months. This improvement was not associated with reduction in seizure frequency [8]. Similar outcomes were reported by a separate independent study in a group of patients with epilepsy and mild depression

($n=11$). After VNS therapy, most patients with clinical significant depressive symptoms showed decreases in scores according to the Montgomery-Asberg Depression Rating Scale (MADRS) at 6 months. Interestingly, in terms of antiepileptic effect, only 2 out of the 11 patients were considered responders [9]. Those findings suggested that VNS has a separate and distinct effect on depressive symptoms not related to outcomes on seizures reduction [6, 8, 9].

5.2.2 Open-Label Studies in TRD

At least two pilot studies of VNS in treatment-resistant depression (TRD), with no history of epilepsy, have been carried out. The first trial included 30 patients with chronic unipolar or bipolar depression without psychotic features or rapid cycling. Patients had failed at least two adequate antidepressant trials and remained on their existing antidepressant treatments. A response rate of 40 % and a remission rate of 17 % were achieved after 10 weeks of VNS stimulation [6, 10].

A second report with a bigger sample (30 subjects from the initial sample plus 30 additional subjects all with TRD) showed a less robust effect after 10 weeks [11] with a response rate of 30 % on the 28-item Hamilton Depression Rating Scale (HAM-D), 37 % on the Clinical Global Impression of Improvement Scale (CGI-I), and 34 % on the MADRS. Remission (HAM-D score ≤ 10) rate was 15 %. Subjects in the second report appeared to have a more severe treatment-resistant course as evidenced by an average of 16 antidepressant treatment failures and about 40 % failure to respond to ECT in the current depressive episode [11]. The higher level of treatment resistance may have been responsible for the less favorable results in that sample. Nonetheless, under those circumstances, a response to VNS of 30–37 % indicated a therapeutic signal worthy of study under controlled conditions [6, 11].

These initial open-label studies limited the time of exposure to VNS to only 10 weeks. This is perhaps a short time to fully evaluate benefits of a long-term intervention. Marangell et al. [12] reported longer-term outcomes in the first cohort ($n=30$). They observed both increases in response rate from 40 to 46 % and increase in the remission rate from 17 to 29 % at the end of 12

months (9 months after completion of the initial 3 months acute phase treatment). Improvements in the level of patient's functioning were also noted. These authors pointed out that patients not only tolerated VNS well (91 % continuing to be responders) but also continued to improve over time [6, 12].

5.2.3 Results from the RCT of VNS in TRD

Rush et al. carried out the first randomized controlled study of VNS in patients with treatment-resistant depression [13]. They enrolled 225 patients from 21 different study sites and monitored results after 10 weeks of stimulation. Both the active group and the sham group were implanted with VNS, but only the active group had the device turned on. Patients in the active and sham group had equal number of visits, and sham adjustments were made in the sham group to preserve the blinding [13].

Unfortunately, this was a negative trial with a response rate of 15 % ($n=112$) on the 24-item HAM-D (primary outcome) and a response rate of 10 % in the sham arm ($n=110$) without reaching statistical significance ($p=0.238$) after 10 weeks. Only a secondary measure, the 30-item Inventory of Depression Symptoms (IDS-SR-30) indicated some benefit in the active group with a response rate of 17 % versus a response rate of 7 % in the sham group and statistical significance ($p=0.032$). A reassuring finding was the tolerability of the stimulation; in general patients tolerated it well and only 1 % of patients withdrew due to side effects [6, 13].

5.2.4 Longer-Term Outcomes with VNS versus Treatment as Usual

Following the 10-week randomized controlled trial and given the clinical suspicion that longer exposure to VNS could lead to better therapeutic effects, this cohort was followed in a 12-month naturalistic study [14], and significant reductions on the HAM-D 24 were observed over time. This measure decreased by 0.45 points per month (SE = 0.5) [14].

In light of the abovementioned findings, a standard comparison group was sought to better interpret outcomes with VNS. The comparison group was a group of depressed patients with chronic or treatment-resistant mood disorder. This group ($n=124$) was receiving "treatment as usual" (TAU) including medications, psychotherapy, or other somatic treatments (e.g., light therapy, electroconvulsive therapy, or transcranial magnetic stimulation) and was compared to a group of TRD patients who received VNS along with treatment as usual (VNS plus TAU, $n=205$) [15]. Clinical and health cost outcomes were prospectively followed for 12 months. This nonrandomized trial was conducted at 12 academic medical centers in the USA. The groups were comparable at baseline with highly similar characteristics. However, a few clinical and demographic characteristics differed at baseline including a greater proportion of previous depressive episodes in the TAU group, more exposure to ECT in the VNS plus TAU group, and slightly more ethnic minorities other than Caucasians in the TAU group [6, 15]. In both groups, most patients had a long history of illness (25 years), and the majority had a diagnosis of unipolar or bipolar depression. About 70 % were in a chronic depressive episode and had failed an average of 3.5 adequate antidepressant trials in the current episode. Baseline 24-item HAM-D mean scores were 28 for the VNS plus TAU group and 27.5 for the TAU group.

Subjects in the VNS plus TAU group had a greater reduction in the IDS-SR 30 scores (0.40) per month than the TAU group [SE = 0.10, $t(1092)=4.09$, $p<0.001$]. The IDS-SR indicated a response rate of 22 % for the VNS plus TAU group versus 15 % for the TAU group. The 24-item HAM-D showed a 30 % response rate in the VNS plus TAU group versus 13 % response in the TAU group. The CGI indicated a 37 % response rate in the VNS plus TAU group and a 12 % in the TAU group [6, 15]. The durability of effect of VNS was also analyzed, demonstrating that more than half of the responders (16 of 29) at 3 months continue to respond at 12 months in the VNS plus TAU group. On the contrary, only one of the seven responders to TAU at 3 months continues to respond at 12 months [15]. Overall these outcomes suggested that the use of adjunctive VNS increased the response rate in patients with treatment-resistant depression by 2–3-fold which, despite the

low absolute response rates, it implies an adjunctive benefit worthy of clinical consideration in patients with severe illness [6].

5.2.5 FDA Approval of VNS for TRD

In 2005 the FDA approved VNS as an adjunctive treatment for treatment-resistant depression. The FDA indication is limited to adult patients with chronic or recurrent unipolar or bipolar depression without psychotic features who have failed to respond to at least four previous antidepressants. The device should be implanted only by surgeons with experience operating within the carotid sheath, usually neurosurgeons or vascular surgeons. Patients should be followed by psychiatrists trained in programming the device and with expertise in treatment-resistant depression [6, 16].

Even though the FDA's approval of VNS represented another therapeutic option for patients with TRD, its approval was controversial, despite the safety, meaningful, and durable results observed over the long term. The failure of active VNS to separate from the sham control condition in the 12-week randomized control trial and the use of a matched control group instead of a randomized control group in the long-term data were sources of contention [6].

A main polemic point was the misunderstanding regarding the regulatory standards for approval of medical devices. The FDA's Medical Devices Amendment Act of 1976 defines the types of data to be used in support of safety and effectiveness for a given medical device. These include not only randomized controlled trials but also observational and epidemiological studies [17]. In addition, while for approval of medications the FDA requires two pivotal trials, one positive-controlled multicenter trial represents sufficient effectiveness evidence for medical devices. In the case of VNS, the one-year controlled trial of VNS plus TAU vs. TAU alone fulfilled this requirement [6].

Furthermore, prior to VNS, ECT was the only approved medical device used in TRD. In accordance with the FDA Modernization Act of 1997, treatments that address unmet medical needs, such as adequate treatment of TRD or antiretroviral agents for HIV infection, are eligible for fast-track approval. Manufacturers of treatments approved via the fast-track process are required to conduct

adequate follow-up studies to further characterize efficacy and safety [17]. Such a post-marketing study is currently ongoing for VNS in patients with treatment-resistant depression [18].

The controversy surrounding the FDA approval of VNS has impacted the availability and coverage for VNS therapy. In our own practice in the treatment-resistant depression clinic at an academic medical center, most insurance companies refuse coverage for VNS. In many cases, the therapy is considered "investigational" despite of the FDA approval. A cumbersome appeal process to the initial denial is necessary in the very limited cases that are finally approved [6].

5.3 VNS Basics

5.3.1 Vagus Nerve Anatomy

The vagus nerve exits the cranium through the jugular foramen and travels in the neck between the jugular vein and the carotid artery in the carotid sheath. The vagus nerve provides innervation to the larynx, esophagus, trachea, heart, aorta, and gastrointestinal organs [7, 19]. The right vagus has an important role on heart rate regulation as it innervates the sinoatrial node which is involved in the pace maker function of the heart.

The left vagus innervates the atrioventricular node having less influence in heart rate. It has been demonstrated that stimulation of the left vagus nerve, even at high levels, has no effect on heart rate [7]. Afferent fibers of the left vagus nerve bifurcate to innervate the nucleus tractus solitarius (NTS) bilaterally when they reach the brainstem. The NTS relays information to other brain regions such as the parabrachial nucleus (PBN), the cerebellum, the raphe nuclei, the periaqueductal gray matter (PAG), and the locus ceruleus, as well as to limbic, paralimbic, and cortical regions. The PBN relays information to the hypothalamus, thalamus, amygdala, and nucleus of the stria terminalis. Subsequently, the thalamus relays information to the insular, orbitofrontal, and prefrontal cortices, and other higher brain structures [19]. Vagal projections to the locus ceruleus and raphe nuclei are important because they contain noradrenergic and serotonergic projections, respectively,

implicated in the mechanism of action of traditional antidepressant medications [20].

5.3.2 Mechanism of Action in Depression

As in epilepsy, the mechanisms that mediate the beneficial effects of VNS therapy for depression are incompletely understood. However, evidence from neuroimaging and other studies suggests that VNS therapy adopts a bottom-up approach to modulating the neural circuitry of depression by stimulating vagal afferent fibers in the neck that innervates the NTS, and project rostrally to reach structures that are associated with the regulation of mood and emotions [19]. Functional magnetic resonance imaging (fMRI) studies have also explored VNS' mechanism of action [21–23]. Kosek et al. [22] used single-photon emission tomography (SPECT) to study depressed patients ($n = 15$) who received 10 weeks of VNS stimulation and showed that VNS caused increased regional cerebral blood flow (rCBF) in the left dorsolateral and ventrolateral prefrontal cortex (Brodmann areas 46 and 47) which are known to have decreased regional cerebral blood flow and glucose metabolism in patients with MDD [24]. These findings seem to be in line with the results of studies that assessed the effects of other neuromodulation therapies like the transcranial magnetic stimulation (TMS) and electroconvulsive therapy (ECT) [22, 25]. Heterogeneous stimulation parameters, small sample sizes, and variable imaging methodologies result in significant limitations in order to draw conclusions regarding possible mechanisms of action, but hopefully further hypothesis-driven clinical and imaging studies will increase our understanding of the mechanisms of action of VNS in depression.

5.3.3 VNS Device Surgery

The VNS device consists of an implantable generator connected to electrodes that deliver low-frequency, chronic, intermittent-pulsed electrical signals to the left cervical vagus nerve (Fig. 5.1). The pulse generator is roughly the size of a pocket watch and is

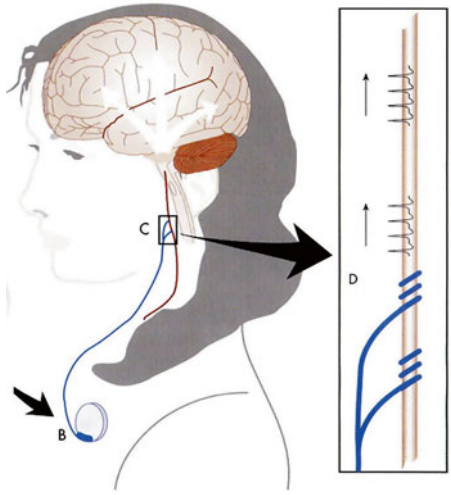

Fig. 5.1 The VNS device consists of an implantable generator that is connected to electrodes by a *thin* and flexible wire. It delivers electrical signals to the left cervical vagus nerve. Adapted from Higgins ES, George MS. Brain stimulation therapies for clinicians. Washington, DC, American Psychiatric Publishing, Inc. 2009

implanted subcutaneously in the anterior chest wall by a surgical procedure similar to a cardiac pacemaker implantation. Through a separate incision in the neck, the surgeon wraps the bipolar nerve-stimulating electrodes around the left cervical vagus nerve. Subsequently, the electrodes are connected to the implanted generator by a thin, flexible wire via a subcutaneous tunneling procedure [6, 19, 26, 27].

5.4 Managing Patients with VNS in the Office

5.4.1 VNS Device Programming

Psychiatrists manipulate the VNS device noninvasively by placing a programming wand over the site of the pulse generator implant. The programming wand is connected to a handheld computer with software installed that facilitates the adjustment of

stimulation parameters. Patients are supplied with a magnet that can be held over the generator to temporarily suspend stimulation, allowing immediate control over side effects if needed. Programmed stimulation resumes when the patient removes the magnet [6, 19, 26, 27].

5.4.1.1 Candidates for Therapy

VNS is an adjunctive option treatment for patients with unipolar or bipolar depression with a treatment-resistant course. Per FDA label, patients should have failed to respond to at least four adequate (in both duration and dose) trials of antidepressant medications [16]. Ideally but not required, patients should have had a trial of psychotherapy before considering adjunctive treatment with VNS [6].

A failed trial of ECT is not a requisite for VNS eligibility. In fact, given the different estimated time of improvement with these treatment modalities, it may be appropriate, in some cases, to use ECT acutely for severe symptoms followed by VNS as a long-term maintenance intervention [6]. Of note, the VNS device should be temporarily shut off while the patient received ECT and then restarted immediately after the procedure. Similarly, and due to its nonsystemic nature, VNS can be combined safely with antidepressant including MAOIs [6].

5.4.1.2 General Precautions and Contraindications

VNS is not approved for major depression with psychotic features or schizoaffective disorder. The presence of paranoid delusions would make placement of an implanted device not ideal. Unstable axis II conditions, such as borderline personality disorder, should be considered a relative contraindication because the patient may lack sufficient stability to comply with the demands of a surgical intervention, frequent follow-up, and slow trajectory of response. VNS has not been studied during pregnancy. However, given that it is a nonsystemic treatment, one might assume that it has a very limited effect on the fetus [6].

Both patients and physicians should be aware that MRIs are contraindicated. Nonetheless, by using special send-receive coils, it is still possible to obtain an MRI of the brain; otherwise, a CT scan should be used instead of an MRI [6].

If VNS fails to provide clinical improvement, the device can be switched off and be left in place. Other options include explantation of the pulse generator; however, it is generally recommended that the electrode (attached to vagus nerve) remains in situ because of concerns that adhesions around the vagus nerve might increase the risk of nerve injury during the removal procedure. If the electrodes remain in situ, the MRI-associated precautions remain in effect. Other devices such as cell phones, microwave ovens, or airport security systems should not have any adverse effects on functioning of the VNS device [6].

5.4.2 Dosing Parameters

During the office follow-up visits, the psychiatrist assesses the clinical progress, monitors side effects, and performs adjustments of the stimulation. Actual adjustment of the stimulation settings usually takes about 10 min. The patient holds a programming wand over the implanted pulse generator (on the skin or thin layer of cloth), and the clinician interrogates the device by means of a handheld computer. Four principal settings are adjusted: current charge (mA), pulse width (microseconds), frequency (Hz), and duty cycle (percentage the device is on/off) [6].

***Current Charge*:** Patients are generally started at 0.25 mA, which is then gradually increased in 0.25 mA increments while maintaining a comfortable tolerance level [6]. Indication that the maximum tolerable level has been reached/exceeded is immediately obvious, as the patient will report significant discomfort or cough. Current dosing ranges from 0.25 to 3.5 mA [6]. The median dose in the 12-month pivotal trial was 1.0 mA [15].

***Frequency and Pulse Width*:** Frequency ranges from 1 to 30 Hz and a typical value is 20 Hz. Stimulation frequencies of 50 Hz and above can cause major irreversible damage to the vagus nerve [7]. Pulse width ranges from 130 to 1000 μs and a typical value is 500 μs [6]. Pulse width of 130 μs is less frequently used because they are thought to be subtherapeutic.

***Duty Cycle*:** It refers to the on-time relative to off-time of the stimulation in seconds, and it is expressed as a percentage. The stimulus on-time ranges from 7 to 60 s with a typical value of 30 s. The off-time can be set anywhere from 0.2 to 180 min, and a typical value is 5 min [6]. Tables for easy and safe adjustment of duty cycle are available and should be provided by the manufacturer.

The first dosing visit is done about 2 weeks post surgery to allow for healing of the tissue postoperatively. Weekly visits are recommended for the first month to closely monitor tolerance and mood changes. Initial titrations occur at 0.25 mA increments in current so that a target dose of 1.0 mA is achieved after a month. Subsequent visits can be conducted every 2 weeks and then spaced to once a month if there is sustained clinical improvement. By 3 months, if the current amplitude is optimal in the range of 1.0–1.5 mA but the patient has not improved, then the duty cycle can be increased. A significant proportion of responders to VNS only emerge in the second 6 months of stimulation. A full VNS trial may require up to a year [6].

5.5 VNS Effectiveness in Clinical Practice Post: FDA Approval

Research data on long-term efficacy lead to the FDA approval of VNS. However, how these research results translate into clinical practice was an important question to address. This background question led our group to publish the one-year clinical outcomes under routine clinical circumstances in our patients ($n=15$) who received VNS implants for depression in the first 18 months after the FDA *approval* [28]. This small investigation included 10 patients with major depression and 5 patients with bipolar depression. All patients received VNS implants for severe depression with previous nonresponse to a minimum of four antidepressant trials. VNS was used as an adjunct to existing medications. Results showed a statistically significant decrease in the Beck Depression Inventory (BDI) after VNS therapy, from a baseline mean score of 37.8 (SD = 7.8) (severe depression) to a mean score of 24.69 (SD = 11.4) (moderate depression) ($p<0.01$). Response rate and remission rates were 28.6 % and 7 %, respectively, according to

the BDI. Secondary outcomes such as the HAM-D 24 indicated a 43 % response rate and a 21.4 % remission rate. We attributed the numerically lower rates in the BDI (a self-reported measure) compared to the HDRS to the fact that depressed patients may be less aware of their improvement due to their negative perception or pessimism as a core feature of their illness [28].

We also directly compared our one-year clinical response rates to those previously reported in efficacy trials after one year [28]. We observed that according to the HAM-D (the most commonly used scale in clinical trials), our patients' response rate of 43 % fell in between a 46 % response rate previously reported by Marangell et al. [12] in an open-label VNS trial and 30 % response rate from the pivotal VNS plus treatment as usual (TAU) trial by George et al. [15].

Interestingly, our VNS cohort had more prior exposure to ECT, greater number of lifetime major depressive episodes, and higher number of previous suicide attempts and hospitalizations compared to that of subjects in the VNS plus TAU study patients [15]. Nevertheless their clinical improvement was significant. We also compared categorical outcomes on the HDRS—24 items end-point scores at one year between our study and the pivotal VNS with TAU trial and found no statistically significant differences in outcomes in between our results and that trial [28]. Thus, this effectiveness study found comparable results in standard clinical practice with VNS as in the research trials even though the cohort of clinic patients was a relatively more severe TRD patient population.

