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Obsessive-Compulsive Disorder: The Orbitofrontal-Striatal Model, and Deep Brain Stimulation

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Abstract

OCD is a serious neuropsychiatric illness with a distinct epidemiology, social, educational and economic impact. Suicide is a lethal outcome of OCD. Treatment-resistant OCD is uncommon, but highly debilitating. Clinical symptoms of OCD are characterized by obsessions and compulsions. Treatment of OCD includes Cognitive Behavioral Therapy (CBT) and pharmacotherapy. Treatment refractory OCD may respond to Deep Brain Stimulation (DBS). The evidence for the role of orbitofrontal-striato-thalamic circuits in mediating emotion, learning, and reward-focused behavior is presented. The evidence that these important brain systems are dysfunctional in patients with OCD is also presented.

Introduction

Epidemiology of OCD

Obsessive-Compulsive Disorder (OCD) is a chronic neuropsychiatric illness. The population from which data is gathered, as well as the diagnostic criteria used to identify this condition, affects eventual measured prevalence of OCD. For example, in early epidemiologic studies, DSM criteria were not used to diagnose OCD. Estimated lifetime prevalence of OCD was 1.9%-3.3%. In other early studies that did use DSM criteria to diagnose OCD, estimated lifetime prevalence of OCD was 1.2%-2.4%, lower than in the previous studies [1-3]. Presumably, the prevalence of OCD in studies using DSM criteria to diagnose OCD was lower because patients with sub-syndromal symptoms—such as those with Obsessive Compulsive Personality Disorder—were excluded [4].

The prevalence of OCD estimated by the NIMH Epidemiologic Catchment Area (ECA) study were estimated using population-based data, gathered from five different US communities, and included more than 18,500 outpatients who participated in a well-funded national epidemiologic study of psychiatric illness [5]. In contrast, the data obtained from earlier aforementioned studies was gathered from smaller clinical populations. Therefore, the lifetime prevalence of OCD estimated by the ECA study was more accurate than earlier studies, and, 25-60 times higher than previously calculated.

Extrapolating from the estimated 2.5% lifetime prevalence of OCD calculated in the ECA study, applying it to the current US population of 325.7 million people, it follows that slightly more than 8 million Americans suffer from OCD during their lifetime. Extrapolating from the 1.3% 1-month prevalence rate of OCD calculated in the ECA study, applying it to the same US population, then slightly less than 3.5 million Americans suffer from OCD during a given month. Clearly, each month and every year, OCD affects millions of Americans.

Economic Impact of OCD

OCD affects the American economy in a measureable manner. Direct yearly medical costs from OCD are $2.1 billion. Indirect costs from lost productivity due to OCD reach $5.9 billion [6]. Health care expenditures in the United States are steadily increasing, $253 billion in 1980, $714 billion in 1990, and $2.3 trillion in 2008 [7]. The direct and indirect economic costs of OCD will increase in the future, based not only on the assumption that both the US population and US health care expenditures will continue to increase, but also the lifetime prevalence of OCD in the US will remain at 2.5%.

Social, Educational and Occupational Impact of OCD

Economic indicators non-withstanding, the broader impact of OCD on social, educational, and occupational function is also significant. The symptoms of OCD seriously affect social function. Hollander and colleagues demonstrated that in OCD patients: 92% reported lowered self-esteem; 73% had interference with family relationships, and; 62% noted difficulty maintaining relationships [8]. OCD also profoundly affects educational achievement. Hollander and colleagues also report that 58% of patients with OCD demonstrated lower academic achievement. Notable decreases in occupational functioning described by Hollander and colleagues include: lower career aspirations observed in 66%; work interference seen in 47%, and; lost time from inability to work, found in 40%.

Suicide in OCD

Suicide is the most lethal outcome of untreated and refractory psychiatric illness. Suicidal thoughts are closely interrelated with suicide attempts, but are not equivalent. For example, in 2008, 666,000 persons visited hospital emergency departments for nonfatal, self-inflicted injuries, but 36,035 persons died from suicide [9]. 8.3 million Adults per year—3.7% of the adult U.S. population—reported suicidal thoughts between 2008 and 2009. 2.2 million Adults per year—1.0% of the adult U.S. population—reported suicide plans between 2008 and 2009. 1 million adults per year—0.5% of the U.S. adult population—reported a suicide attempt between 2008 and 2009. Prevalence of suicidal thoughts, suicide planning, and suicide attempts is higher among adults aged 18–29 years than adults aged ≥ 30 years. There is no statistically significant difference in the prevalence of suicide planning or suicide attempts between males and females, but the

prevalence of suicidal thoughts is significantly higher among females than males [9].

Suicide is also the most serious complication of mood and anxiety disorders. 13% of OCD patients attempt suicide [8], but there is no data to describe whether the aforementioned risk factors of gender or age conveys altered risk for suicide attempts or completion in OCD. Completed suicide in OCD patients leads to not only emotional distress in family members, friends, community members, but also trauma, PTSD, complicated bereavement, as well as lost parental supervision leading to childhood parentification. Before completing suicide, an OCD patient already suffers from reduction in relationship, educational and vocational function. After completing suicide the social and economic impact of the patient is not eliminated, rather it is magnified. Completed suicide of an OCD patient results in the greatest impact on both broad social consequences as well as on direct and indirect economic costs.

