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# **Pathophysiology of Obsessive–Compulsive Disorder: Affected Brain Regions and Challenge Towards Discovery of Novel Drug Treatment**

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## **1. Introduction**

Obsessive–compulsive disorder (OCD) is a mental disorder characterized by absurd, recurrent and uncontrollable thoughts (obsessions) that produce anxiety, which are followed by repetitive behaviors (compulsions) aimed at reducing anxiety. OCD may be looked upon as a condition in which the affected person frequently experiences irresistible urges to perform repetitive rituals (compulsions). OCD may be defined as the irruption in the mind of uncontrollable, egodystonic and recurrent thoughts, impulses or images. In OCD, repetitive rituals serve to counteract the anxiety precipitated by obsessions. The OCD patients realize the irrational nature of thoughts and rituals but feel helpless and hopeless about controlling them. Obsessive-Compulsive disorder can impair all areas of brain functioning and produce devastating effects on patients and their families. Classic psychoanalysis, as pioneered by Freud, interpreted obsessive-compulsive disorder as unconscious conflicts, which were defensive and punitive (Rapoport et al., 1993). In modern psychoanalysis, obsessive-compulsive disorder is described as a portrayal of ambivalence, with confusion of thoughts and actions that are paradoxically manifested by rigidity and abnormal behaviors. Dynamic psychiatry interprets obsessive-compulsive symptoms as a reflection of feelings and thoughts that provoke aggressive or sexual actions that might produce shame, weakness, or loss of pride (Baer, 1993). The thoughts and behaviors associated with OCD are viewed as senseless, and egodystonic and they stand contradictory to the individual's motives, goals, identity, and self-perception thereby creating significant subjective distress. The excessive nature of the compulsion, however, creates its own distress and it appears that the individual may be caught up in a kind of negative reinforcement loop (David et al., 2004) The obsessive-compulsive spectrum disorders are Tourette's disorder, Body dysmorphic disorder, Hypochondriasis,

Pathological jealousy, Trichotillomania, Skin picking, Nail biting, Compulsive buying, Kleptomania, Pathological gambling, Nonparaphilic sexual disorders, Obsessive compulsive personality disorder.

OCD is a psychiatric affliction with a lifetime prevalence of 1–3% (Rasmussen and Eisen, 1992; Sasson et al., 1997). According to the Diagnostic and Statistical Manual of Mental Disorders (4th ed; DSM IV), the essential features of OCD are recurrent obsessions and/or compulsions (e.g., doubting, checking, washing) that are time consuming (i.e., they take more than 1 h a day) or cause marked distress or significant impairment. To date, the most effective treatments for OCD are pharmacological treatment, using serotonin reuptake inhibitors (SRIs, e.g., Masand and Gupta, 1999; Piccinelli et al., 1995; Pigott and Seay, 1999; Stein et al., 1995; Zohar et al., 1992), and behavioral treatment, using the response exposure and prevention technique (e.g., Simpson et al., 2004). Yet, around 30% of the patients are refractory to pharmacological and behavioral therapy (Eddy et al., 2004). Some of these treatment-resistant patients are treated by lesions to structures and pathways within basal gangliathalamo-cortical circuits (Lopes et al., 2004) as well as by high frequency stimulation (HFS) of the ventral striatum region (Aouizerate et al., 2004, 2005; Greenberg et al., 2006, 2008; Rauch et al., 2006; Sturm et al., 2003) the subthalamic nucleus (Mallet et al., 2008), and the thalamic reticular nucleus and the inferior thalamic peduncles (Jimenez et al., 2007; Jimenez-Ponce et al., 2009). Several neural systems have been implicated in the pathophysiology of OCD: The results of neuroimaging studies in OCD patients have implicated most consistently the orbitofrontal cortex, the cingulate cortex and the basal ganglia, and more recently also regions within the parietal lobe, in the pathophysiology of obsessions and compulsions (for review see Menzies et al., 2008; Rotge et al., 2009; Saxena et al., 1998; Stein, 2000). Dysregulation of the serotonergic (5-HT) system has been suggested primarily on the basis of the effectiveness of SRIs and selective serotonin reuptake inhibitors (SSRIs) in alleviating obsessions and compulsions in patients (Zohar and Insel, 1987; Zohar et al., 1992), and has received further support from neurobiological, pharmacological and more recently genetic data (for review see Murphy et al., 2001; Ozaki et al., 2003; Sasson and Zohar, 1996; Stein, 2000, but see Baumgarten and Grozdanovic, 1998). Abnormalities of the dopaminergic system have also been implicated in the pathophysiology of OCD, based on surplus therapeutic benefits obtained with co-administration of SSRIs and dopamine blockers (McDougle et al., 1990, 1994; Sasson and Zohar, 1996) as well as on clinical observations of obsessions and compulsions in basal ganglia-related disorders, such as Tourette's syndrome (Frankel et al., 1986; Grad et al., 1987; Pitman et al., 1987). More recently, an increasing body of evidence points also to the involvement of the glutamatergic system in OCD (for review, see Pittenger et al., 2006), including association of certain polymorphisms in the NMDA receptor gene with susceptibility to OCD (Arnold et al., 2004); elevated glutamate levels in the cerebro-spinal fluid of drug-naïve patients (Chakrabarty et al., 2005); correlations between symptom severity and the level of several glutamatergic metabolites (Starck et al., 2008); improvement of symptoms following treatment with d-cycloserine (DCS), a partial NMDA agonist (blinded controlled trials, Kushner et al., 2007; Wilhelm et al., 2008), riluzole, a glutamatergic antagonist (open-label trials, Coric et al., 2005; Grant et al., 2007), and memantine, a non-competitive NMDA antagonist (an open-label trial, Aboujaoude et al., 2009). There