5.6 Safety and Tolerability

5.6.1 Surgery Complications

Pain and wound infection are the most common surgical complications. Wound infection occurred in about 3–6 % of patients in the clinical trials and although generally were managed with antibiotics, removal of the device has been required in rare occasions. Transient left vocal cord paresis has been reported. Most worrisome but rare asystole has occurred in the operating room during lead testing in 1 per 1000 implants. No deaths have been reported due to surgical implantation [6, 29].

5.6.2 Side Effects Related to Stimulation

Side effects related to the stimulation are the most common. Patients experience them only while the stimulation is on. They are generally mild and related to the intensity of the output current with hoarseness, dyspnea, and cough being the most commonly reported. Side effects tend to decrease over time, although hoarseness persists in about 27–54 % cases [6, 15, 29].

5.6.3 Psychiatric Adverse Events

Treatment emergent hypomania (1.2 %) and mania (1.2 %) have been reported with VNS. They have occurred mostly in bipolar patients, and in most cases VNS has been continued safely after resolution of symptoms [6, 14].

Another important outcome for any antidepressant treatment is the risk of suicidal ideation and suicidal behavior. For VNS therapy, the pivotal trial adjunctive VNS vs. TAU defined treatment emergent suicidality as a two-point increase on the suicide item of the HAM-D 24. The rate of treatment emergent suicidality was 3 % for the VNS group (5/181) and 2 % (2/184) for the TAU group. The difference was not statistically significant; therefore, there is no suggestion that VNS would specifically exacerbate suicidality [6, 30].

The risk of suicidal behavior was summarized in the executive summary and discussion of the VNS therapy indication for depression presented to the FDA. This summary estimated the rate of suicide attempts in the combined VNS studies in TRD ($n = 345$) to be 3.5 % per patient year. A patient year was defined as one subject receiving VNS therapy for 12 months [30]. This rate is very similar to that described by Khan et al. [31], who reported a 3.4 % suicide attempt rate in a review of 45 studies of major depression comprising 7 standard antidepressant medications (fluoxetine, sertraline, paroxetine, nefazodone, mirtazapine, bupropion, and venlafaxine) in nearly 20,000 patients. Likewise, the rate for completed suicides for the combined VNS studies was 0.4 % patients per

year, which is also comparable to a 0.7 % suicide rate reported by Khan et al. on antidepressants [31]. These data suggest that VNS does not possess an increase in suicidal risks superior to that of antidepressants [6, 30].

Finally, no cognitive side effects have been reported with VNS, but to the contrary, a trend toward improvement in cognitive functions was reported by Sackeim et al. [6, 32].

5.6.4 Adherence to Treatment

Rush et al. reported a 90 % continuation rate of VNS therapy after a year. Side effects were responsible for a 3 % discontinuation rate. The remaining patients discontinued to lack of efficacy [14]. This rate decreased at 2 years with an adherence of 80 % to treatment as reported by Nahas et al. [33]. The expected battery life for this device is 5–10 years, after which surgical replacement of the battery can be pursued.

5.7 Summary

Well established data supports VNS's efficacy and safety in TRD. Nevertheless, it is not devoid of limitations including the fact that the randomized controlled trial over 12 weeks was a negative study. However, results from a controlled post-marketing study as suggested by the FDA (results expected in 2012) may help clarify VNS' role in depression and will likely determine its future as a neuromodulation treatment option in TRD [18].

In the interim unfortunately, there is very limited access to VNS for patients, despite FDA approval. The recent decision by Centers for Medicare and Medicaid Services (CMS) on behalf of Medicare to not cover the costs of VNS implants in TRD has been a major deterrent to the coverage of VNS by all insurance companies, as a reasonable therapeutic option even in the most refractory cases of depression.

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Neurosurgical Ablative Procedures for Psychiatric Disorders

6

Simon Ducharme, Bruce H. Price, and Darin D. Dougherty

6.1 Introduction

Neurosurgical ablative procedures are occasionally performed for psychiatric disorders in selected treatment-refractory cases. These include anterior cingulotomy, anterior capsulotomy, subcaudate

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J.A. Camprodon et al. (eds.), *Psychiatric Neurotherapeutics*, Current Clinical Psychiatry, DOI 10.1007/978-1-59745-495-7_6

tractotomy, and limbic leucotomy. All these surgeries are performed with MRI-based stereotactic guidance to produce restricted focal lesions in order to minimize the burden of adverse effects. Neurosurgical treatments of mental disorders (also known as "psychosurgery") are rooted in a controversial history, including great scientific achievements, but also unacceptable ethical violations. Despite this complex background, neurosurgical treatments have been continuously performed up to this day in a handful of specialized clinics worldwide, with a good profile of safety and efficacy.

The two principal clinical indications for psychiatric neurosurgeries are major depressive disorder (MDD) and obsessive-compulsive disorder (OCD). In current practice patients with severe disabling symptoms are carefully selected and required to have no adequate responses to most, if not all, available psychotherapeutic and pharmacological treatments. After a brief historical overview, this chapter describes the four most frequently used procedures, along with a review of the available data on efficacy and adverse effects.

6.2 Historical Perspective

Neurosurgical interventions to relieve mental distress have their origins in prehistorical times, with documented use of trepanation up to 10,000 years ago [1]. The modern rebirth of the neurosurgical approaches to treat psychiatric illnesses came in the 1940s with the development of prefrontal leucotomy [2]. The popularity of this procedure had an exponential rise over a few years, followed by a drastic decline in the following decades [3]. The enthusiasm for the early uses of psychosurgery in the 1930s must be understood within the historical context of that era [2]. Up to the twentieth century, there were no effective treatments for patients plagued by major mental illnesses and the role of the psychiatrist was largely curatorial. The development of the "malaria cure" for general paresis of the insane (tertiary neurosyphilis) by Dr. Wagner-Jauregg (1927 Nobel Prize) first demonstrated the ability to treat, and even cure, chronically ill patients within asylums. Attempting to help the great number of patients who remained untreatable, a

number of therapies were attempted over the next couple of decades, including hydrotherapy and insulin shock treatment. Unfortunately, none led to a safe and effective cure for patients institutionalized on overflowing psychiatric wards.

It was in this context that the development of neurosurgery to treat patients with severe mental illness took place. At the 1935 International Neurological Congress in London, two physiologists from Yale University (Jacobsen and Fulton) presented their findings on the behavioral impact of bilateral frontal lobe ablations in two chimpanzees. Dr. Egas Moniz, professor and chair of neurology at Lisbon, was in attendance and became intrigued by these behavioral findings. Over the next few months, Moniz and the neurosurgeon Almeida Lima began testing prefrontal leucotomy on patients with psychosis. After various attempts, they elected to perform interventions with a steel leucotome to sever white matter pathways within the prefrontal cortex [4].

Walter Freeman, professor of neurology at George Washington University, was at the same conference in London. After hearing about Moniz's work, he collaborated with the neurosurgeon James Watts to develop "frontal lobotomy" in 1936 [5]. By 1942, they had treated over 200 patients, and initial results suggested that this procedure was helpful in a large percentage of their patients, though there were adverse events including seizures and apathy in a many cases [6]. Freeman subsequently modified the procedure by using an ordinary ice pick (and later a specially crafted surgical leucotome) to break through the orbital bone and sever the prefrontal cortex immediately above it using electroconvulsive therapy as the only form of anesthesia, which led to the end of the collaboration with Watts. Freeman enthusiastically began touring the country with great media fanfare to perform this transorbital procedure [3]. In 1961, a British review of over 10,000 prefrontal lobotomies concluded that, although 70 % of patients had some improvement, there were unacceptable 6 % mortality, 1 % seizure, and 1.5 % disinhibition rates [7].

In the early 1950s, there was a steep decline in the use of all forms of psychosurgeries, which is most likely attributable to the development of chlorpromazine (followed by other medications) for the treatment of severe psychiatric disorders, and increasing

concern over the cognitive and motivational effects of frontal lobe ablation [2]. With progressive developments in psychopharmacology and the rise of psychoanalytical theories, the existence of psychosurgery was almost forgotten in the second half of the twentieth century. Despite these challenges and the opposition from various political and social advocacy groups, neurosurgical procedures for psychiatric disorders have been continuously performed throughout this period in specialized centers including the Massachusetts General Hospital (MGH).

As the concerns for adverse effects of early psychosurgeries increased, physicians began to test whether smaller focal lesions could replicate the benefits of prefrontal leucotomy with less adverse sequelae. Over time, four different stereotactically guided procedures ablating three different areas emerged as the safest and most effective: anterior cingulotomy targeting the anterior cingulate cortex (ACC), anterior capsulotomy targeting the anterior limb of the internal capsule, subcaudate tractotomy targeting the basal forebrain (substantia innominata), and limbic leucotomy combining the anterior cingulotomy and subcaudate tractotomy. In current practice, these procedures are almost exclusively done in patients with treatment-refractory OCD and MDD.

6.3 Neurocircuitry of MDD/OCD

In order to understand the rationale underpinning targets of ablative neurosurgical treatments, it is critical to understand the neurocircuitry of mood disorders and OCD. Although the precise pathophysiology of MDD and OCD remains elusive, multimodal imaging methods have greatly improved our understanding of the neurocircuitry underlying these disorders [8, 9]. For a detailed discussion of the neurocircuitry of MDD and OCD, the reader is referred to Chaps. 1 and 2. In summary, the neurocircuitry of OCD is based on dysfunction in cortico-striato-thalamo-cortical loops, in particular the OFC (ventral cognitive) circuit, the ACC (affective) circuit, and the caudate nucleus which all play central roles [8]. MDD is related to dysfunction within an extended network

including the medial prefrontal cortex and anatomically related limbic, striatal, thalamic, and basal forebrain structures [9]. Key nodes include the anterior subgenual anterior cingulate cortex (area 25), the medial orbitofrontal cortex, the anterior cingulate cortex, and the amygdala.

6.4 General Caveats of the Literature

When reviewing the 50-year-old literature on the efficacy of neurosurgical procedures for psychiatric disorders, several factors have to be taken into account [10]. First, procedures varied from site to site and have changed over time. In the early reports, patient populations were heterogeneous, relating to the fact that diagnostic criteria for psychiatric disorders have changed over time, only becoming more clearly operationalized in 1980 with the third edition of the Diagnostic and Statistical Manual of Mental Disorders. The use of standardized disease-severity scales is a relatively new phenomenon, with the vast majority of the older literature defining outcomes on nominal scales (e.g., improved, moderately improved, markedly improved).

In terms of patients undergoing these procedures, it is important to note that, with the development of an increasing array of medications and validated therapies, the concept of treatment-refractory illness has changed over time. Current surgical patients are probably more ill than those in the past. In addition, since procedures are only performed in a few specialized centers, and on only a few patients annually at each site, most efficacy reports have small sample sizes. Fortunately, in recent years major academic centers have developed protocols to gather high-quality prospective data using standardized scales. Finally, probably the most significant caveat is that the unethical nature of "sham" psychosurgery involving craniotomy has limited the possibility of gathering randomized controlled data. The development of noninvasive gamma knife procedures has permitted the circumvention of this problem in the recent years.

6.5 Anterior Cingulotomy

Stereotactic anterior cingulotomy was developed by Foltz and White initially for the treatment of the emotional component of chronic pain [11]. Subsequently, Ballantine and colleagues improved the technique and widened the applications to MDD and OCD [12]. In today's practice, anterior cingulotomies are performed under local anesthesia using a stereotactic frame guided by MRI, targeting the ACC (Brodmann area [BA] 24 and 32). Lesions are produced with a thermoelectric ablation electrode (10 mm exposed tip heated at 85 °C for 60 s) through bilateral burr holes. Initially, a single pair of lesions was made in the ACC, 2 cm posterior to the most anterior part of the frontal horn of the lateral ventricle, 0.7 cm lateral to midline, and 0.5 cm superior to the corpus callosum. Around 2000, the procedure performed at MGH was modified to a triple anterior cingulotomy, adding two pairs of lesions to the standard one, each 7 mm anterior and 2 mm inferior to the previous ones [13]. This change was implemented because a significant number of patients who received an initial smaller lesion ultimately required additional lesions to achieve benefit. Each lesion is approximately 2 cm in height and 8–10 mm in diameter [14], with an estimated lesion burden of 13.3 ml [15] (Fig. 6.1). Patients are ambulatory 12 h post-procedure and discharged 3–5 days later.

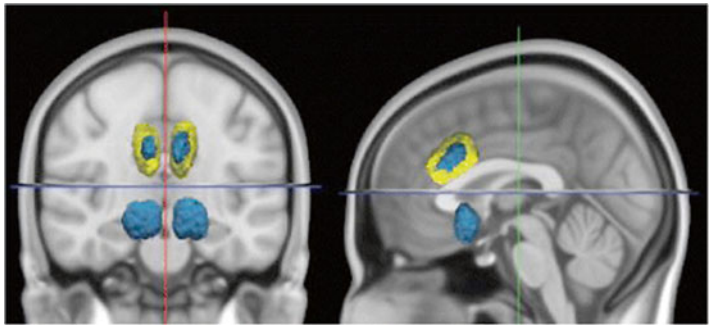

Fig. 6.1 Three-dimensional projection of representative anterior cingulotomy (*yellow*) and limbic leucotomy (*blue*), displayed on coronal and sagittal T1-weighted mni152 templates (*left* to *right*). *From Yang, J. C. et al. (2014). Lesion analysis for cingulotomy and limbic leucotomy: comparison and correlation with clinical outcomes. J Neurosurg, 120(1), 152–163*

At MGH, the current philosophy is to make the smallest possible lesions in a first surgery and to perform a revision procedure to extend lesions (either a larger cingulotomy or limbic leucotomy) if needed after at least 6 months. Approximately 40 % of patients need a second procedure [16]. This is thought to be the optimal approach since the size of cingulotomy lesions is not necessarily directly correlated to clinical response [17].

Although the ACC is the main target of this procedure, during the process of creating the lesions, the electrode passes through the cingulate cortex to interrupt the underlying white matter fasciculus known as the cingulum bundle. It remains undetermined in which proportion the cortical or the white matter components are responsible for clinical benefits. Independent of the precise mechanism of action, because of the relative success and low morbidity and mortality rates, the anterior cingulotomy has been the most widely used psychiatric neurosurgical procedure in North America over the last several decades.

6.5.1 Efficacy of Anterior Cingulotomy

Early reports on cingulotomy usually included mixed samples of psychiatric disorders including MDD and OCD, but also other anxiety disorders, schizophrenia, pain disorders, personality disorders, eating disorders, and violent/aggressive behavior in patients with autism/intellectual disability. In 1987, Ballantine and colleagues reported a prospective analysis of the safety and efficacy of anterior cingulotomy in a sample of 198 patients with heterogeneous psychiatric disorders [18]. Although the mixed population and lack of control procedures limit interpretation, this remains the largest published prospective cohort. Considerable improvement or remission was observed in about 64 % of mood disorders, 56 % of OCD, and 79 % of other anxiety disorders. Subsequently, Spangler and colleagues reported a retrospective analysis of MRI-guided cingulotomy in a mixed sample of 33 patients. The response rate using conservative criteria was 53 % in patients with mood disorders and 27 % of patients with OCD [19]. In terms of mood disorders, there was better response in MDD than in patients with bipolar disorder.

Since the 1990s, anterior cingulotomies have mainly been performed in carefully selected cases of treatment-refractory OCD and MDD. Requirements for consideration of surgical treatments include inadequate response to most if not all available pharmacological strategies, cognitive behavioral therapy (including intensive exposure with response prevention therapy), and ECT for MDD.

The largest prospective study on OCD was reported by Sheth and colleagues (2013) in a cohort of 64 treatment-refractory patients [13]. At the first follow-up (mean 10.7 months), response rate was 35 % and there was partial response in 7 %. There was a 26 % mean decline on the Yale-Brown Obsessive Compulsive scale (YBOCS). Of those 64 patients, 30 patients underwent a second procedure (either a second cingulotomy or subcaudate tractotomy). At the last follow-up (mean 58.5 months) for patients who only had a cingulotomy, the response rate increased to 38 %, with an additional partial response in 25 % of patients. In the complete sample including subjects with multiple procedures, the final response rate was 47 %, plus 22 % of partial response. A small study from another group ($n=17$) obtained fairly similar results, reporting a 47 % response rate over a 24-month follow-up [20].

For MDD, Shields and colleagues (2008) reported a prospective cohort of 33 patients with well-characterized treatment-refractory illness over a mean follow-up of 30 months [21]. Clinical response was defined as a 50 % decline on Beck Depression Inventory (BDI) and Clinical Global Improvement (CGI) scale rating of 2 or less (i.e., much or very much improved). Partial response corresponds to a 35 % decline on the BDI and CGI of 2 or less. Of these 33 patients, 17 only underwent the anterior cingulotomy procedure. Of those 17 patients, there was a 41 % response rate with an additional 35 % of patients with partial response. The other 16 patients had subcaudate tractotomy as a second surgical intervention because of limited benefit at 1 year. For the whole sample, there was a 33 % response rate and a 42 % partial response rate.

6.5.2 Adverse Effects of Anterior Cingulotomy

Since 1962, over 1000 stereotactic anterior cingulotomies have been performed at MGH and the procedure has never been directly implicated in a patient's death. In addition, of the 150 MRI-guided

procedures done since 1991, only two patients have experienced severe adverse events: one with a hemorrhagic stroke and cerebral abscess and the other with a cerebral abscess and hydrocephalus. The most common adverse events can be divided in three broad categories: seizures, urinary problems, and cognitive changes [10, 14]. Postoperative seizures occur in approximately 1–5 % of patients, but are almost always a transient phenomenon. They most often occur in patients with a preexisting seizure history. The new onset of recurrent seizures is very rare. Prophylactic treatment with anticonvulsant medication is not recommended. Urinary incontinence or retention is relatively common in the immediate postoperative phase, but also almost always transient. With regard to cognitive impairment, multiple reports using neuropsychological batteries similarly concluded that the adverse effects of cingulotomy are negligible [20, 22, 23]. One study by Long and colleagues (1978) even reported improvements in cognitive function postoperatively in 68 % of the patients. However, there are some reports of deficits in sustained attention [24], self-initiation [25], higher visual cognition [26], action initiation [27], and performance on a reward-based task [28]. Of note, some of the older studies were done in patients with chronic pain as opposed to MDD/OCD, and the functional impact of these findings in real life is uncertain.