Clinical Symptoms of OCD

OCD is currently defined by the presence of obsessions and compulsions. Obsessions are recurrent, unwelcome thoughts such as 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, or; inordinate concern with order, arrangement and symmetry. Compulsions are repetitive behaviors performed in response to obsessions, to lessen distress. By responding to obsessions by performing compulsions, a short-term gain of reduced anxiety comes at a long-term cost of frequent repetition of problematic behaviors. The experience of obsessive thoughts—wondering if the stove was left on or the front door left unlocked—and compulsive behavior—feeling compelled to return and check the to make certain the stove is turned off and the door locked—is not common. Many can identify with symptoms that a patient with OCD experiences on an individual level.

The professional community defines the diagnosis of OCD, using criteria outlined in the DSM-V [4] diagnosis of OCD using modern criteria requires obsessions, defined by:

- 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, and/or
- the individual attempts to ignore or suppress such thoughts, urges, or images, or to neutralize them with some other thought or action (by performing a compulsion).

The diagnosis of OCD using modern criteria requires compulsions defined by:

- 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, and
- 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.

Obsessions or compulsions must be time-consuming (more than 1 hour per day) or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. The symptoms may not be attributable to the effects of a medical condition. 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.

An individual with OCD may be distracted 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 OCD may have constant thoughts that they are sinful, which the patient attempts to undo with repetitive prayer. Those who suffer from OCD 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 OCD not unlike that experienced in other severe neurodevelopmental disorders, such as schizophrenia. Like schizophrenia, there is likely both a genetic and environmental contributors to OCD [10]. The altered life trajectory of patients with OCD is quite sobering.

Treatment of OCD

Effective treatments for patients with OCD 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 and ideas, but are discouraged from carrying out compulsive responses. Studies do show successful results for extended periods. CBT can fail if:

- treatments is poorly executed;
- the patient or family is noncompliant;
- psychiatric comorbidities such as severe depression or a personality disorder are present, if patients have poor insight (~5% of patients) or;
- if the illness is severe and treatment refractory.

CBT requires patients that are highly motivated and diligent. CBT is more likely to be successful when combined with pharmacotherapy. Traditional psychotherapy generally not helpful as a stand-in

Therapy for symptoms of OCD symptoms, although it is appropriate for the ongoing difficulties with adjustment experienced by patients with OCD.

With respect to pharmacotherapy, specific medications have shown some effectiveness in controlling the symptoms of OCD, 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 OCD is said to occur when patients with OCD fail to benefit from treatment. By conservative estimate, 5% of patients with OCD are treatment resistant. If 5% of Americans have treatment-refractory OCD, then according to the aforementioned monthly or yearly prevalence rates, then 175,000 Americans each month, or 400,000 Americans in their lifetime are afflicted with treatment resistant OCD. Treatment options treatment refractory OCD are very limited, neither ECT nor TMS have been found to be particularly effective.

Pathophysiology of OCD

Orbitofrontal-striatal function

The importance of brain circuits connecting frontal lobe to the basal ganglia was first observed in primates by Alexander et al. [11] and

colleagues, 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. He proposed that they were organized in parallel, linking the basal ganglia to the frontal cortex. He also proposed that each circuit played a functional role based on its connections to particular regions of the frontal cortex. The limbic structures—hippocampus, anterior cingulate, basolateral amygdala and others—have dense interconnections with the orbitofrontal cortex. Therefore, other investigators [12,13] have suggested that both the limbic structures and the lateral orbitofrontal circuit comprise a "greater lateral orbitofrontal circuit". Since the "limbic" brain, regions play a role in affective states and emotional perception, so it can be hypothesized that the function of the greater lateral orbitofrontal circuit plays a role in perception of affect and emotion [14-16].

The orbitofrontal cortex is a key brain region, not only in emotional behavior, but also for motivation [17,18]. This was first shown by Harlow et al. [19] who provided a naturalistic description of profound changes in behavior of a 19th century railway worker— Phineas Gage—who sustained a severe left frontal lobe injury, after a tamping rod was launched through his left forehead and out his skull, when a charge detonated. Reported changes in Gage's behavior following the accidental orbitofrontal cortex damage included inappropriate emotional responses as well as impulsive, poorly thought out decisions. These reported behavioral changes are characteristic of those described in patients with orbitofrontal cortex lesions [20-22].

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 with trouble 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 [15,23,24]. Furthermore, patients with focal lesions either in the striatum or the ventral palladium—an area the striatum projects to—demonstrate behaviors very consistent with those observed in OCD [25,26].

The results of functional imaging research [27] have provided complementary evidence to 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 [27,28]. 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 [29]. This would imply that dysfunction of the lateral orbitofrontal cortex prevents inhibition of behavior reinforced previously by a reward.