is also some evidence suggesting the involvement of nitric oxide (NO) in OCD. Atmaca et al. (2005) found that OCD patients have higher NO levels in their plasma compared to healthy subjects and that these levels are positively correlated with the severity of OC symptoms. The possibility that high NO levels are related to OC symptoms is supported by the fact that SSRI's, anti-dopaminergic drugs and the NMDA antagonist memantine, all used to treat OCD patients, inhibit the synthesis of NO (Almeida et al., 2006; Park and West, 2009; Zhang et al., 2010). Reports that life events related to the female hormonal cycle may trigger or exacerbate OCD in women patients (Abramowitz et al., 2003; Labad et al., 2005; Maina et al., 1999) suggest that ovarian hormones play a modulatory role in OCD (Uguz et al., 2007). Indeed, gonadotropine-releasing hormone (GnRH) agonists were reported to ameliorate OC symptoms in OCD patients (Casas et al., 1986; Eriksson, 2000). The understanding and treatment of diseases such as OCD must rely heavily on appropriate animal models that closely mimic their behavioral and if possible their neural manifestations. This is especially true for OCD as its neuropathological mechanisms are still largely unknown, and many patients are either treatment-resistant or experience only partial alleviation of symptoms. Before reviewing animal models of OCD that are currently in use, we discuss the criteria for the validation and evaluation of animal models.

## 2. Clinical features

The OCD is clinically manifested by a wide range of symptoms. The most common types of obsessions are related to contamination, pathological doubts, somatic dysfunctions, need for symmetry, aggression and hyper sexual drive. The classical forms of compulsions include checking, washing, counting, need to ask, precision and hoarding. In OCD, senseless, repetitive rituals (such as counting, washing etc.) serve to counteract the anxiety precipitated by obsessive thoughts e.g. Symmetry and exactness preoccupations. Fears of contamination and illness produce washing and cleaning compulsions (Leckman et al., 1997). Some symptoms get stable over a time period i.e. sexual/religious obsessions. The symptoms that is more likely to change are aggressive and contamination obsessions. Changes usually occur within rather than between individual symptom dimensions (Mataix-Cols et al., 2002). Patients with OCD may report only one or, more typically, multiple symptoms that cut across dimensions (Stein et al., 1997).