6.6 Anterior Capsulotomy

Inspired by early procedures targeting the bilateral dorsomedial thalamic nuclei [29], the Swedish neurosurgeon Lars Leksell developed a lesion procedure targeting the anterior aspect of the internal capsule [30]. The procedure named anterior capsulotomy creates lesions (12–20 mm height) within the anterior limb of the internal capsule, impinging on the anterior ventral striatum (Fig. 6.2) [31]. This has the effect of interrupting fibers connecting the prefrontal cortex to subcortical nuclei, including the dorsomedial thalamus. Anterior capsulotomies are traditionally performed with thermocoagulation, but can now also be done less invasively with gamma irradiation (gamma knife). The gamma knife makes craniotomy unnecessary, producing smaller lesions in the ventral

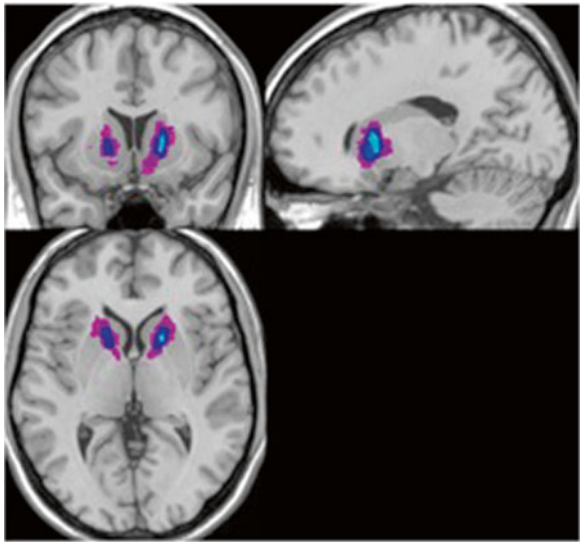

Fig. 6.2 Orthogonal sections through the anterior capsule showing the site of the capsulotomy lesions (thermocapsulotomy and gamma capsulotomy patients combined). The amount of lesion overlap across participants is color coded (*light blue*, highest overlap; *purple*, least). The coronal, sagittal, and axial views (clockwise) are overlaid on a spatially normalized brain form a healthy participant for display purposes only. *From Ruck, C., et al. (2012). Predictors of medium and long-term outcome following capsulotomy for obsessive-compulsive disorder: one site may not fit all. Eur Neuropsychopharmacol* ***22*** *(6): 406–414*

capsule and opening the door to sham-controlled trials. Indications are similar to other procedures, mainly treatment-refractory OCD and MDD.

6.6.1 Efficacy of Anterior Capsulotomy

Early data from Leksell and colleagues indicated good efficacy in both OCD and MDD, with respective response rates of 50 % and 48 % [30]. More recently, this procedure has been used primarily for patients with intractable OCD and less so for mood disorders. In a large retrospective review of 213 OCD patients, [32] reported

a response rate of 64 %. Two different prospective studies of capsulotomy for OCD ($n = 35$ in both studies) demonstrated excellent response rates of 70 % [33] and 86 % [34]. A few other smaller prospective reports from different groups also indicated good efficacy of thermoablation capsulotomy, with response rates (defined by a 33 % drop in YBOCS) in the 50–60 % range [35, 36]. Anterior capsulotomy has also been shown to have some efficacy in severe non-OCD anxiety disorders [37].

There are some data on gamma knife capsulotomy from a prospective study by Rück and colleagues in 25 subjects with treatment-refractory OCD [38], eight of which were treated with the gamma knife procedure. Outcomes and lesion size were similar in thermoablation and gamma knife cases. For the complete sample, there was a mean 49 % YBOCS reduction, 48 % response rate, and 36 % remission rate (YBOCS < 16). Secondary outcomes showed improved functioning in social and family life, but not in occupational aspects. A follow-up analysis suggested that symptoms of symmetry/ordering were associated with worse outcomes [31]. There are other small reports of positive outcomes with gamma knife capsulotomy for OCD [39, 40].

Finally, a group from Brazil has developed a gamma knife capsulotomy creating a lesion in the more ventral area, which they refer to as ventral capsule/ventral striatum. This is also a target for deep-brain stimulation of OCD and MDD [41, 42]. They initially reported clinical response in 3/5 OCD patients at 48 months [43]. This group recently completed a one-year randomized sham-controlled clinical trial of this procedure for intractable OCD, with preliminary results showing clinical response in 3/8 patients in the active treatment group compared to no response with the sham procedure [44].

6.6.2 Adverse Effects of Anterior Capsulotomy

The common but transient postoperative side effects of anterior capsulotomy include headaches, urinary incontinence, and confusion. In terms of more severe acute complications, one group reported a case of hemiplegia due to perioperative hemorrhage [36]. Postoperative weight gain seems to be a more specific adverse

effect of capsulotomy, with a reported average 10 % increase in body weight [32, 38]. In two separate cohorts, persisting seizures requiring treatment occurred in 1/24 and 1/15 patients [32, 35]. Of note, gamma knife can lead to acute and delayed radiation-induced brain edema and cyst formation [38]. Development of clinically significant edema reflects individual differences in sensitivity to radiation that remain poorly understood. Late cyst formation (from 2 to greater than 5 years post surgery) has occurred from 1.6 to 3.6 % of patients after surgery for arteriovenous malformations and may in part be related to the extent of postoperative radiation-induced edema [45].

Initial studies did not find evidence of cognitive impairment or alteration in personality after capsulotomy, though there were reports of behavioral dyscontrol [35], diminution in self-care [46], and amotivational states [10, 37]. In their recent prospective report, Rück and colleagues (2008) described a more sobering picture, with significant adverse effects in 40 % of the 25 subjects. These included apathy, mild difficulties with executive functions, and one case of severe sexual disinhibition. Of note, 6/10 subjects who experienced adverse effects had undergone multiple surgeries or high doses of radiation, potentially contributing to these negative sequelae. However, the cognitive impact of capsulotomy is not all negative. One study showed post-capsulotomy improvement on multiple measures of executive functions, verbal fluency, and the Iowa Gambling Task [47].

6.7 Subcaudate Tractotomy

Based on early work by Scoville, subcaudate tractotomy was developed in the 1960s by Dr. Geoffrey Knight in Great Britain as one of the first attempts to limit adverse effects by restricting lesion size [48, 49]. Through an empirical process, Knight refined a surgical procedure in which a lesion is created bilaterally in the most posterior territory of the basal forebrain, i.e., the substantia innominata [50, 51]. The substantia innominata is the white matter located just inferiorly to the head of the caudate nucleus. A lesion in this area interrupts white matter tracts connecting the OFC and subcortical structures (Fig. 6.1).

The stereotactical procedures were at first performed via the implantation of yttrium-90 seeds, but have been more recently done with electrical thermocoagulation. As demonstrated by a recent imaging study, subcaudate tractotomy lesions encompass the nucleus accumbens (ventral caudate), in addition to the subgenual cingulate cortex (BA 25) and the medial OFC [15]. Lesions interrupt the uncinate fasciculus, which is the white matter tract connecting the limbic system to the OFC, and the white matter adjacent to the medial OFC. Current indications for subcaudate tractotomy include treatment-refractory MDD, OCD, and occasionally other severe anxiety disorders.

6.7.1 Efficacy of Subcaudate Tractotomy

The early experience of Knight's group suggested that subcaudate tractotomy is effective in patients with both MDD and OCD [52]. Defining response as either recovery or mild residual symptoms with little interference on daily life, response rates were 68 % (53/78) in depressed patients (better response for recurrent episodes than chronic subtype) compared to 50 % (9/18) for "obsessional neurosis." The other anxiety disorders showed an intermediate profile, with a 62.5 % response rate (15/24). A subsequent review examining outcomes for all tractotomies performed between 1979 and 1995 indicated that 34 % of the 234 patients with MDD/OCD were well 1 year postoperatively [53]. Across all diagnoses, authors reported that 40–60 % of nearly 1300 patients were living normal or near normal lives with maintenance medication, including a reduction in suicidality [54]. A different group reported clinical response to subcaudate tractotomy in nine patients with bipolar disorder [55]. Using subjects as their own controls, there was reduced frequency and severity of both depressive and manic episodes in a majority of subjects, with some of them becoming responsive to medications that were inert pre-surgery [55]. There are limited recent data on the efficacy of isolated subcaudate tractotomy, as most groups have used this procedure as part of more extensive limbic leucotomies (discussed below).

6.7.2 Adverse Effects of Subcaudate Tractotomy

Adverse sequelae from subcaudate tractotomy include transient headaches, confusion, disinhibition, and somnolence. In the initial report, personality changes were noted in 6.7 % of patients and seizures in 2.2 % [52]. In the later reviews, the rate of seizures remained unchanged but no enduring personality changes were observed [54]. A prospective neuropsychological study indicated that, although there were decrements in recognition memory and performance on tasks sensitive to frontal lobe functioning during the early postoperative period, there was no evidence of significant long-term cognitive deficits secondary to subcaudate tractotomy [56].

6.8 Limbic Leucotomy

Limbic leucotomy was developed in England in the 1970s by Dr. Desmond Kelly and colleagues [57]. This procedure is a combination of the previously described anterior cingulotomy and subcaudate tractotomy (Fig. 6.1). At MGH, subcaudate tractotomies are usually done as a second-step procedure in patients with treatment-refractory MDD or OCD who did not have a satisfactory response at least 6 months after an initial anterior cingulotomy [21]. Patients undergoing repeat surgeries have much higher response rates (53 %) than patients who continue treatment as usual (17 %), with subcaudate tractotomy showing better outcomes than a repeated more extensive anterior cingulotomy (64 % vs. 38 % response rate) [16].

6.8.1 Efficacy of Limbic Leucotomy

In an early report by Kelly and colleagues on a series of 66 patients (mean follow-up 16 months), there was significant improvement in 89 % of patients with OCD, 78 % with MDD, and 66 % for other anxiety disorders [58]. In a retrospective assessment of 21 patients (15 with OCD and 6 with MDD) who underwent limbic leucotomies at MGH, up to 50 % had a positive outcome [59].

Whereas 62 % of patients with OCD rated themselves as very much improved or much improved, only 17 % of patients with a primary diagnosis of MDD reported this level of response. One group described long-term outcomes of limbic leucotomies in 16 patients with bipolar disorder [60]. 68.8 % of patients had a "marked response," with mean declines of 52 % on the Hamilton Depression Rating Scale and 45 % on the Hamilton Anxiety Rating Scale. However, there was no improvement on the Young's Mania Rating Scale. Although this is not currently a common indication for surgery, one small case series highlighted the potential utility of limbic leucotomy in the treatment of severe self-injurious behaviors [61]. There was sustained improvement of self-injurious behavior in 4/5 subjects, reduced need for psychiatric care, and decreased assaultive behavior in 2/3 patients.

The most recent publications by the MGH group have employed subcaudate tractotomies in patients who did not have adequate responses to anterior cingulotomies; therefore, lower response rates than initially reported are expected. In MDD, out of 16 patients who did not respond to the initial procedure, there was a 25 % response rate, in addition to a 50 % partial response rate after limbic leucotomy [21]. For OCD, out of the 30 patients who did not respond to an initial cingulotomy, there was a 59 % response rate with an additional 19 % partial response after a second procedure (limbic leucotomy or repeat cingulotomy) [13]. At 5-year follow-up, mean decline in YBOCS was 45 % and mean decrease in BDI was 41 %.

6.8.2 Adverse Effects of Limbic Leucotomy

In Kelly's first report, short-term side effects of limbic leucotomy included headaches, confusion, loss of sphincter control for a few days to a few weeks, and persistent lethargy in 12 %. There were no seizures or deaths [58]. While most of these effects are transient, it is common for confusion to last several days. Thus, patients often have a longer postoperative hospital stay with this procedure than with either cingulotomy or subcaudate tractotomy. Montoya and colleagues (2002) also described transient side effects, mainly apathy, urinary incontinence, and short-term memory deficits. In the cohort of patients that underwent either an

anterior cingulotomy or a limbic leucotomy described by Shield and colleagues (2008), there was a 24 % adverse effect rate, including transient urinary incontinence in 12.1 % (lasting a few months in one patient). There was one case of new-onset tonic-clonic seizures, one case of intracranial abscess, one patient who reported subjective short- and long-term memory impairment, and one patient who noted increased anxiety and involuntary movements that improved over time [21]. In the case series of Sheth and colleagues (2013) combining 64 cases of cingulotomy and limbic leucotomy, there were a total of 19 adverse events. Four patients had postoperative apathy that improved over the ensuing few days. Three patients had intraoperative seizures, including one who developed a sustained seizure disorder requiring anticonvulsive medications. One patient had an intraoperative empyema, and one patient suffered a pulmonary embolus while on a long plane trip returning home. Both of these patients recovered without clinical sequelae. Finally, there were two suicides 8 days and 3 months postoperatively in patients with comorbid mood disorders [13].

6.9 Mechanism of Action

It is believed that ablative surgeries act by perturbing the aberrant fronto-limbic pathways involved in the psychopathology. However, the specific details by which this occurs are only cursorily understood. The typical 3- to 12-month delay between ablation and maximal benefit suggests that neuronal reorganization plays an important role in efficacy. One study found that anterior capsulotomy was associated with a reduction of metabolism on FDG-PET in brain areas known to be hyperactive in OCD, including the prefrontal cortex, dorsal ACC, caudate nucleus, and mediodorsal thalamic nucleus [62]. In particular, the reduction of metabolism in the dorsal ACC was positively correlated with outcomes. Another study suggested that subjects with MDD in recovery following a subcaudate tractotomy had decreased sensitivity to negative feedback on the Iowa Gambling Test, which was not observed in postsurgery patients who remained depressed or in subjects who recovered from MDD with medications [63]. This suggests a treatment-specific effect of the surgical procedure.

A few studies have attempted to use neuroimaging biomarkers to preoperatively predict response to surgical treatments. In OCD, higher right posterior cingulate cortex metabolism on preoperative FDG-PET was found to predict better response to cingulotomy [64]. Another small study by the same group suggested that higher metabolism in the left subgenual prefrontal cortex and left thalamus preoperatively measured with FDG-PET was associated with higher response rates to cingulotomy in patients with MDD [65]. Although these are intriguing findings, they need to be independently replicated before being considered as useful clinical tools.

Given the delays between neurosurgical interventions and clinical response, patients usually require ongoing pharmacological and therapeutic management. In fact, the alteration in neurocircuitry induced by focal lesions could increase sensitivity to previously inert medications [55]. In our opinion, the postoperative period constitutes a great opportunity to have OCD patients undergo intensive exposure with response prevention therapy, which they often have not been able to tolerate before the procedure.

6.10 Future Directions

Despite the controversies, long-term experience with lesion-based neurosurgical procedures for psychiatric disorders suggests that overall they lead to clinically significant improvement in 40–70 % of carefully selected patients, including about 25 % showing outstanding improvement. As with all invasive neurosurgical procedures, there are occasional acute complications, but the overall adverse effect burden is acceptable for patients with chronic severe distress due to treatment-refractory major mental disorders. In terms of cognition, mild frontal lobe function impairments can be seen post surgery, but there are minimal long-term effects, with some studies showing improvement in global cognitive functions, most likely related to improvement in the underlying primary psychiatric disorders.

Over the last 20 years, there has been increasing emphasis on careful patient selection. The current procedures are performed almost exclusively in patients with well-defined treatment-resistant MDD and OCD. At MGH, a multidisciplinary group reviews all

potential cases, with a strong emphasis on the necessity to obtain informed consent from patients. In addition, all patients must have access to a psychiatrist who can provide long-term outpatient clinical care before undergoing surgical treatment.

Tremendous progress has been made between the early application of poorly targeted prefrontal lobotomies and modern focally targeted ablative neurosurgical procedures, including less invasive gamma knife cingulotomies. There is ongoing research to obtain better data on efficacy and also to optimize patient selection. At present, these procedures are reserved for patients with the most severe illness, who have been refractory to most therapies. It is conceivable that some patients will be better candidates than others based on symptom profile [31]. The long-term hope is to be able to augment this phenomenological profile with specific neuroimaging biomarkers that could predict good surgical outcomes [64, 65]. More work is also needed to clarify the optimal target location for specific disorders and determine the underlying mechanism responsible for the efficacy of the procedures. It is also essential to compare efficacy of ablative procedures to reversible neuromodulation treatments such as deep brain stimulation. Although newer neuromodulation techniques are gaining acceptance due to their reversible nature, there is no proof that they are either more effective or have less adverse effects than stereotactic lesion-based neurosurgical procedures. This is a crucial question given the higher costs over time of implanted stimulators compared to single surgical interventions.

There is historically a great synergy between experimental neuroscience and the development of neurosurgical procedures for psychiatric disorders. The study of these patients, both intraoperatively and postsurgically, continues to provide an exciting and unique perspective into the workings of the human brain, advancing our understanding of neuroanatomy, neurophysiology, and neuropsychology [33, 66]. It is our hope that this specialized area of psychiatry will continue to be developed in a scientifically and ethically responsible way, encouraging the new generation of psychiatrists to be innovative while not forgetting cautionary tales from the past.

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7 Deep Brain Stimulation for Obsessive-Compulsive Disorder and Major Depressive Disorder

Nicole C.R. McLaughlin, Catherine Stewart, and Benjamin D. Greenberg

7.1 Introduction

A subset of patients with OCD and depression are not responsive to medication or psychological/behavioral therapies [1–3]. After other avenues of treatment have been attempted, neurosurgery, including DBS, has been used as a treatment for a very small number of patients with "intractable" OCD or depression. Although neurosurgery for psychiatric disorders has been conducted for decades, current techniques have evolved past the initial, relatively primitive methods. Surgical interventions include lesion procedures, with ablative surgeries requiring craniotomy, and radiosurgery that allows stereotactic lesion placement without craniotomy. Although not fully clarified, the pathophysiology of OCD appears to involve abnormal functioning in the medial and orbital frontal-basal ganglia-thalamic circuits. Lesions and stimulation in the anterior limb

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J.A. Camprodon et al. (eds.), *Psychiatric Neurotherapeutics*,
Current Clinical Psychiatry, DOI 10.1007/978-1-59745-495-7_7

of the internal capsule, the anterior cingulate, and/or the subcaudate region, all of which are involved in this circuit, seem to be useful in the treatment of highly refractory OCD. Likewise, the pathophysiology of depression seems to be due to dysfunction in the interaction between limbic-cortical brain systems, including the prefrontal and cingulate cortex, the hippocampus, the striatum, the amygdala, and the hypothalamus. Furthermore, neuroimaging studies suggest that some areas of the depressed brain are underactive while others are overactive, a result of an impairment in regulatory mechanisms controlling these regions [4, 5]. Antidepressant medications or behavioral therapies have shown efficacy in reversing the metabolic dysfunction seen in these brain areas.

Deep brain stimulation uses craniotomy to implant electrodes to modulate brain function (see Fig. 7.1). The FDA has granted approval to use DBS to treat essential tremor (1997) and Parkinson's disease (2002), for which it is the standard of care. In February 2009, the FDA approved DBS for a humanitarian device exemption (HDE) for the treatment of OCD. The use of DBS for depression remains investigational.

When using these relatively novel techniques, it is important to exercise caution with regard to patient selection, procedure implementation, and follow-up care. Neurosurgical procedures are carried out only on carefully selected patients who have debilitating and severe treatment-refractory illness. Methods are strictly regulated, and clinical processes are meticulously followed. There are now centers throughout the world carrying out systematic prospective studies and controlled trials on these interventions. Long-term data collection for all patients is critical in order for the burdens and benefits of these procedures to be adequately assessed. Data indicate that these interventions hold promise for the treatment of otherwise intractable OCD and depression. There is a very strong argument to be made for focusing their use at expert psychiatric neurosurgery centers.

7.2 History of Deep Brain Stimulation

Neurosurgical interventions for psychiatric disorders have a long history, marked by initial enthusiasm, followed by indiscriminate use, and then by belated attention to severe adverse effects.

