

Review of Obsessive Compulsive Disorders Theories

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Abstract: The present review aimed to analyze the scientific literature until 2010 about the theories of Obsessive Compulsive Disorder in order to make clear how a biological and cognitive hypotheses might be integrated in a comprehensive point of view.

In the analysis, at biological level were included neuroanatomic and neurophysiologic models and animal models; instead at cognitive level were included different theories of Salvoskies, Van den Hout, Mancini e Rachman. Biological, cognitive, and behavioral elements of the theories have to be clearly distinguished between specific and general conditions, as do critical past events and current trigger conditions. The theories compared were drawn from the neuro-biological, cognitive, and behavioral literature that proposed empirical supported models. We conclude that there are substantive differences among the cognitive theories and between the biological theories reviewed. However, cognitive and biological theories appear to be compatible in principle. It is not clear whether substantive differences among theories are due to the existence of subtypes of OCD or due to the predominance of multifactorial cause.

It is argued that current treatment methods imply particular theories, and that particular patterns of success and failure can be understood in relation to theory through the methods we have employed.

Keywords: Multifactorial cause, animal models, neuroanatomic and neurophysiological factors, neurochemical and genetics aspects, repetitive thoughts, compulsive behavior.

1. INTRODUCTION: THE OBSESSIVE-COMPULSIVE DISORDER

The main aspect of Obsessive-Compulsive Disorder (OCD) is the presence of obsessive and compulsive behaviors of considerable length, more than an hour a day, generating discomfort and suffering (DSM-IV; American Psychological Association APA, 1994).

Comprising the diagnostic criteria of DSM-IV, the diagnosis of Obsessive-Compulsive Disorder requires the presence of five general criteria (a, b, c, d, e):

- a) The Presence of obsessions and / or compulsions as described by the following criteria

Obsessions

1. Thoughts, impulses or images recurrent and persistent, experienced, some time during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress;
2. Thoughts, impulses, or images are not simply excessive worries about real-life problems;

3. The person tries to ignore or suppress such thoughts, impulses or images, or to neutralize them with other thoughts or actions;
4. The person recognizes that the obsessive thoughts, impulses, or images are a product of his mind (not imposed from outside);

Compulsions

1. Repetitive behaviors (eg., Hand washing, ordering, checking) or mental acts (eg., Praying, counting, repeating words silently) that a person feels obliged 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 distress or preventing some dreaded events or situations; however, these behaviors or mental acts are not connected in a realistic way with what they are designed to neutralize or prevent or they are clearly excessive.
- b) At some time during the disorder, the person has recognized that the obsessions or compulsions are excessive or unreasonable (this does not apply to children).

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- c) The obsessions or compulsions cause marked distress, they are time consuming (more than an hour a day), or significantly interfere with the person's normal routine, with occupational (or academic) functioning, or usual activities or social relationships.
- d) If there is another disorder of the same axis (DSM-IV), the content of the obsessions or compulsions is not restricted to it.
- e) The disorder should not be due to direct physiological effects of a substance or of a general medical condition.

A Obsessive-Compulsive Disorder is specified as "with poor insight" when the patient does not recognize the excessiveness and unreasonability of obsessions and compulsions for most of the time. Then obsessions are defined by the DSM-IV as ego-dystonic thoughts characterized by high persistence. The most frequent obsessions that have been reported are contamination (e.g.: contaminated by someone shaking hands), repeated doubts (e.g., wondering if the car is closed, if you have been hurt someone driving); and aggressive impulses (e.g. attacking someone, shouting obscenities in church). Compulsions, however, are implicit mental acts or explicit repetitive and ritualized behaviors. The purpose of both symptom expressions is to prevent or reduce anxiety and the discomfort associated with certain situations. In terms of cognitive-behavioral approach it results in the implementation of neutralization behaviors and in the avoidance of potentially dangerous situations. Simple circumscribed obsessive and compulsive behaviors may also occur in the every daily life of people not characterized by an OCD, where a persistent connotation of anguish and suffering is lacking.

Periodically, different models of OCD have emphasized the role of responsibility [1,2], the fusion of thought and action [3]; of metacognition [4], the salience of intrusive thoughts [5], the fear of guilt [6].

All of these models include in the analysis of the cognitive processing many factors and the relations among them. However, they rarely consider the environmental and the biological factors which could be related to the aetiology and maintenance of the disease.

Recently, many theories on OCD that analyze the biological components of the disorder have been developed, some of them considered more specifically

the neuroanatomic and neurophysiological factors of the disease and some others considered more in detail the neurochemical and genetics aspects.

