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Advances in Neuromodulation: The Orbitofrontal-Striatal Model Of, and Deep Brain Stimulation In, Obsessive-Compulsive Disorder

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The chains of habit are too weak to be felt
until they are too strong to be broken
Samuel Johnson

1. Introduction

Obsessive-compulsive disorder is a common chronic neuropsychiatric illness. Estimates of the lifetime prevalence rate of obsessive-compulsive disorder will vary depending on the methods used to gather the epidemiological data and the diagnostic criteria used to define obsessive-compulsive disorder. Estimates of the lifetime prevalence of obsessive-compulsive disorder have been reported to be to be between 1.9%-3.3%, when obsessive compulsive disorder was defined without DSM-III criteria. A slightly lower prevalence of obsessive-compulsive disorder was reported to be between 1.2%-2.4%, when obsessive-compulsive disorder was defined using DSM-III criteria[1][2][3]. These estimates of the prevalence of obsessive-compulsive disorder are likely to be accurate because they are based on: a.) population-based data; b.) that was gathered from five US communities; c.) from more than 18,500 outpatients; participating in the NIMH Epidemiologic Catchment Area (ECA) a Study. The lifetime prevalence rates obtained from the NIMH ECA study were 25-60 times higher than previous estimates, which were based on studies of clinical populations. If the true lifetime prevalence of OCD in the United States is 2.5%, then it follows that 6.5 million Americans will be affected by obsessive-compulsive disorder during their lifetime. If the 1-month prevalence rate of OCD in the United States is 1.3 %, then approximately 3.4 million Americans suffer from obsessive compulsive disorder each Month[4]. Regardless of the specific epidemiological and diagnostic methods used to estimate the incidence or prevalence of obsessive-compulsive disorder, literally millions of Americans are affected by the symptoms.

There is strong evidence that obsessive-compulsive disorder impacts the American economy measureably. This premise is supported by the following. First, medical costs, yearly, from

obsessive-compulsive disorder have been estimated to be $2.1 billion. Second, indirect costs due to lost productivity have been estimated to be $5.9 billion[5]. Third, health care expenditures in the United States surpassed $2.3 trillion in 2008, were $714 billion spent in 1990, and equalled $253 billion in 1980[6]., Therefore, it is highly likely that both the direct and indirect costs of obsessive-compulsive disorder continue to increase.

Economic indicators non-withstanding, the broader impact of obsessive-compulsive disorder on social, educational, and occupational function was addressed in a recent study. The investigators found that the symptoms of obsessive-compulsive disorder affected socialization by various means. Lowered self-esteem was observed in 92% of patients sampled, interference with family relationships reported in 73% of patient's sampled, and difficulty maintaining relationships was noted by 62% of patients[7]. Lowered academic achievement was observed in 58% of patients with obsessive-compulsive disorder, indicating that the disorder profoundly impacts educational achievement[7]. Occupational functioning is also affected in patient's with obsessive-compulsive disorder, through: lowered career aspirations, observed in 66% of patients sampled; work interference in 47% of patient's sampled, and ; lost time due to inability to work, reported in 40% of patients[7].

Suicide is the most serious complication of anxiety disorders. Suicide attempts secondary to obsessive-compulsive disorder symptoms have been reported in 13% of patients[7]. Obviously, if a suicide attempt is completed, progress in all three important areas of life function—relationships, educational and vocational function—halt permanently. Harm to family members through related injury, bereavement, lost spousal support, childhood parentification, and impact on the surrounding community is also significant after a completed suicide. In 2008, a total of 36,035 persons died as a result of suicide and in the United States approximately 666,000 persons visited hospital emergency departments for nonfatal, self-inflicted injuries[8]. Although suicidal thoughts do not always lead to a lethal or life threatening suicide attempt, suicidal thoughts and behavior even in the absence of suicide attempt are important. Public health surveillance is performed on suicide-related issues by gathering data at the state level by a national- and state-level survey—the National Survey on Drug Use and Health (NSDUH). Between January 1, 2008–December 31, 2009, the NSDUH obtained data from 92,264 respondents, a representative sample of the civilian, noninstitutionalized U.S. population aged ≥12 years, of various race/ethnicity. In 2008 and 2009, an estimated 8.3 million (annual average) adults aged ≥18 years in the United States (3.7% of the adult U.S. population) reported having suicidal thoughts in the past year[8]. An estimated 2.2 million (annual average) adults in the United States (1.0% of the adult U.S. population) reported having made suicide plans in the past year[8]. An estimated 1 million (annual average) adults in the United States (0.5% of the U.S. adult population) reported making a suicide attempt in the past year[8]. The prevalence of suicidal thoughts, suicide planning, and suicide attempts was significantly higher among young adults aged 18–29 years than it was among adults aged ≥30 years[8]. The prevalence of suicidal thoughts was significantly higher among females than it was among males, but there was no statistically significant difference for suicide planning or suicide attempts[8]. Although the NSDUH did not attempt to gather data according diagnosis, as indicated above, suicide is a primary comorbidity of mood and anxiety disorders. Therefore, the premise that obsessive compulsive disorder has a large impact through its direct and indirect economic costs, as well as its broader social consequences, is significant is ample.