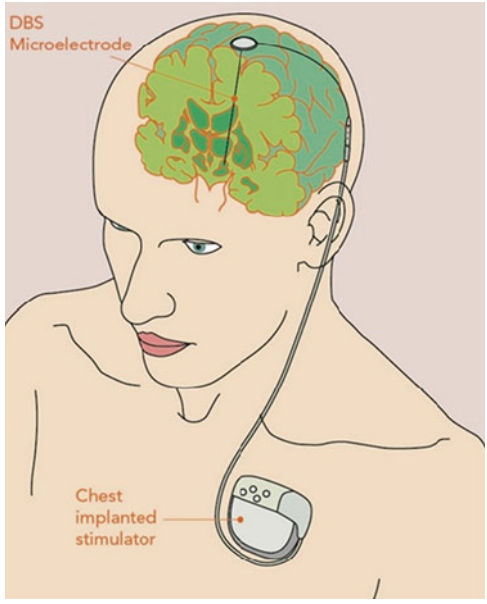

Fig. 7.1 This shows a deep brain stimulator system with the implanted microelectrode; the microelectrode is connected to a programmable stimulator, which is implanted under the skin

Initially, surgeons used ablative (or lesion) procedures to treat psychiatric syndromes. Although much earlier in development than ablative procedures, deep brain stimulation has been of interest for many decades. The first direct electrical stimulation of an animal (a dog, to elicit limb movement), was carried out by Fritsch in 1870 [6]. In 1874, Bartholow elicited contralateral movements in a terminally ill cancer patient; however, the stimulation induced recurrent seizures, resulting in death [7]. In 1948, Poole implanted an electrode in the caudate nucleus to treat depression and anorexia [8]. By 1951, electrical stimulation was used to determine location of "eloquent" brain structures in order to avoid them during ablative procedures [7]. Temporary electrodes were placed into the brain for pain control in the 1950s [7]. In 1963, Fessard stimulated the thalamus for treatment of tremors [9]. There are reports from the early 1970s of chronic deep brain stimulation (DBS) to the

thalamus for chronic pain. In 1976, the neurological division of Medtronic was developed in order to focus on DBS for chronic pain. Also in the 1970s, DBS was attempted for cerebral palsy, spasticity, vegetative states, and epilepsy [7]. More current uses of deep brain stimulation began with thalamic DBS for tremor by Benabid in 1987. In the 1990s, work by Benabid and Blond and Siegfried on thalamic DBS for tremor indicated that DBS was safer than thalamotomy. In 1997, Medtronic's Activa system for thalamic DBS for essential tremor and tremor for PD was FDA approved [9]. Approval was extended to the globus pallidus and the subthalamic nucleus in 2002 [7]. A humanitarian device exemption (HDE) was developed for subthalamic nucleus and globus pallidus DBS for dystonia in 2003. Progress on FDA approval for depression and OCD has been more recent. A HDE was granted for OCD in 2009, while DBS has full approval in the European Union. DBS for depression remains investigational.

7.3 Scientific Context

Over the years, selection of brain targets for ablation or stimulation has largely been empirical. Recent research has expanded our knowledge of the psychophysiological processes in major neuropsychiatric disorders, allowing addition of hypothesis-driven approaches. Safety and efficacy over the long term remain crucial issues. Research focusing on neurophysiological and behavioral mechanisms of DBS and lesion procedures is expanding.

7.4 Procedures and Practices

Neurosurgical interventions for OCD and depression, including DBS, are infrequently used. The majority of patients respond to conventional behavioral and medication treatments. In addition, even severe patients continue to have concerns about adverse effects following the neurosurgical procedures, though they are dramatically improved compared to those of the mid-twentieth century.

Expert centers engaged in neurosurgical interventions for OCD typically follow specific procedures (partially taken from the 2002 OCD-DBS Collaborative Group [10] and a 2006 paper by Fins et al. [11]). Most importantly, they emphasize a cautious and comprehensive approach to the assessment, treatment, and follow-up of patients. Specific key recommendations include having an ethics committee (e.g., Institutional Review Board, IRB) with oversight of the procedures, as well as an external data safety monitoring board (DSMB) for research studies. Typical inclusion criteria for both OCD and depression are meeting criteria for severe, intractable illness. For OCD, the FDA criterion for humanitarian use is a Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) severity score of 30 or more despite aggressive and ongoing conventional treatments. For MDD, typical inclusion criteria also include a score of 20 or more on the 17-item Hamilton Depression Rating Scale and a score of 50 or less on the Global Assessment of Functioning [12].

In addition, previous therapy and drug-mediated treatment is required. For OCD, patients must have received treatment with exposure and ritual (or response) prevention (ERP), generally for 20 or more hours with an experienced therapist. Members of the assessment team should contact previous behavior therapists to ensure that real ERP was delivered, and, if not completed, that therapy was interrupted due to marked intolerance of the procedures and not simply minimal to moderate discomfort. For MDD, an adequate trial, typically more than 20 sessions, of individual psychotherapy is required [13]. For OCD, the patient must have undergone extensive prior treatment, including treatment with several serotonin transporter-inhibiting antidepressants (SRIs; usually a trial of clomipramine is required, alone or carefully combined with a more selective SRI) and two augmenting agents, at maximally tolerated doses for at least 12 weeks. For MDD, the participant must have failed to respond to at least four antidepressant trials and must have scored a three or higher on the antidepressant treatment history form, which will be verified through medical records [14]. Additionally, potential candidates must also have undergone, and not benefited from, more than six bilateral treatments of electroconvulsive therapy [13].

Psychiatric comorbidities should be assessed as well, although OCD or MDD should be the primary disorder. DBS is typically not carried out on individuals who are judged to be imminently or who have recently been suicidal. Bipolar disorder may be a contraindication, especially to DBS, as there is a potential for manic episodes post-surgery. Patients must also be free of illicit substances. Case with patients of limited intellectual capability must be evaluated carefully, as there is a need to be able to understand the procedure and consent process and to be able to actively participate in treatment; preoperative assessment should include an extensive neuropsychological battery, to be used both in assessing intellectual limitations and as a baseline measure for comparison of future cognitive skills. Medical conditions that increase neurosurgical risks are contraindications, as are patients over 65. Patients under the age of 18 years are also not optimal candidates. EEG and MRI, as well as specific laboratory tests (e.g., PT, INR), are typically included in the preoperative assessment. The patient *must* have access to postoperative care. Continued psychiatric and psychotherapeutic treatment is essential after these surgical treatments. In some cases, surgery may enhance the patient's ability to engage in ERP. Devices may also have to be surgically replaced, an expensive process not always covered by health insurance.

Patient information is reviewed by a clinical committee for regular clinical care. For clinical trials, information is typically reviewed across more than one site, by all investigators and by a data safety monitoring board, to ensure that all inclusion and exclusion criteria are met. Approval for surgery in our current collaborative National Institute of Mental Health (NIMH)-sponsored trial of DBS for OCD requires that patients be accepted as appropriate for surgery by an independent multidisciplinary group, which reviews each case in detail and typically asks for additional information from referring centers. In Britain and Belgium, a similar function is performed by National Multidisciplinary Boards. If independent review deems a patient appropriate, an extensive consent process follows. This process is actively assessed, at collaborating US centers, by independent consent monitors. During this monitoring and throughout the evaluation process, prospective candidates should be assessed for their expectations of

improvement after surgery and (in the case of DBS) ongoing stimulation. Patients might have unrealistic expectations of dramatic or rapid improvement in many if not all spheres of their lives after such dramatic interventions. Such expectations, if not elicited and addressed before surgery, might lead a patient to precipitously discontinue needed medications after surgery. Alternatively, a patient, even after marked improvement in their psychiatric illness severity, might commit suicide if their psychosocial functioning and quality of life do not improve to match expectations they had before surgery [15].

Long-term data collection for all patients undergoing neurosurgery for psychiatric reasons is essential. All of these treatments are developing at an accelerating pace, but optimal targets, device design, and selection criteria have not yet been determined. Systematic data collection across institutions is needed to advance our knowledge of procedure outcomes. To this end, the creation of a national registry for reliable data collection of this information remains a very important goal. This was initially proposed by the National Commission in 1977 but never implemented.

7.5 Neuromodulation

For both DBS for OCD and depression, electrodes are placed (via burr holes in the skull) into particular targets (discussed below) and connected to a pacemaker-like device. The electrodes typically deliver high-frequency stimulation to a defined brain target site. Lead placement is usually bilateral and is guided by imaging and targeting platforms. A neurostimulator is placed subdermally, for example, in the upper chest wall, and is connected to the brain leads through wires under the skin (see Fig. 7.1 [16]). Neurostimulation can be independently adjusted in several important ways, via stimulation polarity, intensity, and frequency, and by the number of active contacts on a lead. Patients may opt for DBS over lesion procedures because DBS may be considered reversible. In addition, stimulation may be modified to optimize benefit or changed or stopped to improve DBS-induced side effects. However, the procedure is not innocuous (potential risks are described below).

7.6 Deep Brain Stimulation of OCD Patients and Circuits

Individuals with OCD most likely have dysfunction in frontal-subcortical circuitry, especially between the orbitofrontal cortex (OFC)/cingulate and the thalamus and/or basal ganglia [17]. See Fig. 7.2 for circuitry information [18]. OCD patients in a resting state have an increase in metabolic activity of the orbitofrontal circuit, cingulate, and caudate nucleus [19]. There is increased connectivity at rest between prefrontal and subcortical regions [20, 21]. There is normalization of this activity after drug or behavioral therapy in responsive participants [17]. Neurosurgical approaches, including DBS, target one or more areas in these tracts. However, mechanisms of DBS remain unclear. As noted in Bourne 2012, it was initially thought that DBS created a functional lesion, though now it appears that other mechanisms of action may be implicated [22]. For example, possibilities include activation of axonal fibers in relevant circuits, alteration of oscillatory activity, or release of neurotransmitters secondary to stimulation. The first DBS target developed for OCD was the ventral capsule/ventral striatum (VC/VS), based upon the beneficial effects of anterior capsulotomy lesions on OC symptoms. DBS to the VC/VS likely has an inhibitory effect on the abnormal connections between the frontal lobe and the basal ganglia [23]. Pathways coursing through the ALIC have been shown to be important to the neurocircuitry models of OCD [18]. The subthalamic nucleus (STN) of the basal ganglia has also been used as a DBS target for OCD, which was initially chosen due to the use of STN DBS in PD demonstrating effects on mood and cognition [24]. The STN has been shown to be involved in compulsive behavior in animals [24]. Several PD individuals with comorbid OCD showed improvement in OCD symptoms with STN DBS [24]. Animal studies potentially indicate that DBS to the STN inhibits local neuron output but causes antidromic activation of efferent projections, modulating abnormal circuitry in OCD [22]. STN DBS in animals also seems to impact dopamine levels in the NAcc. The inferior thalamic peduncle has been used on a small number of OCD patients and likely has an effect on projections from the striatum and OFC entering the thalamus [23].

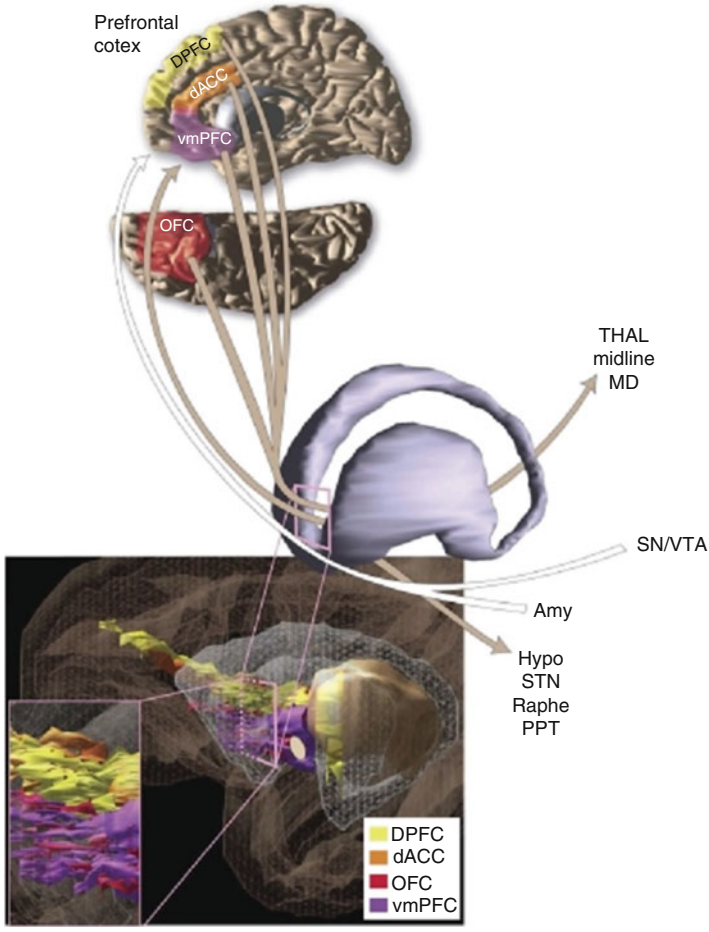

Fig. 7.2 Representation of reciprocal connections between prefrontal cortex regions and the ventral portion of the anterior limb of the internal capsule and the adjacent ventral striatum (VC/VS). Prefrontal cortex—VC/VS connections are color coded to delineate pathways linking specific prefrontal regions. Other connections of the VC/VS represented: *THAL* mediodorsal and midline nuclei of the thalamus, *SN/VTA* substantia nigra and ventral tegmental area, *Amy* amygdala, *Hypo* hypothalamus, *STN* subthalamic nucleus, *Raphe* raphe nuclei, *PPT* pedunculopontine tegmental nucleus. Greenberg BD, Rauch SL, Haber SN. Invasive circuitry-based neurotherapeutics: stereotactic ablation and deep brain stimulation for OCD. Neuropsychopharmacology. 2010;35(1):317–36.

7.6.1 Clinical Outcomes

Postoperative improvement is typically measured in terms of improvement in OCD severity (typically with the Y-BOCS) and global improvement, by such instruments as the Clinical Global Improvement Scale (CGI) and the Global Assessment of Functioning (GAF). Early indications suggest that effectiveness of ablation and DBS may be similar [25]. An issue to keep in mind, as this field develops, is that patients receiving lesion procedures versus DBS may not be fully comparable. For example, DBS requires very close and essentially indefinite follow-up, which in turn requires a degree of psychosocial stability and resources that other patients with intractable OCD may not possess.

Ventral Capsule/Ventral Striatum (VC/VS) and Anterior Limb of the Interna)l Capsule (ALIC. Patients treated with VC/VS DBS have shown decreased Y-BOCS scores along with improvement in GAF, with improvements in self-care, independent living, and work, school, and social functioning [25]. Twenty-six participants showed a 35 % or more improvement on the Y-BOCS in the initial group, with over 70 % response rate in the second and third patient cohorts, potentially because of refinement of implantation site to a more posterior location [25]. Another study indicated that after 12 months of DBS to the VC/VS, 66.7 % of patients met responder criteria [26]. A small study of DBS to the VC/VS indicated greater than 35 % improvement on the Y-BOCS after 24 months, with a decrease in depressive symptoms and an increase on GAF [27]. A recent review indicated that, of 69 patients across multiple sites who have undergone VC/VS DBS for severe OCD, 50 % of them showed a reduction in OCD scores, depression, and anxiety [23]. Numerous case studies have indicated a beneficial response to DBS for OCD at multiple targets [28–31]. DBS to the ALIC in four patients has demonstrated significant benefit in one patient (73 % improvement from baseline), with moderate benefit (44 % improvement from baseline) in a second patient [15]. These patients also showed decrease in metabolic activity over the orbitofrontal cortex [32].

Nucleus Accumbens. In one trial, DBS to the nucleus accumbens (NAcc) caused a Y-BOCS decrease of 46 % after 8 months, with 9 out of 16 patients considered responders (>35 % Y-BOCS improvement). These improvements continued to at least 21 months post-surgery. In the double-blind phase, the Y-BOCS difference between the active and sham groups was 25 % [33]. Another small study ($n = 10$) showed a significant decrease in OCD symptoms from baseline to 12 months after unilateral stimulation [34]. Five out of the ten patients showed a decrease of more than 25 %, and 1 out of 10 showed a decrease of more than 35 %.

Subthalamic Nucleus (STN). In a small study by Charbardes, 3 out of 4 patients showed more than 70 % improvement in OCD symptoms after 6 months of STN DBS [24]. In a double-blind crossover study, DBS to the STN showed significantly lower Y-BOCS scores after active versus sham stimulation [35].

Inferior Thalamic Peduncle (ITP) With DBS to the ITP, another small study (six patients) showed a 51 % decrease in OCD symptomatology at the 12-month follow-up [36].

Adverse Effects. Although DBS for OCD generally appears to be well tolerated, complications have included asymptomatic hemorrhage, one instance of a single seizure, superficial infection, and hypomanic/manic symptoms. In addition, battery depletion may lead to worsened depression and OCD [37]. Stimulation may cause transient sensorimotor effects, such as paresthesias, muscle contraction, dysarthria, and diplopia. Adverse effects have ranged from transient psychiatric symptom exacerbations [25] to permanent neurological sequelae [35] or, on longer-term follow-up, suicide in the context of psychosocial stress [15]. But, as is also the case for efficacy, only quite tentative conclusions about safety can be drawn given the data available.

7.7 Deep Brain Stimulation of MDD Patients and Circuits

Patients diagnosed with MDD most often show dysregulation between brain regions. It is suggested that the dysregulation lies in underactive frontal lobes and an overactive limbic region [4]. SPECT imaging corroborates these findings showing hypometabolism in specific brain regions such as the dorsal prefrontal cortex and the cingulate cortex. Also seen are abnormalities in amygdala, basal ganglia, and thalamus [38]. FGD PET studies of depressed patients show ventral prefrontal and anterior temporal metabolic irregularities, further supporting the role of paralimbic and neocortical pathways in MDD [5]. The lack of a specific causal brain region as well as the functional connections these regions create with other brain areas has resulted in a wide range of DBS targets, all of which have promise in the treatment of intractable MDD.

Subcallosal Cingulate Gyrus (SCG) The subcallosal cingulate (i.e., BA25 or CG25) is metabolically overactive in patients with MDD and, due to its extensive connections with other brain regions, is hypothesized to cause widespread metabolic and physiologic dysfunction, resulting in an array of depressive symptoms [12]. Transient sadness in healthy subjects also seems to result in overactivity of the SCG [39]. Researchers hypothesize that targeting the white matter tracts bordering the SCG will modulate the hyperactivity in this area as well as within the network of brain areas involved with the SCG [40]. It is important to note that various nonsurgical interventions have resulted in a decrease in SCG activity and a lessening of depressive symptoms, further supporting the application of DBS within this brain region [39]. A study of 21 patients with treatment-resistant depression found a 62 % response rate (defined as a reduction of 40 % on the HAM-D; [41]). However, a recent industry-supported trial has not yielded significant support, and the stimulation target continues to be refined.

Ventral Capsule/Ventral Striatum (VC/VS) The ventral capsule/ventral striatum was chosen as a target based on DBS studies conducted by Nuttin et al. and Greenberg et al., in which the VC/

VS target resulted in benefit not only for OCD but also for depressive symptoms [42]. Lesion studies targeting the VC/VS also resulted in improvement of depressive symptoms. Its usefulness may be a result of the proximity to and involvement of the VC/VS in circuitry controlling emotional processing [43]. A sham-controlled trial of DBS at the VC/VS target for depression found no differences between groups at the end of the controlled phase, but 20–26.7 % of patients achieved response during the open phase [44].

Inferior Thalamic Peduncle (ITP). Inferior thalamic peduncle lesion studies conducted on OCD patients resulted in improvement not only for OCD but also for depressive symptoms [45]. It has been suggested that the ITP is metabolically abnormal in patients with MDD [46], a theory that was corroborated by functional imaging and PET studies. These studies also showed that the hyperactivity is reversed with pharmacological treatment [47], suggesting that DBS to this region may also improve the metabolic hypoactivity of the frontal cortical regions [45, 46]. Researchers also noted that because of its small size, the ITP may be increasingly beneficial, as a small target that relates directly with depression implies high specificity and a potentially better outcome [45].