Many children with obsessive-compulsive disorder (OCD) suffer from an almost pathological doubting, which can vary from a mild form to an incapacitating form of extreme severity, in which the child is uncertain about its own understandings. Other high frequency symptoms are checking, fear of harming others, obsessions relating to death or sex produce compulsions serving to avoid a horrible event. Indecisiveness is frequently found in children with OCD and ranges from difficulty in making minor decisions. Following Group A Beta–Hemolytic Streptococcal (GABHS) infections, it was noted that OCD symptoms along with choreic movements in sydenham chorea became worse, and this was mediated by antineuronal antibodies that adversely affected basal ganglia cells. It was later hypothesized that this abnormal reaction to GABHS might play a part in the etiology of OCD.<sup>1</sup> This subgroup of OCD

patients has been termed PANDAS (for Pediatric Autoimmune Neuropsychiatric disorders Associated with Streptococcal Infection). Asbahr, Ramos, Negrao and Gentil presented four cases of children with PANDAS. They suggested that OCD may occur after repeated streptococcal infection as all four cases developed OCD only after the second infection. MRI tests showed that children with PANDAS have enlarged basal ganglia. The frontal-lobe function compared in 21 children and adolescents with OCD who were approximately 12 years of age and in matched healthy subjects, investigators found no cognitive impairment on the basis of performance on frontal tests and concluded that OCD symptoms may not interfere with cognitive abilities at early stages in the illness. The study with 42 children and adolescents (mean age, 14 years) and 35 normal subjects and concluded that subjects with OCD have impaired executive functions and nonverbal memory. Andres administered a neuropsychological battery to 35 OCD patients without psychiatric comorbidity aged between 7 and 18 years and 35 healthy controls and found that children and adolescents with OCD had impairments in visual memory, visual organization.<sup>2</sup>

The performances of 21 obsessive-compulsive children compared with 21 healthy controls on neuropsychological tests, including the Stroop test, Wisconsin Card Sorting Test, Verbal Fluency test, California Verbal Learning Test, Grooved Pegboard Test suggested there were no differences in neuropsychological performance between obsessive-compulsive children and the healthy controls. Therefore, it was concluded that obsessive-compulsive children do not show clinically significant cognitive impairment during the early stages of the illness, but a deficiency may become significant over time. The doubting and checking are found frequently in OCD patients which associated with memory dysfunction of OCD patients. The children with tic disorder frequently show OCD symptoms. The negative emotions such as anxiety have an adverse effect on memory function. The most striking feature of the symptoms presented by obsessive-compulsive children is the severity of the psychopathology in the absence of formal thought disorder. Thus, Obsessive-Compulsive disorder can impair all areas of brain functioning and produce devastating effects on patients and their families. Therefore, there is necessity to aware about the OCD in children and different treatments for it's management.

Sr.	Obsessions	Compulsions
1.	Concern with cleanliness (dirts, germs, contamination)	Excessive and ritualized bathing, washing and cleaning
2.	Concern with exactness (symmetry and order)	Ritualized arranging and rearranging
3.	Concern with household tools (dishes, spoons, soap)	Checking, rechecking and keeping inventory with detailed description of tools, objects, and appliances
4.	Concern about body secretions (saliva, urine, stool)	Rituals to remove body secretions
5.	Sexual obsessions (aggressive sexual actions)	Ritualized and rigid sexual relationship

**Table 1.** List of typical obsessive thoughts compelling repetitive actions

### 3. Causes

- Serotonin is involved in regulating anxiety
- Abnormality in the neurotransmitter serotonin
- In order to send chemical messages serotonin must bind to the receptor sites located on the neighboring nerve cells
- OCD sufferers may have blocked or damaged receptor sites preventing serotonin from functioning to full potential
- Possible genetic mutation
- Some people suffering have mutation in the human serotonin transporter gene



OCD patients have lower serotonin levels than control subjects. Source:  
<http://neuron.med.wayne.edu/OCD/slide.htm>

**Figure 1.** OCD patients have lower serotonin levels than control subjects.

### 4. Epidemiology

The frequency of compulsions in 8-year-old German children, to be 4.6% (moderate severity) and 2.8% (severe symptomatology). Later, the prevalence of compulsive checking in the same population (13 years old) was 3.4%, all of moderate severity. 2.3% reported compulsion for

cleanliness and 4.0% experienced obsessive thoughts. OCD in the child psychiatric population found as 0.2-1.2%. In an epidemiological study of 5000 high-school students, Flament found that 0.35% fulfilled the criteria of OCD, as defined by DSM-III (American Psychiatric Association, 1980). They calculated a lifetime prevalence of 0.4%. In their Isle of Wight-study, 2000 children examined at the age of 11 and found no children who fulfilled the criteria for OCD. They found eight children whom they diagnosed with "mixed emotional disorder" (with obsessive-compulsive features).