However, the symptoms of obsessive-compulsive disorder are experienced at the level of the individual patient. It is at the level of the individual patient, that anyone can identify with symptoms of obsessive-compulsive disorder. The experience of intrusive, *obsessive* thoughts—wondering if the stove was left on or the front door was left unlocked while driving away from home—and *compulsive* behavior—being compelled to return home and check the stove or the door—is very common.

Obsessive-compulsive disorder is currently defined by the presence of obsessions and compulsions. Obsessions are recurrent, unwelcome thoughts, that may include: fear of dirt, germs, contamination; fear of acting on violent or aggressive impulses; feeling overly responsible for the safety of others; abhorrent religious and sexual thoughts, and/or; inordinate concern with order, arrangement and symmetry. Compulsions are repetitive behaviors that are performed in response to obsessions, in order to lessen the distress caused by obsessions. The short-term gain of reduced anxiety comes at a long-term cost of frequent repetition of these behaviors. Compulsions may affect social and occupational function to a profound degree as described above.

The professional community defines the diagnosis of obsessive-compulsive disorder, using criteria outlined in the DSM-IV[9]. The diagnosis of obsessive-compulsive disorder using modern criteria requires: the presence of obsessions and/or compulsions; recognized as excessive or unreasonable; causing marked distress, time-consumption (>1 hour/day), or interference with functioning. The obsessions and compulsions cannot be due to another Axis I psychiatric disorder, due to substance abuse, substance dependence, substance withdrawal, or due to a medical condition. For example, an individual with obsessive-compulsive disorder may be besot by unwanted and inappropriate sexual thoughts about neighbors, coworkers or family members, and will attempt to "undo" the obsessions by compulsive checking. Similarly, and individual with recurrent obsessions about the fact that they may have harmed individuals, which the patient tries to "undo", by returning over and over to the place where the thought occurred. Alternatively, a patient with obsessive-compulsive disorder may have constant thoughts that they are sinful, which the patient attempts to undo with repetitive prayer. Those who suffer from obsessive-compulsive disorder may be unable to carry out their responsibilities: at work, leading to unemployment; at home, resulting in marital conflict as well as disturbed family relationships, and; in society, leading to social isolation. The disruption of normal social and emotional development in obsessive-compulsive disorder not unlike that experienced in other neurodevelopmental disorders, such as schizophrenia. Like schizophrenia, there is likely both a genetic and environmental contributors to obsessive-compulsive disorder[10]. The altered life trajectory of these illnesses is quite sobering.

The two current effective treatments for patients with obsessive-compulsive include cognitive behavioral therapy (CBT) and pharmacotherapy. CBT consists of a technique called exposure and response prevention, in which patients deliberately and voluntarily expose themselves to fears/ideas, but are discouraged from carrying out compulsive responses. Studies do show successful results for extended periods of time. CBT can fail for various reasons, including, poorly executed treatments; patient or family noncompliance, psychiatric comorbidity such as severe depression or a personality disorder, poor insight (~5% of patients) or severe illness. CBT requires patients that are highly motivated,

cooperative, and diligent, and is more likely to be successful when combined with pharmacotherapy. Traditional psychotherapy generally not helpful as a stand-alone therapy for OCD symptoms, although it is appropriate for the ongoing difficulties with adjustment experienced by patients with obsessive-compulsive disorder.