Nucleus Accumbens (NAcc). PET imaging studies reveal metabolic hypoactivity of the nucleus accumbens in depressed patients compared to control patients [48], which has been implicated in anhedonia, a major feature of depression [48, 49]. Research has also shown that changes in the dopaminergic receptor density within the nucleus accumbens may lead to features associated with depression such as learned helplessness [47]. One such study, facilitating hypercortisolism-induced depression, showed that increased cortisol levels were associated with lower dopamine levels [50]. The nucleus accumbens also creates connections with the limbic loop of the basal ganglia making it an ideal target for DBS due to its association with other brain regions implicated in depression [48]. Therefore, researchers hypothesize that DBS targeting the nucleus accumbens will alter the deficits seen within reward circuitry.

Medial Forebrain Bundle (MFB) The medial forebrain bundle is responsible for interconnecting the reward pathways. The draw to the MFB is not necessarily its direct role in depressive symptoms but rather its proximity to the ventral tegmental area and its functional connection to other target areas [51]. The experimenters targeting this area hypothesize DBS in closer proximity to the VTA will be more effective in righting the metabolically dysfunctional reward circuitry [51].

Other Targets The lateral habenula and the rostral cingulate gyrus have also been suggested as potential targets for MDD, but clinical and preclinical trials have yet to be conducted [52, 53].

7.7.1 Clinical Outcomes

Postoperative response is typically measured in terms of improvement of depressive symptoms using a variation of the Hamilton Depression Rating Scale (typically the 17-item HAM-D) as well as the Global Assessment of Functioning (GAF). Secondary measures of improvement vary with clinical trial but most often include the Beck Depression Inventory (BDI), the Montgomery-Åsberg Depression Rating Scale (MADRS), and the Inventory for Depressive Symptomatology Self-Rated (IDSSR).

Patients receiving DBS for MDD generally show decreased HAM-D and GAF scores with each surgical target as well as significant reductions in HAM-A and the IDSSR for depression self-rating [48]. 55–66 % of participants treated with SCG DBS were considered responders, while 35 % achieved or were within one point of remission status [12]. Additionally, patients reported significant improvement in mood, anxiety, sleep, and somatic complaints related to MDD [12, 54]. In a 15-patient study of VC/VS DBS, 5 patients achieved remission status (defined as a score of 10 or lower on both the MADRS and the HDRS), while 8 patients achieved clinical response (defined as a 50 % or greater reduction in the MADRS). The mean reduction scores at each follow-up were similar across the MADRS and the HDRS and were 52.6 %

at 3 months, 47 % at 6 months, 45.7 % at 1 year, and 56.4 % at last follow-up (ranging from 14 to 67 months) [42]. A case report of ITP-DBS saw dramatic improvement in HAM-D and BDI even before stimulation. At one-month and eight-month follow-up, the patient reported a nearly symptomless state [45]. Five patients treated with NAcc-DBS were considered responders, and improvements were seen as early as one month post-op [48]. In an additional NAcc study of 11 patients, researchers analyzed response stability over the long term and found five patients reached response criterion at 1 year, while six remained nonresponders. This remained stable into the second follow-up year [55]. Finally, patients treated with MFB-DBS reported immediate acute changes in mood and anxiety, and during final follow-up at 33 weeks, 6 of 7 patients were considered responders [56].

Adverse Events. Postoperative measures of adverse events include the Young Mania Rating Scale, Hamilton Anxiety Scale, and the North American Adult Reading Test to test baseline IQ as well as a battery of tests measuring cognitive function. Overall, DBS for MDD seems to be well tolerated and in general shows no permanent or serious adverse effects and no negative effects on general cognition [12, 54]. Complications were transient and seemed to be related to parameter change during the acute stimulation phase. These complications included vertical nystagmus, increased anxiety, increased heart rate, increased blood pressure, erythema, sweating, blurred vision, and strabismus [45, 48, 51]. One study reported a case of occipital pain associated with location of the extension and one case of lead fracture [42]. Other adverse events were related to the surgery itself and included infection in the chest or scalp [54] as well as intracranial bleeding, transient hemiparesis, and dysarthria [51]. One reported adverse event of unknown cause resulted in two syncopal episodes, DBS therapy continued, and the patient was treated with anticonvulsant medication [42]. All reported cases of worsened depression and suicidal ideation were associated with battery depletion and accidental deactivation of the battery pack. Symptoms were transient and seemed to be reversible with

implantation of a new battery pack [42]. Importantly, only one clinical trial saw hypomanic episodes which were attributed to the patients' bipolar disorder and were resolved with stimulation parameter modification [42]. The few suicide attempts reported were determined to be unrelated to the procedure itself.

7.8 Cognition

Neuropsychological assessments are routinely conducted pre- and post-surgery. We think this is highly desirable, though is not universally done. Initially, these assessments were mainly conducted for safety purposes, because of the possibility that neurosurgical interventions may cause a decline in cognitive abilities. Although evaluations continue to be conducted to monitor safety, research has extended into the assessment of effects on neurocircuitry. Traditionally, assessments have examined all cognitive domains with neuropsychological tests commonly used in the clinical setting. Experimental tasks may be added to these batteries in an attempt to increase the sensitivity and specificity of these evaluations. Given the small number of expert centers throughout the world that carry out neurosurgical procedures for OCD, data regarding neuropsychological outcomes are limited. Preliminary case studies have not shown any change in cognitive functioning or personality after DBS for OCD to multiple targets [15, 26, 29, 57, 58]. A recent review of cognitive functioning following deep brain stimulation for psychiatric disorders [59] showed no evidence of substantial cognitive decline after DBS, and several studies indicated that there was an improvement after DBS. Similarly, studies to date have not shown any significant cognitive declines after DBS for MDD [42, 51, 60, 61]. Some studies reported a significant improvement in verbal memory [42] and, more specifically, improvement in prose passage recall [61]. This improvement is unrelated to a change in severity of depressive symptoms and is therefore accredited to DBS itself [61].

7.9 Neuroimaging

Magnetic resonance imaging was utilized in all studies postimplantation to confirm electrode placement. Research has shown decreased PET-FDG metabolism in the frontal cortex after months of ventral capsule DBS [62]. With DBS to the VC/VS, Rauch et al. found significant activation of the orbitofrontal cortex, anterior cingulate cortex, striatum, globus pallidus, and thalamus in comparing acute high-frequency DBS to control conditions [32]. DBS to the STN in 10 participants, with PET-FDG, in the off-stimulation condition, indicated hypermetabolism in the right frontal middle and superior gyri, right parietal lobe, postcentral gyrus, and bilateral putamen, compared to healthy participants. There was also a decrease in cerebral metabolism in left cingulate and left frontal medial gyri in on-stimulation compared to off-stimulation condition. Improvement in Y-BOCS during on-stimulation positively correlated with PET signal changes at the boundary of OFC and medial PFC [63].

PET imaging was also conducted in at least three MDD studies to analyze metabolic changes after stimulation. All studies utilizing PET imaging analysis observed a reversal of metabolic abnormalities post-stimulation compared to baseline. It was noted that this reversal was a result of direct activation of white matter at the target which in turn allowed metabolic activation or inactivation in the various brain sites forming connections with the target [40]. Specifically, in a study targeting the subcallosal cingulate, PET imaging showed local CBF decreases as well as decreases in the orbital frontal cortex, the hypothalamus, the anterior insula, and the medial frontal cortex. This study also showed metabolic increases in the dorsolateral prefrontal cortex, the dorsal anterior and posterior cingulate, and the premotor and parietal regions [54]. Similar to Mayberg et al., an additional study also targeting the subcallosal cingulate showed an increase in the parietal and anterior mid-cingulate activity [40]. In a study targeting the nucleus accumbens, PET imaging showed metabolic decreases in the prefrontal subregions, the subgenual cingulate region, the posterior cingulate cortex, the thalamus, and the caudate nucleus as well as an increase in metabolic activity in the precentral gyrus [48]. It is interesting to note that all brain regions that experienced metabolic

change post-stimulation were the same areas affected by pharmacological and behavioral treatments in imaging studies of depressed patients [54].

7.10 Conclusion and Future Directions

Electrical stimulation of the brain was first studied over a century ago. Throughout the twentieth century, research continued into electrical stimulation to treat tremor and pain and neuropsychiatric illness. Over the last two decades, this area has greatly expanded. DBS is standard of care for medically refractory Parkinson's disease, essential tremor, and, via a humanitarian approval in the USA, dystonia. It has generated tremendous interest as a developing option for some severe, intractable psychiatric disorders. The state of knowledge, however, remains incomplete. Though deep brain stimulation is generally safe, there continues to be the potential for serious adverse effects, either neurosurgical or psychiatric. We remain in the early stages of determining the degree of clinical effectiveness of these procedures (especially over the long term) and the burdens associated with delivery of intracranial stimulation as it currently exists. Critically, there is only partial knowledge of mechanisms that may underlie therapeutic benefit when that occurs. Such knowledge could eventually allow stimulation based on concurrent sensing of abnormal brain activity in one or more variants of "closed-loop" stimulation. More generally, improving the clinical utility of invasive, neurocircuitry-based procedures such as DBS will rely on a stronger understanding of mechanisms at the anatomical, pharmacological, and behavioral levels. We would urge that such treatments continue to be delivered, in investigational or clinical use, by expert multispecialty teams at dedicated clinical centers.

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Transcranial Magnetic Stimulation

8

Joan A. Camprodon

8.1 Introduction

Many patients with neuropsychiatric conditions can be successfully treated with medications, psychotherapy, or a combination of both. However, a significant number of individuals do not respond to these interventions. Studies have demonstrated that about 30–40 % of patients with major depressive disorder (MDD) treated with pharmacotherapy achieve full remission, and 10–15 % experience no symptom improvement [1]. The Sequenced Treatment

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J.A. Camprodon et al. (eds.), *Psychiatric Neurotherapeutics*,
Current Clinical Psychiatry, DOI 10.1007/978-1-59745-495-7_8

Alternatives to Relieve Depression (STAR*D) study found that with each failed medication trial, the probability for remission decreased [2]. Clearly, alternative therapeutic interventions for treatment-resistant patients are necessary. While invasive neuromodulation should be reserved for the most refractory patients, noninvasive techniques are being considered in earlier phases of the therapeutic process and not exclusively for the most severe individuals, as they can be significantly better tolerated than common pharmacological options.

Transcranial magnetic stimulation (TMS) is the most established noninvasive neuromodulation modality. It uses powerful and rapidly changing magnetic fields applied over the surface of the skull to generate targeted electrical currents in the brain, painlessly and without the need for surgery, anesthesia, or the induction of seizures. Since its development in the mid-1980s [3], it has become a widely used tool for neuroscience research and clinical applications (both diagnostic and therapeutic). Diagnostic applications (such as nerve conduction studies) have been approved by the US Federal Drug Administration (FDA) since its earlier days and are used regularly by clinical neurophysiologists [4]. In 2008, the FDA approved the use of high-frequency repetitive TMS (rTMS) to the left dorsolateral prefrontal cortex (DLPFC) for the treatment of MDD [5], and in 2013 the use of deep TMS H-coils was also approved for the same indication [6]. Worldwide, TMS is approved for diagnostic and therapeutic applications (often with wider indications than in the USA) in Canada, Israel, Australia, New Zealand, and many European, South American, and Asian countries.

8.2 TMS Principles

One of the primary advantages of TMS is its noninvasive nature, which is made possible by the application of Faraday's principle of electromagnetic induction. Briefly (and overtly simplified), this principle states that a changing electrical current flowing through a circular coil will generate a magnetic field with its vector tangential to the plane of the coil. This magnetic field will travel unimpeded through any materials that are not electrically conductive (e.g., wood or plastic in a physics lab or bone and soft tissue during TMS), but the moment it comes in contact with a conductive

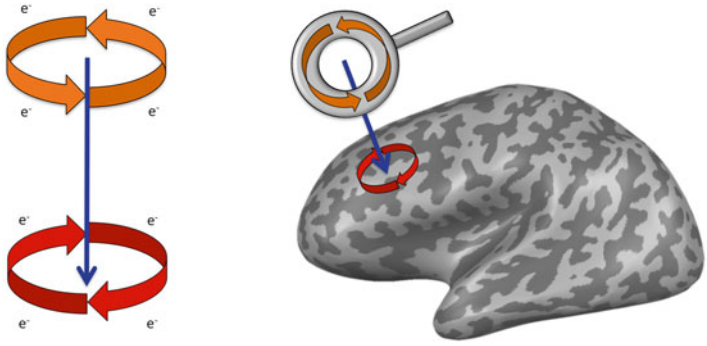

Fig. 8.1 Basic biophysical mechanisms of TMS. The primary electrical field in the coil (*orange*) generates a magnetic field (*blue*) that travels unimpeded until it finds an electrically conductive material such as the cortical neurons, which act as a pickup coil where a secondary electrical field (*red*) is generated. Note that the primary and secondary electrical fields are in the same plane but opposite direction

material (e.g., a cupper pickup coil in a physics lab or cortical neurons during TMS), it will generate a secondary electrical current. This secondary electrical field will be in the same plane but opposite direction than the primary electrical current (Fig. 8.1). TMS systems use an electrical capacitor to generate a powerful and brief electrical current that flows through the TMS coil, which is a circular loop of wire (usually cupper) connected to the capacitor and embedded in a protective plastic case. According to Faraday's principle, when the electrical current flows through the circular coil, a rapidly changing magnetic field is generated. If the TMS coil is placed on the surface of the skull, this magnetic field will travel toward the intracranial space unaltered by the different structures it will cross (soft tissue, bone, CSF, etc.), until it reaches the electrically conductive neurons of the cortex. These neurons will act as an organic pickup coil, and a secondary electrical current will be generated able to trigger action potentials and force brain cells to fire (Fig. 8.1). It is important to note that the stimulation of neurons is actually electrical, not magnetic, and the term "magnetic stimulation" is in fact a misnomer: magnetic fields are used only as a vehicle to noninvasively transfer electricity from the coil to the cortex, without the need of craniotomy or the painful application of strong electrical currents on the skull.

Although the magnetic field is practically unimpeded by the structures it finds on its path to the cortex, its strength weakens as it moves away from its source in the TMS coil. It also becomes wider and less focal. This determines an important property of TMS, its depth: the magnetic field becomes too weak to generate neuronal action potentials beyond the cortical layers of dorsal and lateral brain regions, although new coil designs are partially solving these limitations [7]. Therefore, traditional TMS can only *directly* stimulate superficial cortical neurons, not deeper medial or ventral cortex and not subcortical structures. Nevertheless, the effects of TMS are not only local but circuit wide: once an action potential is generated in a cortical neuron, the volley of activation will travel through its axon and stimulate the postsynaptic neuron, leading to a cascade of events through the entire neural circuit (including deep cortical, subcortical, and contralateral regions). This cascade of electrical events is specific to the brain circuit our target region is connected to, and not generalized like the effects of ECT. Therefore, although it is true that TMS can only *directly* modulate superficial cortical nodes, these nodes are windows that provide modulatory access to an entire functional network of cortical and subcortical neurons [8].

8.3 TMS Parameters

The effects of TMS are not only specific to the target of stimulation but also to the parameters used. This is important as we consider statements such as "TMS is (or is not) effective for a given condition," which are empty and not informative. Alternatively, "TMS applied over a determined anatomical target at a specific frequency and dose for a particular condition" would be more clinically and neuroscientifically meaningful. Since the effects of TMS are specific to the stimulated region and the parameters used, we should certainly expect that stimulating prefrontal cortical areas that process working memory or eye movements would have little effect on mood, anhedonia, or neurovegetative symptoms of depression. Similarly, inhibiting a pathologically hypoactive region will most likely worsen a patient's condition, though its activation may prove therapeutic. Last, applying 2 weeks of stimulation when 6 or more

Table 8.1 TMS parameter space

Anatomical
1. Location or target of stimulation
2. Focality and depth of stimulation
Physiological
1. Frequency of stimulation
2. Stimulation intensity
3. Duration of stimulation (# pulses/session and # sessions/course of treatment)

weeks are needed should have minimal or no therapeutic impact. These examples highlight the need to have a basic understanding of the TMS parameter space that clinicians and scientists are able to control, in order to plan treatments, design experiments, and critically report and understand findings in the literature. The TMS parameter space consists of five primary variables: (1) the location or target of stimulation, (2) the focality and depth, (3) the frequency, (4) the stimulation intensity, and (5) the duration of treatment. While parameters one and two are mostly anatomical, parameters three, four, and five are more relevant to physiology. The concept of "TMS dose" would be determined by a combination of parameters four and five: (4) how much current in a given TMS pulse and (5) how many pulses per session and course of treatment (Table 8.1).

As mentioned above, the choice of the anatomical site of stimulation is crucial, as it defines the cortical window through which we access and modulate an entire circuit of interest. Image-guided TMS using neuronavigation has proved to increase the anatomical specificity and clinical or behavioral efficacy of TMS [9, 10], but although this approach is standard in cognitive neuroscience research, it is still rare in clinical practice. Nevertheless, given our present understanding of the functional neuroanatomy of neuropsychiatric conditions and the availability and common use of TMS neuronavigation technology, the field is ready to move forward and possibly lead the development of individualized therapeutics, abandoning population-based approaches (e.g., the 5-cm rule) in favor of the personalized selection of cortical targets that increase clinical efficacy and reduce response variability.

Similarly, the focality of stimulation will be of relevance to the neurobiological specificity and clinical outcomes of TMS. Although the intensity of stimulation has an influence on the focality of its effect (the stronger the magnetic field, the deeper and less focal its effects) [11], focality is primarily controlled by the choice of TMS coil. Various types of coils are manufactured and commercially available, with differences in their architecture that allow a range of focality and depth options [7]. The most common types remain the circular coil (less focal) and the figure-of-eight or butterfly coil (more focal) [7, 12]. A new generation of deep TMS coils, such as the H-coil [13], has been developed in recent years and received FDA approval for the treatment of MDD in 2013 [6].

Once these anatomical parameters are determined (location, focality, and depth), it is important to focus on physiological variables. Notably, TMS is able to either inhibit (downregulate) or excite (upregulate) populations of neurons, and these selective effects are primarily determined by the frequency of stimulation. With parameters similar to the ones leading to long-term depression (LTD) or long-term potentiation (LTP), low frequencies of 1 Hz are known to be inhibitory [14], while high frequencies of 5Hz or greater (typically 10 or 20 Hz) are excitatory [15].