## 5. Genetics and family lifestyle

Family lifestyle could be regarded as a possible precipitating factor, for developing obsessive-compulsive symptoms in predisposed children. Family functioning was described in 20 Danish children with OCD and later assessed adaptability and cohesion of the family. In studies of children and adolescents most surveys show that OCD patients are generally from white, middle- or upper-class, intact families. Certain myths have prevailed regarding families with OCD children. The families are often said to show a cultural behaviour that emphasises cleanliness and perfection. 9% of mothers and 25% of fathers to OCD children had OCD themselves. 19% of 21 OCD children had one parent with OCD and as many as 52% had parents with obsessive-compulsive symptoms, without meeting the criteria for OCD, when parents were interviewed with standard clinical psychiatric assessments. 52% of children with OCD have a positive family history of OCD amongst first-degree relatives and that risk to relatives is related to the age of onset of the OCD proband: the younger the onset of OCD in proband, the higher risk of OCD or Tourette's syndrome in relatives. 24% of referred OCD children had a first degree relative with OCD.

## 6. Biological aspects

An electrophysiological investigation in obsessional states informed the presence of altered neural inhibition in connection with obsessive symptoms. The EEGs of a group of OCD patients compared with a control group of patients with other neurotic disorders, indicated abnormal findings in two thirds of the OCD patients, which was not significantly higher than in the control group. An orbitofrontal-subcortical hyperactivity in children and adolescent OCD patients may be the result of abnormal neuroanatomical development of these structures. A report suggested OCD develop by head injuries in four cases. The OCD patients have a particularly higher range of neurological diseases in childhood.

## 7. Neurological soft-signs and neuropsychological findings

Soft-signs are non-localized deviant performances in a motor or sensory test, without other signs or presence of focal neurological disorder. Soft-signs in child psychiatric patients have

been well studied and implications of soft-signs have been thoroughly analysed in a general population of pre-school and school-children. 44 out of 54 childhood OCD patients, at the age from 6 to 20 years, had neurological abnormalities. Of these 44 patients 18 had choreiform movements, 13 had non-specific neurodevelopmental signs only, eight had left hemisyn-drome, and five had miscellaneous abnormalities. Most studies conducted on OCD children have resulted an overweight of soft-signs, compared to normal control-groups. The children with early OCD onset, have more soft-signs than children with a later onset. The neurological soft-signs found in 18.6% of 61 OCD-children and adolescents compared to 14.4% in a control group consisting of non-psychotic and non-retarded children and adolescents with psychiatric disorders other than OCD. In studies of children, a pattern of association between OCD and selected neurological disorders has been long recognized. A prominently left frontal dysfunction in OCD patients indicated that cerebral cause had responsible for the obsessive-compulsive symptoms.

## **8. Pathophysiology**

The brain regions impaired in OCD includes dorsolateral prefrontal cortex (DLPC), anterior cingulate cortex (ACC), basal ganglia, orbito-frontal cortex (OFC), striatum, amygdala, thalamus and brainstem.

### **8.1. Dorsolateral prefrontal cortex (DLPC)**

It is the most important cortex part for cognitive functions in human beings. The involvement of the DLPC in working memory was initially demonstrated in primate studies. The DLPC also plays a role in adaptation to changes in the environment. DLPC plays a crucial role in focusing attention on specific stimuli and in decision-making (Miller, 1999). Lesions of DLPC disturb the subject's ability to process temporal information and impair the successful performance of goal-directed behaviors. Functional neuroimaging data have shown diminished activity in the DLPC of patients suffering with psychiatric disorders such as major depression and OCD, which may account for the difficulty in overcoming compulsive behaviors (Saxena et al., 1998).

### **8.2. Anterior cingulate cortex (ACC)**

Neuroimaging studies indicated that the ACC is involved in a variety of cognitive processes such as attention, motivation, reward, error detection, working memory, problem solving and action-plan (Bush et al., 2000). There are two major regions within ACC viz. a dorsal region, known as the cognitive region, and a ventral or affective region. The cognitive region is a part of attentional network and is closely connected with the DLPC, premotor, and parietal cortices whereas, the affective region is linked to the amygdala, nucleus accumbens, hypothalamus, anterior insula, hippocampus and OFC and sends projections to the neuro-vegetative, visceromotor and endocrine systems. Excessive activation of ACC has been reported in patients presenting psychiatric disturbances such as phobias, OCD and mood disorders. Moreover,

electrophysiological studies in man have demonstrated its particular role in error detection processes.