With respect to pharmacotherapy, specific medications have shown some effectiveness in controlling the symptoms of obsessive-compulsive disorder, including: SSRIs (selective serotonin reuptake inhibitors) such as Fluvoxamine, Fluoxetine, Sertraline, Paroxetine, Citalopram, ES Citalopram; SNRIs (serotonin-norepinephrine reuptake inhibitors) such as venlafaxine, and; TCAs (tricyclic antidepressants) such as Clomipramine. Treatment resistance or treatment-refractory obsessive-compulsive disorder is said to occur when patients with obsessive-compulsive disorder fail to benefit from treatment. By conservative estimate, 5% of patients with obsessive-compulsive disorder are treatment resistant. If 5% of Americans have treatment-refractory obsessive-compulsive disorder, then according to the aforementioned monthly or yearly prevalence rates, then 170,000 Americans each month, or 325,000 Americans in their lifetime are afflicted with treatment resistant obsessive-compulsive disorder. Treatment options for these patients are very limited.

2. Orbitofrontal-striatal function

The importance of brain circuits connecting frontal lobe to the basal ganglia was first observed in primates by Alexander and colleagues[11], who reported evidence for an anatomically distinct lateral orbitofrontal circuit loop, comprised of projections from: orbitofrontal cortex to the head of the caudate nucleus and the ventral striatum; to the internal pallidus; to the mediodorsal thalamus; returning from the thalamus to the orbitofrontal cortex. Alexander and colleagues hypothesized: the existence of several relatively specialized fronto-striatal loops; proposed that they were organized in parallel, linking the basal ganglia to the frontal cortex, and; that each circuit played a functional role based on its connections to particular regions of the frontal cortex. Other investigators[12, 13] have suggested that the so-called "limbic" structures (i.e. — hippocampus, anterior cingulate and, basolateral amygdala) ought to include in the lateral orbitofrontal circuit loop circuit, because of their extensive connections to the orbitofrontal cortex. Based on these interconnections, it can be hypothesized that this "greater" lateral orbitofrontal circuit could play a role in emotion, as the function of these so-called "limbic" brain regions play a role in affective states and emotional perception.

The orbitofrontal cortex is a key brain region, not only in emotional behavior, but also for motivation [14-18]. This was first shown by Harlow[19] who provided a naturalistic description of profound changes in behavior of a 19th century railway worker— Phineas Gage—after a charge he was setting, using a tamping rod exploded. He sustained a severe left frontal lobe injury, after the tamping rod was when a was launched through his forehead and out his skull. Reported changes in Gage's behavior following the accidental orbitofrontal cortex damage included not only inappropriate emotional responses, but also, impulsive and poorly thought out decisions, characteristic of behavioral changes in patients with orbitofrontal cortex lesions[20, 21 22].

Since learning-based motivation requires the integration of complex brain systems that include orbitofrontal cortex, researchers have hypothesized that difficulties "unlearning" reinforced behaviors may be associated trouble with sensing change between behavior-reward relationships. Impairment in the unlearning of established reward-motivated behaviors are also observed in animals and humans with orbitofrontal cortex lesions [23] [24] [25]. Furthermore, patients with focal lesions either in the striatum or the ventral palladium, (an area it projects to) demonstrate behaviors very consistent with those observed in obsessive-compulsive disorder[26, 27].

The results of functional imaging research have provided complementary evidence to the lesion studies demonstrating that the orbitofrontal cortex is a key brain region involved in learning and motivation. The human brain's awareness of expecting a reward and the likelihood that a reward will occur is requires an intact orbitofrontal cortex[28-30]. If the orbitofrontal cortex is not intact, a person's behavior may seem impulsive or they may appear to have poor judgment.

The orbitofrontal cortex may have anatomically and functionally segregated orbitofrontal-thalamic striatal circuits. This idea of Alexander and colleagues is supported by research indicating that the lateral orbitofrontal cortex may have a distinct and separate function from medial orbitofrontal cortex, in that the lateral orbitofrontal cortex was activated when suppressing a response already associated with a reward [31]. This would imply that dysfunction of the lateral orbitofrontal cortex prevents inhibition of behavior reinforced previously by a reward.