Within the paper we will go through all the most important theories on OCD analyzing the biological and the cognitive hypotheses, trying to propose an integrative model which includes the most relevant factors in a global point of view.

2. METHODOLOGY

The present study aimed to analyze the scientific literature until 2010 about the theories of Obsessive Compulsive Disorder in order to make clear how a biological and cognitive hypotheses might be integrated in a comprehensive point of view.

In the analysis, at biological level were included neuroanatomic and neurophysiologic models and animal models; instead at cognitive level were included different theories of Salwoskies, Van den Hout, Mancini e Rachman. Biological, cognitive, and behavioral elements of the theories have to be clearly distinguished between specific and general conditions, as do critical past events and current trigger conditions. The theories compared were drawn from the neurobiological, cognitive, and behavioral literature that proposed empirical supported models, as it clearly explained for each hypothesis.

2.1. Biological Hypothesis of OCD

2.1.1. Neuroanatomic and Neurophysiological Models

The present study introduces neuroanatomical and neurochemical correlates of the Obsessive-Compulsive Disorder (OCD). Although neurobiological models have not yet identified any typical structural brain lesion in the genesis of OCD, they agree upon changes of 5-HT metabolism, caused by many possible mechanisms (alterations of serotonergic receptors, intracellular transmission, genic mutations, genic polymorphism). In contrast, neuroimaging (fMRI, MRI DTI – traggography, PET) and electrophysiological recording (conventional and computerized EEG) technologies have identified some cerebral areas involved in OCD-like symptoms: i.e. orbito-frontal, prefrontal, limbic and insula, cortex, and some diencephalic structures (striatum, thalamus), as well.

Orbito-frontal cortex and prefrontal cortex: The Orbito-frontal cortex and cingulates gyrus are part of the associative limbic cortex. They control emotional

behaviour, whereas the prefrontal cortex controls cognitive behaviour and motor planning.

Insula: The insula is a deep cortical area between frontal and temporal lobes.

Through the connections with thalamus, amygdala, striatum and other cortical regions, the insula supports a wide number of high integrated functions: such as perception, motor control, self-consciousness, cognitive and interpersonal experiences. The rostral part of the insula processes both odour [7] and view (contamination, mutilations) disgust-related stimuli. Furthermore, the insula is also activated by similar imagined experiences. Disgust is not a health defense mechanism, but it is strongly conditioned by cultural factors. It is a widespread opinion that disgust serves a strong normative function; it points out a possible isolation from the group, through social aggressive contempt [8]. Fear of guilt can turn into obsessive symptoms because the information about contamination by disgusting elements is processed in a prudential mode. In particular, the fear of feeling guilty guides individuals' hypotheses of danger and safety [9]. Fear of guilt and disgust are similar as far as preventing or neutralizing actions are concerned. These two feelings are able to produce aggressive mental contempt, which is not addressed to powerless subjects, but to the repulsively dirty ones [10]. Salkovskis [11] has demonstrated that OCD patients are distressed by fear of criticism more than other anxious and normal subjects, assigning greater importance to this possibility.

Studies with fMRI indicate that the insula plays an important role in regulating painful experience, in addition to several basic emotions such as anger, fear, anxiety, disgust, happiness and sadness. The insular cortex would be also involved in information and emotion processing regarding rules transgression [12], orgasm [13] and empathy [14], by mean of a mirror neuron system linking inner and external experiences. The rostral right insular cortex could modulate interaction between selective attention involved in task performance, and vigilance, focusing on a part of the environment, ventral attention system [15]. This system of attention regulation could be crucial in prolonged compelling tasks, when attentive resources can get exhausted, causing negligence or anxiety related mistakes.

Corpus striatus: The striatal complex is connected to the cerebral cortex and the limbic system. Corpus striatum, amygdala, subthalamic nuclei and substantia

nigra are subcortical nuclei in the white matter of both hemispheres. These structures are called basal ganglia. The components of "neostriatum" are caudate nucleus and putamen; "paleostriatum" is the globus pallidus. The putamen plays a role in discrete motor movements, receiving inputs from sensory-motor cortex; it sends efferent fibres to the supplementary motor cortex through the thalamus.

Kellner *et al.* [16] suggest that OCD's clinical peculiarities are related to corpus striatum functional abnormalities. In particular, tic symptoms seem to be produced by simple aberrant motor programs, whereas the OCD's ones result from problems in complex motor programs. Both of these symptom groups could be elicited by an abnormal activation. The caudate nucleus is involved in cognitive functioning as well, by mean of the fibers which link associative neocortical areas to the caudate nucleus, thalamus, and prefrontal areas. The hyper- or hypofunctioning of these pathways can probably result in overordering or aggressive stereotyped behaviours.