Newer TMS protocols with more complex patterns of stimulation have been developed in recent years [16]. Theta-burst stimulation (TBS) was developed from observations in animal and in vitro neurophysiological studies assessing LTD and LTP plasticity in hippocampal neurons [17, 18]. Its translation to humans proved these protocols to be safe and capable of inducing similar plastic modulatory changes [19]. Two main protocols have been developed: continuous TBS (cTBS, inhibitory) and intermittent TBS (iTBS, excitatory). Both use triplets of TMS pulses at a frequency of 50 Hz, and these triplets are applied every 200 ms (so 5 triplets in 1 s or at a 5-Hz frequency in the theta range) (Fig. 8.2). The intensity is typically 80 % of the active motor threshold (AMT), and the AMT is lower than the resting motor threshold (RMT). While cTBS applies this sequence continuously, iTBS includes inter-train pauses (usually 2 s of TBS followed by 8 s of no stimulation) (Fig. 8.2). Typical duration of cTBS is 20–40 s (300 or 600 pulses, respectively), while iTBS is 190 s (600 pulses). Despite the much shorter duration of stimulation, the physiological effects of TBS can last longer than

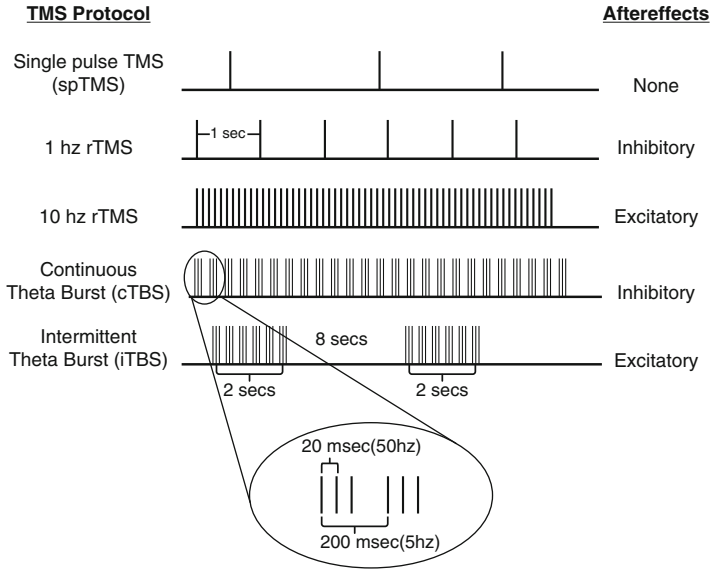

Fig. 8.2 TMS stimulation protocols. Traditional and theta-burst TMS protocols can lead to both inhibitory and excitatory neurophysiological aftereffects

traditional TMS protocols: up to 60 min for 40 s of cTBS and 20 min for 190 s of iTBS. The effects of cTBS are typically more robust than iTBS, in addition to longer lasting [16]. TBS, like traditional rTMS, is state dependent: tonic contraction of the stimulated muscle during cTBS or iTBS abolishes the effects, while contraction 1 min after stimulation enhances iTBS and turns cTBS into excitatory [20]. Because TBS is done using 80 % of the AMT and not the RMT, the muscle of interest is typically in tonic contraction for a few minutes before repetitive stimulation (while the AMT is being assessed), and this also seems to influence the modulatory effects [21]. Finally, TBS is intensity dependent and no modulatory effects were observed at 60 % of the AMT, only at 80 % [20]. Although the use of TBS for therapeutic purposes has only recently been explored [22], early results suggest that its acute antidepressant efficacy may be comparable to traditional rTMS [23]. Although more data is certainly necessary, TBS is likely to have significant clinical impact given its shorter duration of stimulation (20–190 s compared to 37 min with

the standard antidepressant 10 Hz protocol), which would allow treating many more patients in a given day. Also, its longer-lasting physiological effects may translate into fewer treatment sessions in a given course and possibly higher durability of benefit and lower relapse rates. Other novel protocols such as primed TMS [24], repetitive paired-pulse TMS [25], and quadripulse stimulation (QPS) [26, 27] have also been described to induce plastic changes lasting longer than traditional low- or high-frequency rTMS. These other forms of patterned TMS have been used to study mechanistic neurophysiological processes in the human motor system, but their therapeutic potential remains largely untested.

It is important to note that these frequency-dependent physiological effects are well established in the motor system, and although a number of behavioral, neurophysiological, metabolic, and neuroimaging studies confirm their validity in non-motor regions and circuits [28–31], other reports have pointed to their intersubject variability [32] and questioned their direct translation to all cortical areas. It is also crucial to realize that the effects of TMS are state dependent [20, 33, 34], meaning they depend on the pre-TMS physiological state of the brain regions and networks they are trying to change. Complex networks that support affect, behavior, and cognition dynamically fluctuate across different states (even in health, let alone when affected by disease), and these physiological oscillations condition the biological and clinical effects of TMS (and any other intervention, including brain stimulation, medications, and psychotherapy). These complex dynamics are of particular relevance to the treatment of neuropsychiatric conditions that involve, precisely, these very plastic affective, behavioral, and cognitive systems. Nevertheless, while these questions are waiting to be fully explored by translational and basic neuroscience research using multimodal combinations of TMS [35], clinical applications should continue to be developed and implemented in parallel, as long as sufficient proof for safety and efficacy exists in a clinical context that will never be free of uncertainty [36].

Once the target of stimulation and direction of modulation are set, the TMS dose will be determined by deciding the strength of the magnetic field (pulse intensity) and the total number of pulses

(duration). Duration also relates to the number of sessions in a course of treatment, typically daily sessions over the course of weeks. Other more complex variables, such as the waveform of the electromagnetic current, are also relevant to define the dose [37].

As we improve our understanding of the mechanism of action of TMS and the physiology of human brain networks, technical innovations will develop, and other parameters (such as pulse shape) [38] may become neurobiologically and clinically relevant. The parameter space for TMS and other forms of neuromodulation promises to become richer and more complex, granting greater control and specificity to clinicians and scientists [39].

8.4 TMS Safety

The safety profile of TMS is particularly benign [39], given its noninvasive nature. Nevertheless, it is an intervention and as such, an understating of its possible iatrogenic effects is essential. The only contraindication considered to be absolute is the presence of metallic hardware in the area of stimulation, such as cochlear implants, brain stimulators, or medication pumps [39]. Other contraindications are relative and should always be weighted in a standard clinical risk benefit analysis. The primary safety concern with TMS remains the induction of seizures with repetitive trains, even if this is a very rare phenomenon: approximately 20 seizures have been reported out of the estimated 300,000 sessions (clinical or research) since its development in the early 1980s [39]. Since the 2008 FDA approval of the NeuroStar TMS Therapy® system (Neuronetics, Inc.), seven seizures have been reported in the USA from 250,000 treatment sessions in 8000 patients [40]. This represents 1 case in 35,000 patients, which is similar or inferior to the seizure risk of most antidepressant medications. It should be noted that TMS may trigger a seizure but not cause epilepsy: seizures are always during (not after) rTMS and do not lead to spontaneous events afterwards. Nevertheless, one should screen patients for a personal history of epilepsy and possible risk factors that increase their seizure risk (such as brain lesions or medications that lower the seizure threshold). Other less severe but more common side effects include headaches, local discomfort in the area of

stimulation, facial twitching, tinnitus, anxiety, (hypo)mania, and vasovagal syncopes [39]. Safety guidelines are primarily based on traditional low- and high-frequency rTMS protocols, and although more studies will be needed to fully understand the safety profile of newer protocols such as theta-burst stimulation [41], its lower stimulus intensity (80 % of the AMT vs. 120 % RMT of the standard antidepressant protocol) and number of pulses (600 vs. 3000) may possibly be safer than traditional rTMS, despite it using higher frequencies.

8.5 TMS Clinical Applications: Major Depressive Disorder

Therapeutic applications for various neurological and psychiatric conditions have been investigated since the development of repetitive TMS. In this chapter we will focus on therapeutic studies for MDD, since it is the most widely used indication and the only with FDA approval (although other conditions are treated off label). The evidence for the use of high-frequency rTMS to the left DLPFC or low-frequency rTMS to the right DLPFC is supported by multiple clinical studies including over 2000 patients and summarized in more than 10 meta-analyses and critical reviews [42–55]. Although conclusions from these analyses confirm the clinical efficacy of TMS, early trials used highly heterogeneous study designs and stimulation parameters, which in retrospect were often subtherapeutic (e.g., only 2 weeks of stimulation or less than 1000 pulses per session). This is to be expected in the early phases of any treatment development, while the limits of safety are not well defined, but it was particular in TMS as most seizures occurred in the initial years increasing the caution of researchers in the field. As a result, meta-analyses that included early studies were often burdened with excessive variability that compromised the capacity to extract clinically meaningful conclusions. Indeed, Gross and colleagues compared the efficacy of clinical trials published in 2007 against all previously published studies and demonstrated the therapeutic superiority of recent studies [46]. Naturally, as the field developed, the use of more effective protocols became more consistent, and larger studies with more appropriate parameters were conducted.

8.5.1 Pivotal Trial

In 2007, O'Reardon and colleagues published the first large multicenter, randomized clinical trial [5]. This trial was industry sponsored and its data led to the FDA approval of the NeuroStar TMS Therapy® system (Neuronetics Inc.). Similarly large randomized controlled trials, initiated by academic researchers and sponsored by the National Institutes of Health, have subsequently been conducted with similar results [56]. The NeuroStar TMS trial conducted by O'Reardon and colleagues [5] enrolled 325 patients with moderate to severe MDD who had failed at least one but no more than four antidepressant treatments in the current episode. Patients started with a 1-week washout period in which medications were discontinued, as the study aimed to determine the effects of TMS monotherapy. Sessions occurred daily Monday to Friday over the course of 6 weeks and were followed by a 3-week taper period. The parameters of stimulation were 10 Hz (4 s on, 26 s off) over the left DLPFC at 120 % of the resting motor threshold, using 3000 pulses per session. The left DLPFC was identified as the point 5 cm anterior to the primary motor cortex (where the motor threshold was calculated). Using this TMS regimen, which was much more aggressive than previously tested parameters, they proved this intervention to be very safe, not causing any seizures and only minimal risk side effects such as discomfort under the site of stimulation or headaches. Most importantly, TMS proved to be an effective antidepressant with response rates of 23.9–24.5 % (compared to 12.3–15.1 % for placebo) and remission rates of 14.2–17.4 % (compared to 5.5–8.2 % for placebo) after 6 weeks of treatment. It is significant to note that remission rates doubled from week 4 to week 6, and outcomes continued to improve during the taper phase, with response rates increasing from 23.9 to 27.7 % and remission rates from 14.2 to 20.6 % using the primary outcome (Montgomery-Asberg Depression Rating Scale or MADRS).

From a safety perspective, these data demonstrated how conservative TMS protocols in previous studies had been, as the upper limit of tolerable risks seems to be far even from this more aggressive regimen. In terms of efficacy, these results provided robust evidence for the dose-dependent antidepressant effects of TMS, as stimulation over weeks 4 and 6 and the taper period continued to

improve response and remission rates and further separated active from placebo arms. This absence of an efficacy plateau may indicate that longer treatment duration may provide further benefit.

8.5.2 Naturalistic Studies

Randomized controlled trials (RCTs) are necessary to prove the efficacy of any treatment compared to placebo in a controlled manner, but the generalizability of these studies is often challenging given their strict inclusion and exclusion criteria, which do not capture the typical patient in standard clinical settings (e.g., with multiple medical and psychiatric comorbidities, undergoing concomitant treatments, etc.). This is why naturalistic effectiveness studies are also needed to complement RCTs and provide a real-life measure of the risks and benefits of interventions. Carpenter and colleagues [57] conducted a multisite open-label naturalistic trial in which they enrolled 339 patients who, on average, were more refractory, had a longer duration for the current episode, and presented with more complex comorbidities than the cohort in the O'Reardon et al. trial [5] (i.e., they were sicker and more representative of the average clinic patient). All participants were naïve to TMS but were allowed to continue with their ongoing pharmacological and psychotherapeutic treatments, in addition to TMS. They received the same TMS protocol approved by the FDA consisting of 6 weeks of daily left prefrontal 10-Hz TMS. After 6 weeks of treatment, response rate for the primary outcome (Clinical Global Impressions-Severity or CGI-S) was 58 % and remission rate 37.1 %. Secondary outcome measures showed a range of response and remission rates of 41.5–58 % and 26.5–37.1 %, respectively, depending on the metric used to quantify severity. Age and baseline symptom severity before TMS were negative predictors of response, but unlike patient in the pivotal trial, the number of previously failed medication trials did not negatively predict therapeutic response, as both mild and severely refractory patients presented with similar outcomes.

Other naturalistic studies have reported similar results [58]. These studies present effectiveness data in less controlled but more

realistic settings, which better describe the outcomes expected for patients treated in clinics and hospitals with current standard protocols.

8.5.3 Durability and Maintenance

Although most TMS therapeutic clinical trials have focused on its acute efficacy and safety, a number of recent studies have started to investigate the durability of TMS antidepressant benefit and the role of maintenance treatment.

In a naturalistic multisite study, Dunner and colleagues [59] followed 257 patients with treatment refractory MDD after their acute course of TMS, assessing depression severity at 3, 6, 9, and 12 months. The authors reported that among patients who responded to the acute treatment (at least 50 % improvement from pre-TMS baseline), 62.5 % continued to meet response criteria throughout the duration of the study. Similarly, 70.5 % of patients who reached full remission did not relapse over the entire length of the study. The 29.5 % of acute remitters who relapsed did so mostly within the first 6 months. During this 12 months of follow-up, patients were allowed treatment as usual. The mean number of medications throughout the study was similar to study entry for all response categories (remitters, responders, partial responders, and nonresponders). Interestingly, 36.2 % of all patients received additional TMS treatment during the year, with a mean of 16.2 sessions per patient. Additional TMS was more likely in the subgroups that obtained benefit from acute TMS (42.1 % and 61.4 % of remitters and responders, respectively, vs. 32.2 % and 19.5 % of partial responders and nonresponders). In summary, these data suggest that approximately two thirds of TMS responders will maintain their benefit for at least 1 year with continued maintenance treatment. Other studies have reached similar conclusions with smaller samples [60–64]. A significant portion of these patients received additional TMS during this period, although the specific role of maintenance TMS was not assessed in this study.

Richieri and colleagues [65] conducted a maintenance TMS study in which they followed 59 patients with treatment refractory

MDD who had responded to an acute course of TMS. During 20 weeks, 22 patients received no additional treatment while 37 continued with maintenance. At study endpoint, significantly higher relapse rates were observed in patients who did not receive maintenance TMS treatments compared with patients who did (82 % vs. 38 %). Other similar studies have demonstrated the clinical benefit of maintenance TMS beyond the acute 6-week period [58, 61, 63, 66–68], although important clinical questions remain open and need to be addressed empirically, including who should receive maintenance and what protocols would be most effective (and cost effective).

8.5.4 Predictors of Response

As TMS has entered clinical practice with more homogeneous protocols leading to greater effects sizes and decreased variability, researchers have attempted to understand what variables predict the antidepressant response of TMS. Fregni and colleagues analyzed pooled data for 195 patients from six independent studies [69]. They reported that age and the number of previously failed medication trials were negative predictors of response, i.e., younger and less refractory patients had better outcomes. Lisanby and colleagues analyzed the data from the NeuroStar TMS$^{(R)}$ pivotal trial and also identified the number of previously failed trials as a predictor of poor response, in addition to the duration of the current episode and the presence of comorbid anxiety [70]. Interestingly, these clinical predictor variables are not specific to TMS, but they seem to predict antidepressant response across treatment modalities including pharmacological and psychotherapeutic interventions. Nevertheless, Carpenter and colleagues found that in a naturalistic setting, mild and severely refractory patients responded equally to TMS [57]. As the field moves toward and we identify not only clinical and demographic variables but also biomarkers that predict response to treatment, the hope is that this information will help clinicians stratify patients and inform treatment selection, hence maximizing efficacy and safety [71].

8.5.5 H-Coil Deep TMS

As noninvasive brain stimulation technologies evolve, new clinical applications become available. A notable example, given its approval by the FDA and subsequent availability in clinical practice, is the use of the H-coil for the treatment of MDD. While other therapeutic indications are being studied for this family of coils, they remain experimental and their use is off label [13].

In their pivotal double-blind, randomized, placebo-controlled multicenter trial, Levkovitz and colleagues [6] enrolled 212 patients with MDD who had either failed 1–4 antidepressant medications or not tolerated two or more in the current episode. After a washout period of 1–2 weeks in which antidepressants, mood stabilizers, and antipsychotics were stopped (sedatives and hypnotics were allowed to continue at a stable dose), patients were randomized to receive either active or sham TMS monotherapy to the left DLPFC. The treatment protocol included an acute phase of 4 weeks of daily sessions (Monday to Friday) followed by a taper phase of two weekly sessions for 12 weeks. Each session consisted of 1980 pulses at 18 Hz applied in 55 trains (2 s of stimulation, 20 s of pause) for a total duration of 20 min. Stimulation intensity was 120 % of the RMT, and the target of stimulation was 6 cm anterior to the hotspot used to define the MT. This remains the standard H-coil TMS antidepressant protocol. The primary outcome of the study was change in the Hamilton Depression Rating Scale-21 (HDRS-21) at 5 weeks (i.e., at the end of taper week 1). Other symptom severity scales, other time points, and categorical measures of efficacy (response and remission rates) were used as secondary measures. Safety was assessed throughout the study with qualitative and quantitative approaches.

The authors reported a decrease of 6.39 points in the HDRS-21 for the active group, compared with 3.28 for placebo (effect size = 0.76, $p = 0.008$) in their per protocol analysis, which excluded patients who did not complete the entire protocol. The intention to treat analysis showed a smaller effect size (0.58) that bordered statistical significance ($p = 0.0578$). Secondary outcome measures at the 5-week time point reported a response rate of 38.4 % for active TMS and 21.4 % for sham ($p = 0.01$) and remission rate of 32.6 %

for active and 14.6 % for sham ($p = 0.005$). At 16 weeks, response rates were 44.3 % (active) vs. 25.6 % (sham) and remission rates 31.8 % (active) vs. 22.2 % (sham), all significant. Although the effects of treatment were stronger in patients with lower levels of treatment resistance (1–2 failed medications), it was also present and significant for more resistant patients (3–4 failed medications). Common adverse events included application site pain, headaches, muscle twitching, back pain, and insomnia, but only application site pain was different between active and sham groups. Eight serious adverse events were reported, which included suicidal ideation, nausea and vomiting, and nephrolithiasis in the sham group and seizure, cluster headache, and elbow fracture in the active group. Only the seizure was considered device related: it was a generalized seizure that lasted 2 min in a 26-year-old patient reported to have used an "excessive amount of alcohol" the night before treatment. The patient was observed in the emergency department and eventually discharged home without further treatment.

At present, no clinical trials have compared the clinical efficacy and safety of traditional figure-of-eight TMS coils and H-coil TMS. Both technologies have been tested and proven to be safe and effective in patients with treatment refractory MDD, and there is no empirical data to suggest one is better than the other. The shorter duration of the acute phase (4 vs. 6 weeks) and stimulation session (20 vs. 38 min) make the H-coil protocol potentially more efficient, although 6-min treatment sessions with theta-burst TMS using traditional coils have been reported to be as effective as the FDA-approved 38-min protocol [22, 23]. The H-coil trial showed higher response and remission rates than the traditional TMS pivotal trials, but its placebo effect was also greater and its safety and tolerability outcomes could be considered less favorable. The increased depth and decreased focality of the H-coil stimulation though should not be confused with either better efficacy or worse tolerability, as these are clinical and not neurobiological outcomes that need to be explored in a head-to-head clinical trial. For now, clinicians and researchers have two related yet different TMS technologies in their therapeutic armamentarium, both with proven clinical efficacy and safety to treat patient with depression and other neuropsychiatric conditions [13].