3. Evidence for orbitofrontal-striatal dysfunction in obsessive-compulsive disorder

The current most popular model proposed by researchers to explain the neurobiological foundation of obsessive-compulsive disorder focuses on abnormalities in cortical-striatal-thalamic circuitry—the orbitofrontal-striato-thalamic circuits in particular[32-34].

3.1 Evidence from neuroimaging studies

Using techniques that measure brain glucose metabolism, fluorodeoxyglucose positron-emission tomography (FDG PET), investigators demonstrated increased cerebral glucose metabolism present bilaterally in the cerebral hemispheres and orbitofrontal gyrii, as well as both caudate heads, in patient with OCD patients[35] [36]. The findings were replicated[37-42] in FDG-PET studies examining patients both at rest, and while provoking symptoms, although not all studies produced positive findings[43-45]. A meta-analysis[46] confirmed abnormalities were present in the orbital gyrus and the head of the caudate in patients with obsessive-compulsive disorder. The results of PET studies are an important piece of supportive evidence of the orbitofrontal-striato-thalamic model.

3.2 Evidence from deep brain stimulation research

Another strong piece of evidence supporting this model is the symptomatic improvement of patients with obsessive-compulsive disorder undergoing capsulotomy. Focal lesioning

during a surgical procedures for neuropsychiatric disorders has been known as "psychosurgery". Historically, these procedures have been thought not to be discriminate in terms of neuroanatomical location or groups of patients treated[47-49]. Furthermore, informed consent is thought not to be properly obtained, a process which requires careful assessment of an individual's capacity to weigh the risks and benefits of an experimental medical or surgical procedure[50]. Consequently, psychosurgery is not viewed in a positive light in the popular media [51].

Neurosurgery for psychiatric disorders is a highly invasive treatment. However, it is important to view these interventions in the proper historical context. Prior to 1950, psychiatric illness was essentially untreatable, as no specific medications existed for the treatment of severe psychiatric disorders. Since these illnesses were disabling and lethal, the treatments pursued were aggressive and invasive. These interventions included malarial pyrotherapy described by Epstein in 1936[52], hypoglycemic coma described by Sakel in 1937[53], electroconvulsive therapy, described by Bini in 1938[54], as well as neurosurgery. Historically (and currently) the use of neurosurgery has only been used only for intractable psychiatric illnesses[55].

Burckhardt first published a report of the first (unsuccessful surgical attempts to treat severe psychosis in 1891[56]. The first neuroanatomical models describing both function and structural of mood and behavioral regulation were published by Papez in 1937[57]. At this time, a hypothesis was proposed by researchers that abnormal mood and behavioral regulation was caused by dysfunctional thalamo-cortical communication[58], leading to the use of the prefrontal leucotomy (popularly known as the prefrontal lobotomy), a procedure that disrupted white matter tracts connecting these regions. Because the ability of surgeons to localize and severing specific frontal lobe white matter tracks, lesions were indiscriminantly large. After 1950, pharmacologic interventions were identified that drastically reduced the symptoms of psychiatric disorders. The pharmacology revolution of the mid-twentieth-century resulted in the discovery of medications effective: for mania described by Cade in 1949 and Schou and colleagues in 1954[59, 60]; for psychosis described by Bower in 1954[61], and Winkelman in 1954[62], and; for depression described by Bailey and colleagues in 1959[63], Kiloh and colleagues in 1960[64], and Kuhn in 1958[65].

In the early 1960s, investigators reported that stimulation of different brain area induced hypomania, dysphoria, and anhedonia. These early findings suggested the possible efficacy of DBS in treatment refractory psychiatric disorders. One of the earliest anatomically specific psychosurgery consists of ablation of the anterior limb of the internal capsule—the anterior capsulotomy—was found to be efficacious in severely refractory obsessive-compulsive disorder. The first anterior capsulotomies were performed in Europe in the late 1940's. During the procedure, symmetric bilateral lesions are made in the anterior limb of the internal capsule, which is quite near to the ventral striatum. This lesion, whether made by heat (thermocoagulation during neurosurgery or a thermocapsulotomy) or by minimally invasive gamma irradiation (a gamma-capsulotomy), interrupts the passage of white matter fibers between the prefrontal cortex and the subcortical nuclei, the striatum, and the dorsomedial thalamus. A recent prospective study of 35 patients with obsessive-compulsive disorder who underwent thermocapsulotomy showed that that 70% had "satisfactory outcomes" after 3 years[66].