Thalamus: The thalamus is a diencephalic structure involved in several neuronal pathways, and assumes the complex functions of connecting and re-transmission of signals. The thalamus' main efferences are GABAergic; the afferences are mostly excitatory, glutamatergic or aspartergic. The thalamus anterior nucleus is part of the limbic pathway "Papez" and receives afferences from the cerebral temporal lobe and the hippocampus. This structure is involved in mnemonic and olfactory functions. The medial nuclei receive afferences from the brainstem and extensively project to cerebral cortex, amygdala and basal ganglia. The dorsolateral nucleus receives afferences from mammillary bodies, hippocampus and sends efferences to the cingulate gyrus. The ventral anterior nucleus is involved in cortical output modulation; it receives afferences from cortical areas 6 and 8, globus pallidus, substantia nigra, and sends efferences to the frontal cortex and the intralaminar nuclei. The thalamus is a complex, highly organized and compartmentalized relay station for ascending tracts; it plays an important role in integration and re-transmission of both sensorial inputs, in co-working with limbic system, and the motor inputs received through the extra-pyramidal (pallido-thalamo-cortical pathways) and cerebello- thalamo-cortical fibers (control of muscular tone).

Limbic System: "Limbic system" defines the cortical areas around the brain-stem (so-called "primitive cortex"), and is composed of several interconnected structures: cingulate gyrus, hippocampal and

parahippocampal gyri, amygdala, septal area. The amygdala is involved in transmitting motivational stimuli to the cortex, particularly with regard to fear and reward reactions, emotional behaviour and sexual attraction. The hippocampus mediates the storage of information in long term memory, and is involved in spatial orientation with cognitive maps. The parahippocampal gyrus plays a role in spatial memory organization, and cingulate gyrus in cognitive attention system. Hyperactivation of the limbic system can produce compulsive behaviours.

Hypothalamus: The hypothalamus plays a critical role in endocrine, metabolic, autonomic and emotional functions; it attends to emotional reactions and fear responses, physiological expressions of emotions and stereotyped movements.

2.1.2. Neurochemical Models

Serotonin seems to play a more important role than dopamine and norepinephrine in the onset and maintenance of OCDs. Serotonin is a neurotransmitter involved in mood, appetite, sleep, pain control and cerebral activation. Serotonergic neurons are located both in Raphe nuclei, in the midline region of the brainstem, and in adjacent nuclear groups. They project fibers to more rostral centres, such as neocortex, olfactory tubercle, hippocampus and diencephalon. Serotonin can show excitatory or inhibitory effects. These latter can be found in hippocampus, cerebral cortex and neostriatum; serotonin is an ubiquitous neurotransmitter located in the same regions which are involved in the OCD-correlated movement disturbances. Recent evidence seems to confirm the hypothesis based on the genic polymorphism in regions that encode 5-HT transport and reuptake proteins (5-HTTLPR). This hypothesis is consistent with the variation of the anxiety traits, related to personality differences, in the general population. In 1980 was published a double blind study in which 24 OCD patients were treated with placebo followed by a random administration of clomipramine (CMI) or nortriptyline (a tricyclic antidepressant that inhibits serotonin reuptake). Only CMI produced a significant decrease of obsessive symptoms. Other authors compared CMI and desipramine in a double blind study including 48 OCD children and adolescents: once again, CMI resulted more effective than drugs. Several studies evaluated others antidepressant on OCD therapy, without achieving reliable effects. Serotonin active drugs blocking 5-HT reuptake can improve obsessive symptoms in children and adults. Similar drugs without any blocking reuptake mechanism seem less effective. The 5-HT system dysfunctions could

explain many physiopathological aspects of the OCD. Tricyclic antidepressant (TCA) drugs have been used in OCD treatment. Although their action mechanisms are not completely understood, they inhibit serotonin and norepinephrine reuptake. The most used molecule until the fifties was clomipramine. In the eighties, SSRI drugs (Selective Serotonin Reuptake Inhibitor) were introduced in clinical practice: Fluoxetine, Fluvoxamine and Sertraline. Recent SNRI drugs (Venlafaxine, Duloxetine) are selective serotonin and norepinephrine reuptake inhibitors: they show lower levels of collateral effects. Drugs action may be an "agonist" or an "antagonist" one.