Evidence for orbitofrontal-striatal dysfunction in OCD

The current most popular model proposed by researchers to explain the neurobiological foundation of OCD focuses on abnormalities in cortical-striatal-thalamic circuitry—the orbitofrontal-striato-thalamic circuits in particular [17,30-32].

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 patient [33,34]. The findings were replicated in FDG-PET studies examining patients both at rest [35-37], and while provoking symptoms [38], although not all studies produced positive findings [39-41]. A meta-analysis [42] confirmed abnormalities were present in the orbital gyrus and the caudate head in patients with OCD. The results of PET studies are an important piece of supportive evidence of the orbitofrontal-striato-thalamic model.

Evidence from deep brain stimulation research

Another strong piece of evidence supporting the hypothesis that dysfunction of orbitofrontal-striato-thalamic circuits underlies the pathophysiology of OCD. Is the symptomatic improvement of patients with OCD undergoing capsulotomy? Psychosurgery consists of focal lesioning during a neurosurgical procedure for the treatment of a neuropsychiatric disorder [43]. Historically, these procedures have neither discriminated in terms of neuroanatomical target, nor diagnosis of psychiatric. Furthermore, during the early days of psychosurgery, informed consent was not always properly obtained. For example, with the prefrontal leucotomy—popularly known as the prefrontal lobotomy—a procedure that disrupts frontal white matter tracts, surgeons could not localize and sever specific frontal lobe white matter tracks, so lesions were indiscriminant. Informed consent for psychosurgery requires careful experimental medical or surgical procedure [44]. However, significant improvement has assessment of an individual's capacity to weigh the risks and benefits of an occurred with respect to identifying specific anatomical targets, for specific neuropsychiatric disorders, and obtaining ongoing informed consent from patients who have the capacity to do so.

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 [45]; hypoglycemic coma described by Sakel in 1937 [46]; electroconvulsive therapy, described by Bini in 1938 [47]; as well as neurosurgery. Historically and currently psychosurgery has only been used for intractable psychiatric illnesses [48].

Burckhardt first published a report of the first unsuccessful surgical attempts to treat severe psychosis in 1891 [49]. The first neuroanatomical models describing both function and structural of mood and behavioral regulation were published by Papez in 1937 [50]. At this time, researchers proposed a hypothesis that abnormal mood and behavioral regulation was caused by dysfunctional thalamo-cortical communication [51]. This lead 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 indiscriminately large. After 1950, pharmacologic interventions were identified that drastically reduced the symptoms of psychiatric disorder [52]. The pharmacology revolution of the mid-twentieth-century resulted in the discovery of medications effective: for mania described by Cade in 1949 [53] and Schou and colleagues in 1954 [54] for psychosis described by Bower in 1954 [55], and Winkelman in 1954 [56], and; for depression described

by Bailey and colleagues in 1959 [57], Kiloh and colleagues in 1960, and Kuhn in 1958 [58].

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. This anterior capsulotomy was found to be efficacious in severely refractory OCD. 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. The lesion can be made either by heat (thermocoagulation during neurosurgery or a thermocapsulotomy) or by minimally invasive gamma irradiation (a gamma-capsulotomy), as long as it 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 OCD who underwent thermocapsulotomy showed that that 70% had "satisfactory outcomes" after 3 years [58].

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 the hypothesis that the pathophysiology of OCD involves disruption of a greater lateral orbitofrontal circuit. Deep brain stimulation is an invasive, yet reversible, neurosurgical procedure used in an investigative fashion to treat psychiatric disorders, including treatment-resistant major depressive disorder; treatment-resistant OCD; Tourette's Syndrome; Alzheimer's dementia, and; Addictions. The treatment consists of implanting one or more electrode leads into a target in the brain regions through burr holes in the skull using proprietary stereotactic neurosurgical techniques. The optimal route to the target is calculated using a neuroimaging-guided computer, which calculates the optimal route to the target using three-dimensional coordinate system in real space. Current commercially available electrodes are 10– 20 mm in length, have four electrodes, 1-2 mm in length, which are separated by 4-5 mm. The leads are connected to subcutaneous extension wires, which are tunneled surgically to pulse generators implanted in the chest. The pulse generators contain a power source, hardware, and software that drives neurostimulation. A physician programmer adjusts settings using a handheld computer device that connects wirelessly to the implanted neurostimulator.

In the 1960's 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 [59,60], leading to the development of technology first used clinically in Parkinson's disease [61], essential tremor, and extrapyramidal dyskinesias, 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 [62]. Currently, there are many numerous published reports demonstrating the safety and efficacy of DBS for intractable movement disorders.

The positive efficacy and safety data from studies in patients with movement disorders led the FDA to approve the use of OCD 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 the t open label clinical trial of DBS using the VC/VS target suggested that DBS for intractable OCD had encouraging therapeutic effects, with probable benefit even 3 years after surgery [63,64]. The specificity of this lesion is the strongest piece of evidence supporting the dysfunction of orbitofrontal-striato-thalamic circuits as a likely etiology of OCD.

Summary and Conclusions

OCD is a serious neuropsychiatric illness. Treatment-resistant OCD is uncommon, 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 OCD 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 OCD.

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