### 8.3. Basal ganglia-thalamo-cortical circuits

Basically, the role of the basal ganglia is to integrate the various inputs arriving from the cortex and to use this information for selecting certain motor and/or cognitive programs. The point of entry of information to the basal ganglia is through striatum, which receives converging information from the limbic and associative cortices. It then sends projections to the output structures, i.e. the globus pallidus pars internalis (Gpi) and the substantia nigra pars reticulata (SNr), through two pathways: one direct and the other indirect. The indirect pathway successively involves the globus pallidus pars externalis (Gpe) and the subthalamic nucleus (STN). In addition, the cortex sends direct inputs to the STN and the connections between the Gpe and Gpi. These two pathways seem to play opposite roles in controlling cortical activity. Activation of the direct loop facilitates the triggering of programs at the cortical level through a double inhibition. On the other hand, the indirect loop blocks the activation of thalamic relay by increasing the activity of the Gpi, a GABA-ergic inhibitory structure. Dopamine of nigral origin seems to facilitate the direct pathway through  $D_1$  receptors and plays an inhibitory role on the indirect pathway through  $D_2$  receptors. The pathological activation of segregated closed loop circuits involving cortex-basal ganglia-thalamus-cortex pathways would produce reverberating activity and result in a persistent discharge of the innate programs characteristic of OCD. The clinical manifestations of neuronal disorders of the basal ganglia can be viewed as a disruption of information processing at the cortical level due to the loss of the focusing action of subcortical inputs.

### 8.4. Orbito-frontal cortex (OFC)

The OFC is a large brain region, which encompasses both rostral and ventromedial areas. Because, it receives multimodal inputs from the temporal association cortex, amygdala and hypothalamus as well as limbic components of the basal ganglia, it has been viewed as the highest integration center for emotional processing (Krawczyk, 2002). By analogy with the Dorsolateral prefrontal cortex (DLPC), which is the prefrontal area for parietal lobe, the OFC can be regarded as the prefrontal area for the temporal lobe. The OFC seems to play a role in situations involving incentives/bonus/rewards and in conditions, where the subject has to make rapid alterations in behavior to accommodate the environmental changes. Several lines of evidence suggested that OFC played a crucial role in the decision-making process based on rewards. Patients with orbitofrontal damage experience great difficulties in decision-making. They also tend to take risks, whether profitable or not (Miller, 1985). Experimental lesions of OFC in monkeys have shown impairment in reward-related learning tasks and irrespective of the nature of the sensory context. These monkeys also exhibited an absence of emotional reaction to environmental stimuli. OFC neurons become particularly active, when the animal is placed in a situation where, it expects and receives a reward. Interestingly, face selective neurons have been reported in OFC, which may be relevant in the detection of facial expression which is a critical point in social decision. These neurons may be involved in the association

between a positive reward value and a particular facial expression. The OFC seems to play a predominant role in motivational aspects of decision-making. Among the more posterior cortical areas, the left inferior parietal cortex and parieto-occipital junction are involved in cognitive tasks related to visual imagery. The underactivity of these regions could probably explain the spatial memory deficits and visual memory deficits observed in OCD patients. The repetitive rituals (compulsions) and aggressive behavior, which is predominant in OCD patients is probably due to serotonin depletion.

### **8.5. Striatum**

The striatum is known to be formed by two types of information-processing modules: the striasomes and the matrisomes. The striasomes receive information from the limbic structures such as amygdala, OFC & ACC (Eblen and Graybiel, 1995). In turn, they send projections to the dopaminergic neurons of the substantia nigra. These anatomical findings suggest that the striasomes could also play a role in the emotional modulation of cortical information. The matrisomes receive information from the lateral parts of the premotor and prefrontal cortices, which are involved in the anticipation behavior and planning (Flaherty and Graybiel, 1994). The cholinergic inter-neurons of the striatum, viz. tonically active neurons (TANS), may be playing a particular role in integrating the information flowing through the striasomes and matrisomes. These neurons could constitute a neural system that is involved in the processing of several aspects of information, such as the detection of unpredicted events or the context of stimulus discrimination (Ravel et al., 2001).