The recent development of deep brain electrode placement at the ventral capsule/ventral striatum (VC/VS) target is also a very strong piece of evidence supporting this model. Deep brain stimulation is a reversible, neurosurgical procedure. Deep brain stimulation is an invasive neurosurgical intervention being used to treat psychiatric disorders in an investigative fashion. The disorders currently being examined include treatment-resistant major depressive diosrder, treatment-resistant obsessive-compulsive disorder, Tourette's Syndrome, Alzheimer's dementia, and addictions. The actual treatment consists of implanting one or more electrode leads into a particular brain regions through burr holes in the skull using a proprietary stereotactic neurosurgical techniques. Neuroimaging-guided implantation calculates the route to the target using a three-dimensional coordinate system based on external landmark. Current commercially available leads have four electrodes, 1-2 mm in length, separated by 4-5 mm, the complete electrode 10–20 mm in length. The leads connect to subcutaneous extension wires that are tunnelled surgically to pulse generators implanted in the chest. The pulse generators contain a battery and hardware/software that drives the neurostimulation. A programmer can set the programs in the neurostimulator using a handheld computer with a wireless connection.

In the 1960s electrical stimulation of the ventrolateral thalamus was noted to stop tremor. Prolonged electrical stimulation at different targets was found to be effective for treatment-refractory movement disorders, epilepsy, chronic pain and tremor. Investigators then delivered high frequency cathodic (positive) electrical stimulation directly at the surgical target, in order to mimic the effect of a surgical lesion [67, 68], leading to the development of technology first used clinically in Parkinson's disease, essential tremor, and extrapyramidal dyskinesias. Currently, there are many numerous published reports demonstrating the safety and efficacy of DBS for intractable movement disorders[69, 70].

In fact, the efficacy and safety data from studies in patients with movement disorders led the FDA to approve the use of obsessive-compulsive disorder for essential tremor and Parkinson's disease. The FDA eventually approved the use of DBS for dystonia under a Humanitarian Device Exemption (HDE). The results of a recent open label clinical trial of DBS using the VC/VS target suggested that DBS for intractable obsessive-compulsive disorder had encouraging therapeutic effects, with probable benefit even 3 years after surgery [71]. The specificity of this lesion is the strongest piece of evidence supporting the dysfunction of orbitofrontal-striato-thalamic circuits as a likely etiology of obsessive-compulsive disorder.

3.3 Summary and conclusions

Obsessive-compulsive disorder is a serious neuropsychiatric illness. Treatment-resistant obsessive-compulsive disorder is less common, but highly debilitating. The evidence for the role of orbitofrontal-striato-thalamic circuits in mediating emotion, learning, and reward-focused behavior is strong. The evidence that these important brain systems are dysfunctional in patients with obsessive-compulsive disorder is also strong. Expanding knowledge about these brain circuits will provide a rich area for further research and is necessary to develop effective treatments for obsessive-compulsive disorder.

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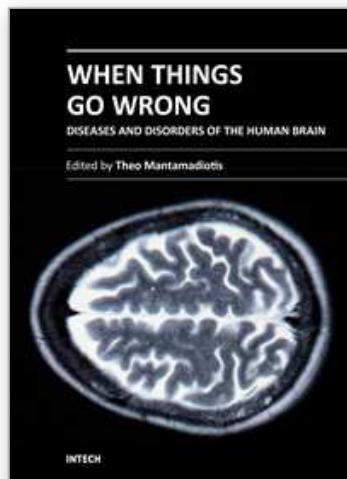
When Things Go Wrong - Diseases and Disorders of the Human Brain

Edited by Dr. Theo Mantamadiotis

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In this book we have experts writing on various neuroscience topics ranging from mental illness, syndromes, compulsive disorders, brain cancer and advances in therapies and imaging techniques. Although diverse, the topics provide an overview of an array of diseases and their underlying causes, as well as advances in the treatment of these ailments. This book includes three chapters dedicated to neurodegenerative diseases, undoubtedly a group of diseases of huge socio-economic importance due to the number of people currently suffering from this type of disease but also the prediction of a huge increase in the number of people becoming afflicted. The book also includes a chapter on the molecular and cellular aspects of brain cancer, a disease which is still amongst the least treatable of cancers.

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