8.6 Summary

In summary, TMS is a powerful research and clinical tool with FDA approval for diagnostic applications in clinical neurophysiology and antidepressant therapy in the USA, although therapeutic indications are wider in other countries. Its noninvasive nature and benign safety profile, added to its proven antidepressant efficacy, have contributed to its introduction in community and academic clinics as a standard of care intervention. Future developments should advance our understanding of the efficacy of different parameters and present new stimulation protocols that expand the indications to other disorders and increase the cost-effectiveness of this now consolidated treatment.

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9 Ablative Neurotherapeutics and Deep Brain Stimulation in Animal Models of Psychiatric Disorders

Christelle Baunez

9.1 Introduction

After Bergman and colleagues had shown that lesioning the subthalamic nucleus (STN) could alleviate some parkinsonian signs in a monkey model of Parkinson's disease (PD) [1], Benazzouz and colleagues showed that unilateral STN high-frequency stimulation (HFS) applied in monkeys rendered hemiparkinsonian with MPTP alleviated the muscular rigidity observed in the contralateral forelimb [2]. This pioneer work was actually at the origin of the idea to apply HFS that had been initiated at the level of the thalamus [3], into the STN in PD patients. In the intact monkey, it was also shown that STN HFS could induce hyperkinetic movements similar to the hemiballism observed after STN lesions [4]. In contrast to what was described after STN lesions, STN HFS does not seem to induce hyperkinetic movements when applied at certain voltage to MPTP monkeys and when compared to L-DOPA effects [5]. Application of STN HFS in PD patients was first performed by the group of Benabid in Grenoble, France [6], and is

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J.A. Camprodon et al. (eds.), *Psychiatric Neurotherapeutics*,
Current Clinical Psychiatry, DOI 10.1007/978-1-59745-495-7_9

currently used worldwide with great success. However, there are still remaining questions regarding its mechanism of action that are still under investigation in both patients and animal models [7].

PD is however not limited to motor symptoms and little consideration was given to the possible non-motor side effects of DBS at the beginning, the basal ganglia being mainly considered as motor structures, although PD can be considered by some authors as a psychiatric disorder [8]. The current focus of clinical and basic research is actually on investigating the effects of DBS on non-motor functions in order to anticipate and/or prevent serious side effects.

The use of animal models carries on further and could contribute to highlight some of the possible non-motor side effects of STN DBS but has also helped to assess the possible use of this surgical strategy for the treatment of other disorders such as obsessive-compulsive disorder (OCD), depression, and addiction. A few examples will be described in this chapter.

9.2 PD: A Psychiatric Disorder? Non-motor Symptoms and Lesions or DBS

The two main targets used for the treatment of PD are the internal globus pallidus (GPi) and the STN. STN is considered the most efficient target but is also the target most likely to induce non-motor side effects [9].

9.2.1 Globus Pallidus Interna/Entopeduncular Nucleus

Unfortunately, only two studies testing the effects on non-motor functions of lesions or DBS to the entopeduncular nucleus (EP), the rat homologue of primate GPi, have been published to date in rats [10, 11]. Since EP is a target for PD and Gilles de la Tourette syndrome, these studies are more relevant in the context of non-motor functions in PD models, although they were not performed in PD animals. It is interesting to note that EP lesions do not seem to affect learning and memory processes nor motivation.

EP lesions, like DBS, prevent the detrimental effects of apomorphine on pre-pulse inhibition, a classic procedure used to assess sensorimotor gating. Given the clinical studies reporting little to no deficit in non-motor functions after pallidotomy or GPi DBS, it supports the fact that EP/GPi may be less involved than STN in non-motor functions, as developed below, and confirms GPi as an efficient target for Tourette, since failure in sensorimotor gating is considered as one of the cause of Tics [12].

9.2.2 Subthalamic Nucleus

9.2.2.1 Subthalamic Nucleus Lesions

STN manipulation in PD models in animals first aimed at assessing the recovery of motor functions. However, using a simple reaction time (RT) task, we have reported possible side effects of STN inactivation in PD that might be related to non-motor dysfunctions related to attention or impulsivity [13]. In this task, rats were trained to press a lever down and sustain their lever press until the occurrence of a visual stimulus (occurring after a foreperiod of either 0.5, 0.75, 1, or 1.25 s.) and had then to release the lever (reaction time, RT) as quickly as possible (maximum RT = 600 ms). In the study, we have shown that 6-OHDA dopaminergic depletion in the striatum (our model of PD in rat) increased RT, suggestive of akinetic deficit that could be corrected by bilateral STN lesions. STN lesions induced however other deficits expressed by increased early withdrawal of the lever that could relate to cognitive deficits such as time estimation, attention, and control of inhibition failure. This finding questioned the possible side effects induced by manipulations inactivating the STN in PD patients.

In the same rat model of PD, visual attention was slightly affected by the DA depletion, in addition to motor-related deficits assessed in the attentional task called the five-choice serial reaction time task. Interestingly, when combining this depletion with STN lesions, the performance was further impaired. One of the most striking effects was observed on perseverative responses toward the food magazine, suggesting an increased level of motivation for the reward [14]. This latter aspect will be addressed in the last part of this chapter.

9.2.2.2 Subthalamic Nucleus DBS

In the first study published on STN HFS in freely moving rats performing behavioral tasks, we used unilateral stimulation in a hemiparkinsonian model consisting in a unilateral 6-OHDA lesion of the SNc. In this work we assessed both basic motor tasks such as haloperidol-induced catalepsy, apomorphine-induced circling behavior, as well as a choice RT task [15]. The parameters were set at 130 Hz, 60–70 μs pulse width, and intensity set just below the threshold of hyperkinetic movements of the contralateral paw (range, 50–150 μA). We showed that the basic motor deficits could be alleviated by STN HFS. Once the efficacy of STN HFS is proven, we investigated the effects of STN HFS on non-motor deficits induced by the DA depletion.

In a choice RT task performed in a three-hole box, the rats were trained to hold their nose in a central hole until the presentation of a light in one of the adjacent holes and then respond by a nose poke in the appropriate hole. After the dopaminergic unilateral depletion, many animals were unable to perform the task, suffering from a kind of apathy, or "psychic akinesia," preventing them to initiate a trial although they moved well and fed themselves in their home cage. Interestingly enough, the STN HFS did not help these animals. Thus, in contrast to the spectacular effect of STN HFS in PD patients, the stimulation applied in the rat could not overcome the profound deficit preventing the animals to perform the task. Interestingly, however, for those able to perform the task, STN HFS alleviated the deficit expressed as a decreased ability to initiate a response toward the side contralateral to the DA lesion [15]. These results suggest that STN HFS could be beneficial for the treatment of motor deficit, but non-efficient when the DA depletion had induced cognitive/psychic deficits, suggesting that further cognitive studies were necessary and better assessment of non-motor functions in PD patients before and after STN DBS was important.

Interestingly, it has also been shown that bilateral STN HFS could alleviate the premature-responding deficit in a choice RT task at lower current intensity (3 μA) than that reducing RT and MT (30 μA) [16]. This latter study provided the evidence that, to treat cognitive and motor deficits, it may be necessary to apply HFS at a different intensity.

The subtle deficits recorded in the five-choice RT task in PD rats were neither further deteriorated by bilateral STN HFS nor alleviated. As for the lesion study, the most striking effect was observed on the perseverative responses recorded in the food magazine that increased under STN HFS in DA-depleted rats, suggesting that STN HFS increases motivation for the food reward [17]. This last finding can be paralleled with the weight gain reported in PD patients subjected to STN DBS [18–21].

Within the non-motor symptoms of PD, one of the most frequently reported is depression. The effects of STN DBS on depression have been assessed in parkinsonian rats and revealed that STN DBS increased depressive-like behavior [22]. This is in line with the fact that depression is often not treated by STN DBS in PD patients, and it was even reported that the rate of suicide increased in STN DBS-treated depressed PD patients, possibly helped by the release of inhibition facilitating the "passage à l'acte" [23, 24].

The evidences gained from these animal studies [15, 16] seem thus to confirm that STN HFS applied at parameters inducing beneficial effects on motor functions does not necessarily correlate with beneficial cognitive effects. This observation has also been reported in human patients [25]. There are now indeed several studies reporting either further impairment, improvement, or no effect by STN DBS in PD patients.

Taken together, these studies confirm the fact that STN DBS, although very efficient as a treatment of the motor symptoms of PD, may be inefficient in treating non-motor symptoms or may even induce side effects, as the clinical studies have reported to date.

9.3 OCD: Impulse Control Disorder

Out of the main target currently used for the treatment of obsessive-compulsive disorders (OCD) (anterior limb of the internal capsule, the nucleus accumbens, the STN, the ventral caudate, and the inferior thalamic peduncle), the nucleus accumbens and the STN have been studied in animal experiments. In animal models, although there is currently no satisfying model of OCD, there are data regarding the effects of manipulation of these structures on

repetitive behavior (related to compulsions of OCD patients) and loss of inhibitory control. Obsessions (unwanted recurrent thoughts) are of course impossible to model in animals. This part of the chapter will thus review the studies reporting effects of NAc or STN manipulations on expression of repetitive behavior or impulse control deficits.

9.3.1 Repeated Behavior as an Index of Compulsion

Repeated behavior assessed in animals can be expressed by stereotyped behavior induced by either high doses of psychostimulants, checking behavior induced by quinpirole, alternation behavior induced by 8-OH-DPAT, or perseverative behavior measured in operant tasks with no necessity of a former pharmacological stimulation.

9.3.1.1 Nucleus Accumbens Manipulations on Various Forms of Repeated Behavior

One of the oldest reports mentioning compulsive behavior after lesions of the ventral striatum/nucleus accumbens was published in 1986 and described compulsive attentive behavior in the cat [26]. Lesions of the nucleus accumbens and stimulation at low frequency have been compared in a model of alternation behavior induced by a 5-HT1A agonist (8-OH-DPAT, 8-hydroxy-2 di-*n*-propylaminotetralin hydrobromide) that the authors consider a model of OCD in the rat [27]. Surprisingly, lesion of the nucleus accumbens and stimulation decreased the alternation behavior, but the authors conclude that the nucleus accumbens is involved in compulsive behavior. In contrast to that study, high-frequency stimulation of the nucleus accumbens has been shown to reduce checking behavior induced by quinpirole [28]. On the same behavior, lesions of the accumbens and the orbitofrontal cortex have been compared and revealed an involvement in reducing the checking, but on different parameters, suggesting various functional roles for these two structures in the generation of compulsions [29].

Effects of excitotoxic lesions of the nucleus accumbens core or shell have been assessed in the five-choice serial reaction time task

and only affected perseverative behavior in certain conditions, particularly after failed trials [30, 31].

These results clearly show that the nucleus accumbens is involved partly in compulsive behavior but not in all aspects.

9.3.1.2 Subthalamic Nucleus Manipulations on Various Forms of Repeated Behavior

Using the specific visual five-choice attentional task, we have studied the effects of STN lesions [32] and STN HFS [17] and showed an increased level of perseverative responses toward the response locations and toward the magazine where the animals collect the food reward, suggestive of deficit in response control (the perseverative responses can be related to compulsions), and an increased level of motivation for the reward [17, 32]. The lesion results were the first to highlight the involvement of STN in cognitive functions. These results were replicated after blockade of the GABA receptors into the STN with muscimol [33]. Furthermore, in a study using a disconnection between the medial prefrontal cortex and the STN, by lesioning the prefrontal cortex on one side and the STN on the other side, we have given the first evidence of a functional role for the hyperdirect pathway in the perseverative deficit observed in this attentional task [34]. These results suggest that perseverations induced by STN inactivation result from the interruption of the hyperdirect pathway. It has also been reported that STN lesions induce perseverative lever pressing in a signal attenuation task, a deficit qualified by the authors as "compulsive lever pressing" [35].

Even though STN HFS did not reduce perseveration in our study [17], it has been reported to reduce stereotyped behavior induced by quinpirole in rats [36] or induced by bicuculline, a GABA antagonist, into the limbic GPe in the monkey [37]. It might explain why, although based on lesion data obtained in rats, we would have argued against the choice of STN as a possible target for the treatment of OCD, the clinical studies using STN DBS report positive results to treat OCD [38–40]. Indeed STN DBS has been reported to abolish compulsions and decrease obsessions in PD patients with OCD comorbidity [39]. A recent study has actually shown that PD patients with impulse control disorders exhibit an activity in the ventral STN that is coherent

with premotor frontal cortical activity, highlighting a role for the "associative-limbic" hyperdirect pathway in impulse control disorders [41].

9.3.2 Control of Inhibition

The control of inhibition can be assessed by using different measures such as premature responding in various operant tasks (where premature responding is used as an index of the ability to "wait" or withhold a planned, prepotent response), the measure of stopping an action already engaged (in the so-called stop-signal reaction time task), and the measure of impulsive choice assessed in the delay-discounting task (in which the animal has the choice between a small immediate reward or a large but delayed reward).

9.3.2.1 Nucleus Accumbens

Surprisingly, although there is a consensus to admit that NAc may be a key structure in the control of inhibition [42], there is little evidence of it. In a task of differential reinforcement of low rates of responding (DRL), in which rats must withhold from responding on a rewarded lever until a specific sequence of events has been completed on a different lever, lesions of the NAc core induce premature responding but not lesions of the shell [43]. However, no lesions of core or shell induce premature responses during performance in the five-choice task [30, 31]. Lesions of the NAc core had no effect either on the ability to stop an ongoing action of lever pressing [44]. On impulsive choice assessed in the delay-discounting task, lesions of the core of the NAc have been shown to increase impulsive choice by inducing a faster shift to the lever delivering a small immediate reward [45].

Since NAc DBS has been proposed as a possible therapy for OCD, high-frequency stimulation (HFS) of the core and shell of the NAc has been tested in rats performing a reaction time task. NAc core HFS was shown to reduce premature responding, while stimulation of the shell increased it [46]. This suggests that depending on the sub-territory targeted, opposite effects may be seen in OCD patients. Interestingly, DBS of the NAc is reported to be

beneficial for the treatment of OCD [47], but it was also reported that DBS of the NAc could induce impulsivity in two OCD patients [48].

9.3.2.2 Subthalamic Nucleus

In both reaction time and attentional tasks, unilateral or bilateral STN inactivation by either lesion, pharmacological blockade increased the number of premature responses [13, 32, 33, 49, 50] (see for review [51]). STN lesions also increased impulsive action in a DRL procedure [52]. This evidence strongly supports a role for the STN in a circuit that inhibits impulsive action under normal circumstances.

Further studies have confirmed that STN lesion increases impulsive action, as expressed by a difficulty for the lesioned rats to stop an ongoing action in a stop-signal task [53]. STN lesions impaired stop-signal task performance, showing an increased number of errors on the stop trials (inability to stop the response), even when the stop signal was presented early in trials (and where subjects should be able to stop on 100 % of trials). In contrast, in a task measuring impulsive choice, STN lesion can help the animals to wait for a larger reward when given the choice between a small but immediate reward and a large but delayed reward [52, 54]. This latter result questions whether or not the effect measured in the delay-discounting task is more related to motivation than to impulsivity.

Interestingly, however, in intact animals, the effects of STN HFS were slightly different to those induced by STN lesions, as premature responses were not affected [17].

Having shown that inactivation of NAc or STN can be detrimental on some aspects of the control of inhibition, either on compulsive-like behavior or on impulsivity, none of these structures, based on the animal data, seem to be appropriate for a treatment of OCD. However, since STN HFS does not increase premature responding and seems to decrease some forms of compulsions, STN may be a more efficient target. Indeed, based on the topographic organization of the STN [55], when the stimulation was applied at the border of the associative and limbic territories (anteroventral), STN HFS has been shown to be efficient to treat compulsions in OCD patients [40].

Animal models for OCD are however not satisfying to date as they rarely combine various aspects of the disease (compulsions, anxiety, impulsivity, etc.). A model combining various criteria of diagnosis matching the DSM IV, as was developed for addiction [56], will be necessary for future investigations.

9.4 Anxiety-Depression

Various areas in the brain have been targeted with successful results in treatment-refractory depressed patients subjected to DBS. These areas are the subcallosal cingulate gyrus (SCG), inferior thalamic peduncle, nucleus accumbens, anterior limb of the internal capsule, or lateral habenula (LHb).

In rodents, the classical test used to test antidepressant treatment is the forced swim test. In this test, the rat is immerged in a tube filled with water and has no possible escape. The time spent by the animal to stop swimming or attempting to climb is measured. A considered "depressed" rat will stop shortly while a treatment with antidepressant effect will increase this time [57]. In rats, the equivalent of the SCG is considered to be the ventromedial prefrontal cortex (vmPFC). Excitotoxic lesions of the vmPFC have been shown to have an antidepressant effect [58]. DBS studies targeting the vmPFC have replicated this result [59–62].

Among the structures that have been targeted for the treatment of depression-related deficits in animals, the NAc, the LHb, and the amygdala have been implanted for stimulation. It has been shown, for example, that NAc chronic and intermittent DBS increases exploration of a new environment [63]. The measure of exploration in an open field and the consumption of sucrose can be sometimes taken as index of depression when they follow repeated exposures to stressors. In this situation, chronic stimulation of the LHb has been shown to be beneficial [64].

Since the amygdala has been shown to be hyperactive in post-traumatic stress disorder (PTSD), recent studies have assessed the effect of amygdala high-frequency stimulation in a rat model of PTSD in order to normalize its activity. This has proven to be beneficial and position the amygdala as an interesting target for future surgical treatments [65, 66].

The targets tested in animals for the treatment of anxiety-depression-related disorders are not necessarily those targeted in human patients, but they may offer alternatives in case of failure of the classical treatment.

9.5 Addiction

9.5.1 Nucleus Accumbens

The involvement of the nucleus accumbens in motivational processes is so well documented that it seems an obvious place to study when assessing possible surgical targets for the treatment of addiction. Vassoler et al. have shown that DBS applied at the level of nucleus accumbens shell could reduce relapse to cocaine, without reducing it for food [67]. Although there were electrophysiological data reporting the possibility for accumbens neurons to respond differentially to natural reward versus drug of abuse such as cocaine [68, 69], there was no other behavioral data showing dissociation between various types of reward after manipulations within the accumbens. The classical view of the reward system does not account for this possibility. Therefore, targeting the nucleus accumbens to treat cocaine addiction was never a hypothesis since reducing its activity may affect all forms of motivation. A recent study has assessed the effects of DBS applied in the various subterritories of the NAc, the core, lateral, and medial shell on motivation for natural reward, and showed that lateral shell DBS diminished motivation for food in a progressive ratio schedule of reinforcement, while the lateral shell stimulation increased food intake and core DBS had no effect [70]. Another study has shown that DBS of the nucleus accumbens (at higher current parameters than those applied in the STN) could reduce the preference and consumption of alcohol in alcohol-preferring rats [71]. Other studies have shown that NAc DBS core, as well as shell, could reduce alcohol consumption in a two-bottle-choice procedure [72] or that chronic NAc core DBS could reduce CPP induced by morphine [73]. In parallel, clinical observations of beneficial effect of DBS in the accumbens on alcoholism in one case [74] or on smoking in patients treated for OCD or Tourette's syndrome [75] have been reported.

It is to note however that a few clinical groups are currently considering, if not assessing already, application of DBS in the accumbens of addicts [76] with successful results as, for example, on one case of heroin addiction [77].