The limbic part of the striatum (ventral striatum) under the control of the dopaminergic afferents might be involved in reward–driven learning processes. On the other hand, the dorsal striatum seems to be involved in the procedural learning of behavioral routines that are performed almost without conscious effort. In particular, in the context of procedural learning, the disruption of the “readiness” and “release” functions ascribed to the striatum might support some aspects of OCD pathophysiology. However, the striatum could also play a part in other processes potentially disrupted in OCD, such as emotional modulation of information and representation of the expected consequences of action. On the other hand, the performance of repetitive behaviors in OCD patients might have a positive effect on the reduction of anxiety, a process that can be assimilated to some form of reward.

### **8.6. Amygdala**

In the past decade, much research has been focused on the neural substrates that are involved in the expressions of fear and anxiety. The amygdala and its various outputs might play a major role in mediating the clinical signs and symptoms of fear and anxiety (Le Doux, 2000). Schematically, the amygdala is comprised of several nuclei, such as the lateral nucleus, basolateral nucleus and central nucleus. However, recent evidence supports the fundamental idea that the amygdala is not only involved in negative emotions such as fear and anxiety but also in reward and motivational processes through reciprocal connections to the nucleus accumbens and the OFC. Thus, the amygdala appears to play an important role in the expressions of emotion and motivation, probably through its connections with the OFC, ACC

and ventral striatum. A dysfunction of this structure, as suggested by some neuroimaging studies in OCD patients, might mediate the non-specific anxiety experienced relative to obsessive thoughts.

### 8.7. Thalamus

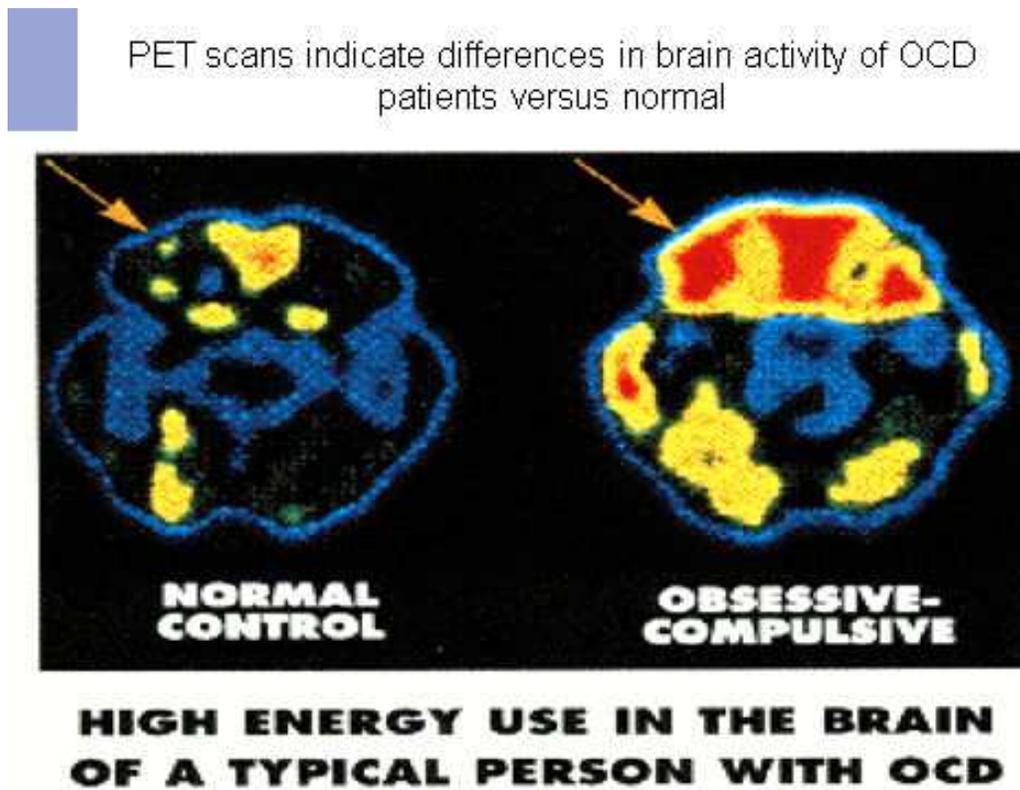
The diencephalic position of the thalamus in the brain explains why it receives large cortical inputs. It participates in emotional expression through the AN (anterior nucleus of the thalamus), which is connected to the MB (mammillary bodies) and, in turn, sends projections to the ACC. The putative role of the VA (ventral anterior nucleus of the thalamus) in cognitive functions involving attention and working memory is based on the link with DLPC. Discrete parts of the MD (medial dorsal nucleus of the thalamus) seem to be important in both emotional and cognitive processing through their preferential anatomical connections with the OFC and DLPC. Thalamic dysfunction has been associated with deficits in executive functions like planning, goal directed behavior, attention, and working memory (Lacerda et al., 2003).

### 8.8. Brainstem inputs

The mesocorticolimbic dopaminergic system emanates from the ventral mesencephalon, which encompasses the Ventral tegmental area (VTA), and projects to the nucleus accumbens with other limbic ventral striatal regions and cortical areas, especially the OFC, DLPC, ACC. The effects of the lesions, receptor blocking agents, electrical stimulation and self-administration of drugs of abuse suggest the effective contribution of the mesocorticolimbic system in the attentional, emotional and motivational processes. Dopamine contributes to the organization and regulation of goal-directed behavior. The serotonin-producing neurons are mainly located in the brainstem raphe nuclei. The description of the anatomy and development of the brainstem raphe nuclei has shown that they form the largest and most complex neurochemical efferent system in the human brain. General theories have attributed a broad range of behavioral functions to serotonin, which is considered as a general inhibitor of motor behavior. In contrast, reduced serotonin function has been shown to increase exploration, locomotor activity, aggression and sexual behaviors in animals and human beings (Lucki, 1998). The repetitive rituals (compulsions) and aggressive behavior, which is predominant in OCD patients is probably due to serotonin depletion.

- PET Scans show people with OCD have different brain activity from others
- Another theory: miscommunication between the orbital frontal cortex, the caudate nucleus and the thalamus
- Caudate nucleus doesn't function properly and causes thalamus to become hyperactive and sends never-ending worry signals between OFC and thalamus OFC responds by increasing anxiety

The Group A Beta-Hemolytic Streptococcal (GABHS) infections produce anti-neuronal antibodies that adversely affect basal ganglia cells, which might lead to the development of OCD (Swedo et al., 1998). The susceptibility marker that may predispose some individuals to



**Figure 2.** High energy use in the brain of a typical person with OCD

develop OCD has been well identified. D8/17 (the antigen present on the surface of peripheral blood mononuclear cells) positive individuals develop OCD as a consequence of their autoimmune response to Group A beta-hemolytic streptococcal infection, a response that is believed to yield antibodies which cross react with basal-ganglia antigens and produce tissue damage. The orbitofrontal cortex that had been demonstrated to be overactive in OCD is a region mediating the active expression of emotional response to significant biological stimuli as well as the inhibition of behavioral response.

## 9. Treatment of OCD

### 9.1. Pharmacological treatments

The serotonin reuptake inhibitors (SRIs) are consistently effective in patients of Obsessive-compulsive disorder. The anti-obsessional effects of potent SRIs produce progressive desensitization of the presynaptic autoreceptors present on 5HT neurons and their nerve terminals, thereby increasing synaptic 5HT release in the orbitofrontal cortex. Clomipramine was the first to show beneficial effects on OCD symptoms. The newer generation of antidepressant drugs viz. fluvoxamine, fluoxetine, paroxetine, sertraline and citalopram have also been found useful in management of OCD. The mean daily dosage is 50–200 mg for sertraline, 20–80 mg for fluoxetine, 40–60 mg for paroxetine and 150–300 mg for