9.5.2 Lateral Habenula, Lateral Hypothalamus, and Prefrontal Cortex

DBS of the lateral habenula (LHb), applied following an unconventional schedule of stimulation, has also been studied on cocaine self-administration in rats and induced a decrease in cocaine seeking, while interestingly, lesions of the LHb had the opposite effect [78]. When similar stimulation of the LHb was tested for sucrose reward, the same authors reported a decreased sucrose intake, while again lesions of the LHb increased it [79]. In another study using repeated short stimulations, Levy et al. [80] showed that stimulation of the lateral hypothalamus (LH) diminished cue-induced seeking but had no effect on drug consumption, while stimulation of the prefrontal cortex reduced consumption and cocaine seeking, suggesting that stimulation of the prefrontal cortex could represent a strategy for the treatment of addiction [80].

9.5.3 STN

9.5.3.1 STN: A Possible Target

We have first shown that bilateral STN lesion does not increase hunger or affect primary processes of motivation whatever the internal state of the animals (deprived or sated) or the reward (standard animal food, palatable food, alcohol, or IV injection of cocaine). STN lesion does not affect these consummatory processes [81–84]. When assessing motivation by measures of reactivity to stimuli predicting food, we found that STN lesions increase responses to these stimuli, suggesting that STN plays a role in incentive motivation [81]. This result was further confirmed by another group [85]. We also showed that STN lesion increases willingness to work on a lever to obtain food pellets and increases the score of preference for an environment previously associated

with food [82]. In contrast to these results, we found the opposite effects when the reward was cocaine, highlighting a possible role for STN to modulate the reactivity of the reward system with regard to the nature of the reward involved [82]. When testing the effects of bilateral STN lesion on motivation for alcohol, we have further shown that it could also affect motivation in an opposite manner depending on the initial preference of the animals for the reward, STN lesions increasing motivation for alcohol in "high-drinker rats" while decreasing it in "low drinkers" [83].

These results position the STN as an interesting target in the brain where dissociation between motivation for drug and other types of reward can be made. The dissociation seems to be even more complex than based on the nature of the reward since the initial preference for it plays a critical role [83], but also since electrophysiological recording in the STN has revealed that the specific value of a reward of the same type (i.e., different concentrations of sucrose) is encoded by different neurons in the STN [86].

9.5.3.2 STN DBS: The Possible Strategy

Very recently, we have tested the effects of bilateral STN HFS on motivation for food and for cocaine. As shown after STN lesions [82], bilateral STN HFS reduces the preference for cocaine and the willingness to work to obtain cocaine, while in contrast it increases the preference for food and the willingness to work for food reward [84]. One of the advantages of DBS is the possible reversibility that was tested and confirmed since the motivation to work for cocaine was increased after extinction of the stimulation [84].

These results suggest that not only STN might represent an interesting target for the treatment of cocaine addiction, but STN DBS may be the appropriate strategy to diminish the desire for cocaine, without diminishing other motivated behavior.

Although these data were obtained in intact animals, they are in line with some clinical observations in PD patients after STN DBS, reporting craving for sweet food in some cases or decreased addictive behavior toward DAergic treatment [87–90].

The best target to select for the treatment of addiction is still a matter of debate [91], although the only one that has been tested in human addicts is the nucleus accumbens. Given the knowledge regarding the role of accumbens in mediating motivation for any

type of reward, it seems difficult to imagine that DBS applied in the NAc could selectively reduce the motivation for the object of addiction, leaving intact the rewarding properties of all other rewarding activities. The clinical outcomes will be more helpful than the animal work to sort out this question.

9.6 Conclusion

The various applications of neurotherapeutics in animal models have shown that depending on the disease, the perfect target is still under debate and the pragmatic results obtained in the patients will probably help more than the animal studies. It is interesting to note that animal studies are not always good predictors of therapeutic outcome, as for the treatment of OCD. Since lesions of the nucleus accumbens can induce some forms of impulsivity, it is difficult to anticipate that inactivating the NAc with high-frequency stimulation, assuming that it results in an inactivation, could alleviate OCD. The same applies to STN, as the present chapter has reviewed the numerous deficits induced by STN inactivation on perseverations, index of compulsion, and on impulsivity. However, it seems that compulsions can be treated with STN DBS in OCD patients.

Animal studies have also contributed to highlight the possible targets for the treatment of addiction and especially the STN that has not been tested yet in addicts. In contrast, although the NAc is considered as a key node for motivation for any type of reward, it is puzzling to see the positive outcome of NAc DBS on specific forms of addiction. Further investigation of the general motivational state for other rewards is still needed.

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Future of Neurosurgery

10

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10.1 Introduction

Surgical therapies for psychiatric disorders have a long and rich history, dating back to the frontal leucotomies of Moniz in the late 1930s [1]. The advent of stereotactic surgery [2] increased the precision and improved the safety profile of these interventions. For the next six decades, lesion-based therapies were the mainstay of surgical treatment for refractory psychiatric disease, including major depressive disorder (MDD), obsessive-compulsive disorder (OCD), and others. Anterior capsulotomy, cingulotomy, subcaudate tractotomy, and limbic leucotomy procedures were performed with success rates varying from 35 to 65 % [3]. Considering the severity and refractoriness of the conditions being treated, these

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J.A. Camprodon et al. (eds.), *Psychiatric Neurotherapeutics*,
Current Clinical Psychiatry, DOI 10.1007/978-1-59745-495-7_10

procedures represented an important therapeutic option for patients with otherwise intractable and disabling disorders.

Lessons learned from these ablative disorders, as well as the emerging success of DBS for movement disorders, motivated the application of DBS to psychiatric disorders at the turn of the millennium. Characteristic of many of the advances in psychiatric surgery within the past decade is their basis upon empiric observations of other treatments. The success of the anterior capsulotomy gave rise to DBS of the same region [4]. The observation of improvements in comorbid depression in OCD patients treated with capsular DBS [5] led to trials of DBS for MDD [6], and the observation of improvements in OCD in Parkinson's disease patients treated with STN DBS [7] led to the investigation of STN DBS for OCD [8].

Future advances in surgery and device-based therapy for psychiatric conditions will likely emerge from hypothesis-based studies motivated by a deeper understanding of the involved circuits. Accumulating experience of the effects of various surgical procedures, as well as information from human imaging studies and experiments in animal neurophysiology, will improve our understanding of the normal function of the underlying circuits and the dysfunctions responsible for pathological states. As new applications are derived from these insights, further knowledge will accrue, accelerating advances in the field.

Along with increases in our mechanistic understanding, the future will herald developments in the methods of delivery of neuromodulatory signals to the brain. Whereas the majority of current therapies are based on creating lesions or delivering electrical stimulation, future methods may include optical stimulation, closed-loop stimulators, gene-based therapy, and others.

These parallel advances will lead to more refined approaches to currently treated diseases, facilitating individualization of therapy, and to an expansion of the psychiatric conditions amenable to device-based intervention. This chapter begins by describing potential avenues of research into the circuitry and mechanisms whose dysfunction may contribute to affective and anxiety disorders. The next section describes emerging technologies for therapeutic delivery to the brain. Finally, this chapter concludes with speculations on novel applications to psychiatric conditions not currently treated with device-based therapies.

10.2 Understanding Circuits

The original attempts of ablative procedures for intractable psychiatric diseases arose from observations of physiological and behavioral changes following manipulation of the limbic system in animals [9, 10]. Future development of safe and effective treatments for neuropsychiatric conditions will similarly depend upon a detailed knowledge of the underlying neural circuitry. Because these disorders are experientially exclusively human, with a multifactorial etiology, there is no single animal model that mimics them. Nevertheless, the convergence of information from rodent, nonhuman primate, and human studies will shed light on the functional connectivity of the involved circuits, providing motivation for future improvements in therapeutic design.

Complex psychiatric disorders such as OCD can be described in terms of dysfunction of simpler component behaviors, such as the tendency to promote or suppress anxiety. These basic behaviors can be studied in detail in rodent models with simple classical conditioning experiments. Neurons in the rodent infra-limbic (IL) cortex increase activity during the recall of fear extinction, and stimulation of this region accelerates fear extinction and decreases the fear response [11, 12]. Conversely, neurons in the pre-limbic (PL) cortex increase activity during fear expression [13–15]. Future experiments in rodents could target these areas with electrophysiological recordings and stimulation to understand their function and with immunocytochemical techniques to understand their connectivity.

Rodent experiments also allow genetic manipulation, a limiting feature of primate studies. Visualization of the various neuronal subtypes constituting a region of gray matter, as well as their patterns of projections, is extremely valuable for investigating the structure and function of a putative network. By stochastically expressing different combinations of several recombinant fluorescent proteins, individual neurons can be engineered to fluoresce with a variety of colors. In the so-called Brainbow mouse, a small region of the cerebellum was designed to express scores of these trans-genes, allowing the visualization of numerous axons and synaptic contacts [16]. Creative methods such as these will facilitate the investigation of network architecture in rodent models.

The primate homologs of the rodent IL and PL are the ventral-medial prefrontal cortex (vmPFC) and dorsal anterior cingulate cortex (daCC), respectively [11, 17]. Dysfunction in these regions is recognized in OCD, proffering the hypothesis that OCD may represent a pathological inability to suppress or extinguish anxiety-generated responses, leading to the unprofitable preservation of useless behaviors such as checking, washing, etc. [11, 17, 19, 20]. Experiments in nonhuman primates (NHPs) can be designed to test this hypothesis. Although NHPs are not as suitable for similar genetic manipulation due to their higher cost and longer development period than rodents, they are able to perform complex tasks with behaviors similar to those of humans. Thus, rather than passively experiencing a simple fear conditioning paradigm, NHPs can actively participate in a complex operant conditioning experiment that more closely mimics the human situation. Given the role of the vmPFC and daCC as well as other prefrontal and basal ganglia regions in reward-seeking and avoidance behavior, studies can be designed around tasks that interrogate these behaviors in isolation and in combination. For example, the animal can be forced to decide between accepting rewarding and aversive stimuli and rejecting both. Titrating the relative magnitudes of the two stimuli would establish a rich parameter space that can be explored. Responses of individual neurons in these brain regions can be studied in detail using single-unit electrophysiology.

Similarities between the NHP and human brain will also permit anatomical studies of the involved circuits. Ablative and DBS procedures analogous to those utilized in humans can be performed in NHPs. High-resolution diffusion tensor imaging (DTI) tractography can reveal the white matter bundles in proximity to the lesions or leads that may be involved in producing the therapeutic effect. Furthermore, acute and chronic effects of electrical stimulation can be investigated by performing immunohistochemistry on NHP brains after a defined duration of DBS therapy. Appropriate assays can reveal whether DBS enhances local apoptosis, neogenesis, gliosis, or other cellular processes.

Finally, the future holds promise for furthering our understanding of the neural circuitry underlying psychiatric disorders by studying the human brain itself. Previous work has already demonstrated the involvement of the subgenual cingulate (Brodmann

area 25, cg25) in processing negative emotions across the spectrum of normal subjects and depressed patients [21]. Positron emission tomography (PET) studies showed that blood flow around cg25 increased with acute sadness and decreased with antidepressant treatment. The hypothesis generated from this finding led to the successful attempt of DBS in this region for the treatment of refractory MDD [22]. This work highlights the utility of functional imaging modalities for understanding human neurophysiology. PET in particular is well suited to DBS investigations due to its insensitivity to metal devices, as opposed to functional MRI. PET studies of humans with OCD and MDD treated with DBS can help identify regions involved in the disorder and how activity changes with and without stimulation. For example, imaging correlates to acute changes in stimulation can be studied using [^{15}O] water PET in subjects engaged in a behavioral task similar to that described above for NHPs.

The application of microelectrode recording (MER) during DBS surgery has shed light on functional aspects of several regions of the human brain, including the subthalamic nucleus [23, 24], thalamus [25], globus pallidus internus [26], and substantia nigra [27]. MER provides information on firing patterns of individual neurons with the precision usually only afforded by NHP studies. Intraoperative MER can be utilized in the subgenual cingulate or the ventral capsule/ventral striatum targets to interrogate their function, and the results compared to similar recordings in NHPs. Such cross-species comparisons will be useful not only in understanding function but also in appreciating similarities and differences in homologous regions. This information may inform the development of better animal model systems for certain disorders. As the field's experience with DBS grows, so will the population of potential study subjects.

Future research efforts across a variety of fields will produce new discoveries that will continue to improve our understanding of the neural circuitry underlying psychiatric disorders. This endeavor remains one of the most exciting and open frontiers of neuroscience and holds great promise for uncovering the mechanisms of human disease. These efforts will be crucial for advancing the development of effective treatment options.

10.3 Modes of Delivery

The development of targeted methods for modulating specific circuits in a deliberate and controlled fashion represents an essential step toward maximizing therapeutic efficacy and minimizing adverse effects. The advent of stereotactic procedures in the 1940s, for example, improved outcomes and reduced complications of lesional procedures compared to those of frontal lobotomies. Even within the past decade during which DBS has been employed for psychiatric disorders, there has been an effort to focus stimulation on the maximally effective region. Instead of stimulating a 24 mm length of the anterior limb of the internal capsule for OCD [28, 29], an ongoing trial is testing the efficacy achieved by stimulating the ventral-most 10.5 mm region that appeared most effective (www.clinicaltrials.gov: NCT00640133).

Even with refined DBS leads, however, the resulting electrical field encompasses thousands of neurons and axons, rendering it a relatively blunt tool. The future is likely to herald much more precise methods of targeting. Optogenetics is an intriguing new methodology for driving neuronal activity not with electric current, but with light. Light-sensitive microbial channels can be delivered into and expressed within an individual neuron [30]. Two channels have been developed: a cation channel that produces a depolarizing sodium current when illuminated by blue light and an anion channel that produces a hyperpolarizing chloride current when illuminated by yellow light [31]. Targeted delivery of illumination to neurons expressing these channels can function as a binary on/off switch or as a graded modulator of the cells' activity. Light can be precisely delivered to the desired location using small stereotactically placed optical fibers attached to a light source that could be implanted subcutaneously, similar to a DBS battery.

This approach has already been used successfully to control and study dopaminergic neurons in parkinsonian mice [32]. Applying this technology toward the treatment of psychiatric conditions is foreseeable in the near future. The efficacy of cg25 DBS for MDD may be caused by stimulation-induced suppression of neuronal activity, as a beneficial response to pharmacological treatment was attended by decreased blood flow in this region [21]. Expression and activation of the anion channel in cg25 may

therefore provide benefit to these patients. Similarly, the success of the anterior capsulotomy for treating severe OCD and depression suggests that a reduction in firing in the anterior limb of the internal capsule is therapeutic for these disorders. Instead of creating a lesion or placing a macroscopic DBS lead, the anion channel could be precisely delivered to the appropriate cells. Activation of the channel would decrease firing output of the targeted cells. This approach simultaneously reduces nonspecific stimulation to surrounding cells and allows superior spatial and temporal control over the frequency and amplitude of stimulation.

Intervening at the genetic level represents another possible future avenue for exploration. The higher concordance rate among monozygotic compared to dizygotic twins for OCD (68 % vs. 31 %) [33], MDD (53 % vs. 30 %) [34], and schizophrenia (48 % vs. 17 %) [35] suggests a genetic basis for these disorders. Although they are generally polygenic, there may be subtypes that are associated with certain specific alleles. Mutational studies in animals and polymorphism analyses in humans have revealed several plausible candidate genes, including those involved in serotonergic [36–38], dopaminergic [36, 38], and glutamatergic [39] neurotransmission, as well as synaptic mechanics [40]. Despite widespread expression of the allele, its effect may be limited to a particular node in the circuit. For example, a mutation in a synaptic scaffold protein may uniquely cause a disturbance in corticostriatal neurotransmission, producing an OCD-like phenotype [40]. If subpopulations of patients can be identified in whom a narrowly expressed genetic variant is present, gene therapy approaches may allow corrective genetic material to be introduced to the region to restore normal function. Clever combinations of vectors that allow anterograde and retrograde axonal transport, such as the rabies virus, versus strict unidirectional transport, would potentially permit precise targeting.

Another advancement in neuromodulatory procedures for psychiatric conditions would include closed-loop devices. Rather than providing constant output, a closed-loop device employs a feedback system to modulate output based on some kind of measured input. Such a device has been developed for the treatment of epilepsy: when a sensor detects a burst of epileptiform activity,

the microprocessor triggers an abortive output stimulation [41]. A similar device is imaginable for psychiatric disorders, in which a sensor, perhaps employing microdialysis or electrochemical methods, continuously measures neurotransmitter levels and triggers an output volley when the measured levels achieve some criterion. Candidate sources of the input signal could include dopamine or serotonin levels in a specific structure, such as the striatum. The output could take the form of electrical pulses in the case of a DBS-style device or light pulses in the case of an optogenetic-style device.

10.4 Future Applications

The success of ablative and DBS procedures to date will motivate further expansion of the indications for psychiatric surgery. A deeper understanding of the underlying circuitry and the development of improved delivery methods will further increase enthusiasm, as they are likely to allow individualization of therapy. Anxiety disorders such as post-traumatic stress disorder (PTSD) and debilitating phobias may share some of the aberrancies in circuitry found in OCD and therefore may be amenable to similar treatments. The anatomical and functional abnormalities in schizophrenia [42, 43] suggest that there may be specific targets in that disorder that can be modulated for therapeutic benefit.

As psychiatric neurosurgery continues to gain momentum and increase its applications, ethical considerations will become increasingly important. The frontal lobotomies of the middle part of the last century imparted an unquestionable lesson: the indiscriminate application of an invasive procedure with a high complication rate on a vulnerable population is not acceptable. To allay fears of inappropriate behavioral modification, many centers have adopted strict guidelines governing the patient selection process for psychiatric neurosurgery, based in large part on those set forth by a Congressional Commission in the late 1970s [44]. The centerpiece of these guidelines is the inclusion of a multidisciplinary team [45], including psychiatrists, psychologists, neurosurgeons, and neurologists, that can comprehensively consider all aspects of

the patient's medical and psychiatric history. The judicious application of these practices will ensure that psychiatric neurosurgery continues to develop as a safe, effective and humane treatment for severely treatment refractory patients.

10.5 Conclusions

The last decade has witnessed a resurgence in novel neurosurgical therapy for psychiatric disorders. Several well-designed randomized controlled trials are currently investigating the efficacy of DBS for refractory OCD, MDD, and other conditions, with electrophysiological and functional imaging studies of the participating patients intelligently built into the study design. In addition, substantial research efforts are underway to understand the neurophysiological basis of human cognition and emotion and the disturbances in these circuits that manifest as anxiety and affective disorders. This combination of animal and human studies will be essential for advancing our appreciation of the network involved. In concert, the development of creative mechanisms for delivering neuromodulatory signals to the brain is progressing rapidly. This field will benefit from an expanding armamentarium of delivery technologies, including electrical, optical, genetic, and closed-loop devices.

The convergence of an improved understanding of the circuit and efficient means of modulating it will significantly alter the landscape of neurosurgical therapies for psychiatric disorders. These advances will enable individualization of therapy based on pharmacological responses, functional imaging data, and electrophysiological measurements. And as the arsenal of therapeutic devices expands to meet the demands of an individualized approach, so will the number of conditions amenable to device-based intervention. As enthusiasm for new therapies builds, however, it will be incumbent upon clinicians to exercise sound ethical practices to ensure that this particularly vulnerable population is properly protected from undue risk. Psychiatric neurosurgery is poised to provide an increasing number of patients with debilitating psychiatric illness a safe and effective therapeutic option.

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J.A. Camprodon et al. (eds.), *Psychiatric Neurotherapeutics*,
Current Clinical Psychiatry, DOI 10.1007/978-1-59745-495-7