fluvoxamine. The atypical antipsychotics such as risperidone act as new therapeutic options for refractory OCD. Marble burying behavior of mice has been used to model anxiety disorder including obsessive-compulsive disorder (OCD) due to the excessive nature of the behavior and due to the pharmacological effects of clinical standards. Gaikwad et al., 2007 suggested that LHRH agonist such as leuprolide may be clinically effective in OCD, resulted dose dependently attenuated marble-burying behavior in mice has been used to model anxiety disorders viz. obsessive-compulsive disorder. Acute administration of the neurosteroid allopregnanolone (i.c.v.) or its precursor, progesterone, decreased marble burying in male mice, but administration of the 5-reductase inhibitor finasteride, an allopregnanolone indirect antagonist, did not affect marble burying (Umathe et al., 2009). In addition, acute administration of the 5-HT<sub>2a/2c</sub> antagonist ritanserin abolished the leuprolide-induced decrease in marble-burying of male mice without having any effect on locomotion. Ritanserin treatment on its own had no effect on marble-burying or on locomotion (Gaikwad et al., 2010). These results suggest that the anti-compulsive effects of GnRH may depend upon serotonergic activity, and specifically, that the effects of leuprolide in the marble-burying model are mediated through 5-HT<sub>2A/2C</sub> receptors (Gaikwad et al., 2010).

## 9.2. Neurosurgical treatments

Neurosurgical treatments have been used for the management of chronic, severely distressing forms of OCD where conventional treatments are ineffective. In the United States and Canada, anterior cingulotomy was the most widely used neurosurgical procedure applied in the treatment of anxiety refractory OCD. Two surgical techniques have been used: radiofrequency thermolesion or thermocapsulotomy and the newer radiosurgical or gamma knife capsulotomy techniques. It has been shown that 50–70% of patients with OCD respond favorably to this type of operation at the end of the follow-up period ranging from 1 to 9 years. The Bilateral thermolesions are produced by radiofrequency in the anterior cingulate cortex (ACC) (Brodmann areas 24 and 32). It has found that 25% of patients with OCD were slightly improved, 31.3% were markedly improved, 12.5% were functionally normal on medication or psychotherapy maintenance and 12.5% were essentially well without any treatment at the mean follow-up of 9 years. The Y-BOCS used for assessment of OCD symptom severity, resulted a moderate-to-marked improvement (defined as a 50% or greater reduction in Y-BOCS scores) in 57% of cases at the mean 13-year follow-up. Approximately 50–70% of patients with OCD showed good outcome by surgery, indicated no or mild residual symptoms at the follow-up ranging from 16 months to 8 years. The recent report suggested that good outcome was observed in only 33% of cases within 1 year of surgery. In the United Kingdom limbic leucotomy was developed, a technique based on making bilateral lesions of the cingulotomy, in addition to those of the original subcaudate tractotomy.

## 9.3. Psychological treatments

Psychological treatments based on cognition-behavioral therapy (CBT) are effective in the treatment of OCD, alone or in combination with SRIs. The current procedures are in vivo (real-life) exposure with self-imposed response prevention (EX/RP) which showed benefi-

cial effects of this behavioral approach in two patients with severely disabling OCD. The reduction in OCD symptom severity was found after 3–7 weeks of EX/RP treatment while no change occurred during the control condition. The goal of CBT treatment is to learn to respond appropriately to intrusive thoughts and urges of OCD in new and much more adaptive ways and to reattribute the belief about “false brain messages” as intimately due to a biomedical disease state. The therapeutic effects showed the functional changes in interactions between the limbic cortex (including the orbital cortex and anterior cingulate gyrus) and the basal ganglia that are extremely important in redirecting information flow toward the integration of new behaviorally significant environmental events during learning. This function may be central in the acquisition of more adapted patterns of behavioral responses during the course of CBT.

## 10. Conclusion

OCD is an anxiety disorder featuring intrusive and troubling thoughts, which are perceived as the products of one’s own mind unlike schizophrenia. The Patient affected by OCD feels compelled to carry out certain stereotyped behaviors, although he recognizes that his behavior is at times irrational. Entire brain functioning is disturbed in patients suffering from OCD, thereby producing devastating effects at the work-place as well as at homes of the patients. OCD is a complicated disorder. Selective serotonin reuptake inhibitors (SSRIs) and to some extent tricyclic antidepressants form the main stay in the symptomatic treatment of OCD. Most of the OCD cases are incurable. Therefore, there is a great challenge to discover new drug treatment for the management of OCD.

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