The agonist effect works *via* the following mechanisms:

- Molecular blocking of presynaptic receptors, with increasing neurotransmitter availability in the intersynaptic space.
- Activation of postsynaptic receptors, mimicking the effect of the neurotransmitter.
- Inactivation of a catabolic neurotransmitter's enzyme, with consequent higher level of available neurotransmitter.

The "antagonist" effect usually works *via* a postsynaptic receptor blocking. To conclude in the neuroanatomical and neurochemical models, the orbito-frontal cortex sends excitatory glutamergic output to the striatum. The orbito-frontal cortex is also connected to the limbic system, creating two "loops" with the probable phylogenetical aim of linking the paleocortex to the neocortex. The first loop is composed by a pathway of fibers connecting cingulate gyrus, thalamus, hypothalamus and cingulate cortex again among them; the second loop connects cingulate cortex - septal nuclei - hypothalamus - amygdala - and cingulate cortex. Both the loops constitute a frame between emotional/instinctual and cognitive dimension of the input, enhancing and strengthening the signal, maybe due to neural plasticity mechanisms linked to genic expression of neurotransmission proteins. Some authors hypothesize that OCD symptoms are functionally related to the hyperactivation of the second loop and of the caudate nucleus [17], causing what leading to the typical behavioural symptoms like washing, collecting and over ordering.

2.3. Animal Models

Animal models are used to investigate effects realized in one species in order to understand the

effects that are produced in other species. Owing to the heterogeneity and evolving nature of psychiatric diagnostic categories, current approaches to the development of animal models focus on mimicking only specific aspects of disorders, rather than the entire syndrome [18,19].

Criteria for the validation of animal models for neuropsychiatric disorders have been proposed and refined over the past several decades. The literature suggests that the only necessary and sufficient criterion for the initial use of any type of animal model is predictive validity, which refers to the ability of a model to make accurate predictions about the human phenomenon of interest and to make accurate predictions about the effects of any variable on the human condition of interest, including environmental or epidemiological variables. There are other types of criteria, including construct and face validity. The first show the phenomenological similarity between the dependent measure and the symptom being modeled, while the second concerns whether or not a test or procedure measures or correlates with the theoretical construct it is intended to measure.

The use of animal models is considered a valid scientific tool to clarify the possible neural components of OCDs and to try and identify the genes involved. The basic research, involved to investigate neural and neurotransmitter circuits in OCDs, has employed pharmacological treatment, observing the behavioral effects in laboratory animals after drug administration.

Serotonin Dysfunction

OCD may be accompanied by serotonin dysfunction and drugs like selective serotonin reuptake inhibitors (SSRI) have been shown to benefit 40–60% of patients. However, the fact that SRIs can alleviate OCD symptoms does not provide evidence that OCD symptoms are caused by serotonergic abnormalities.

In a clinical study, dysregulation of neurosteroids has been identified in patients with obsessive-compulsive disorder.

Neurosteroids

Recently, Umathe and colleagues [20] theorised that neurosteroids, like allopregnanolone, may influence obsessive-compulsive behavior. Allopregnanolone is a modulator of the neurotransmitters involved in OCD, since it is active in the central dopaminergic transmission in nucleus accumbens affecting GABA receptors [21] and increases firing rate

of raphe nuclei serotonergic neurons [22]. Accordingly they examined the effects of administering allopregnanolone to mice (1µg/mouse (gr), i.c.v) on “marble-burying” behaviour. Several previous studies employed ‘marble-burying behavior’ of mice as an animal model to screen anti-OCD drugs, due to its high predictive validity. In this study, two different models of stress were evaluated: one of the physical type shown in an acute modality and one of social type, proposed in a chronic modality, because previous studies showed an increase of neurosteroid level due to acute stress [23] and a decrease of these levels due to social isolation stress have been observed [24]. The results revealed that allopregnanolone reduced marble burying behavior with comparable effects to fluoxetine drug (10 mg/kg, i.p.). However, data showed a significant reduction of marble burying behaviour after 3 hours (acute) when mice were exposed to restrain stress, while this mice showed an increase of marble burying behaviour at the end of chronic psychosocial stress.

Gene Studies

Despite these scientific validations of pharmacological treatments of OCD, the greater part of the experimental studies on animal models have focused on genetic manipulations in order to clarify the role of the target or candidate gene in the pathophysiology of OCD. In particular, the experiments that offer a greater validity are those which have been investigated the role of:

- a) levels of dopamine transporter (o carrier) (DAT)
- b) functionality of the 5-HT_{2c} receptors
- c) NR2B (glutamate) receptor antagonist
- d) the SAP90/PSD95 associated protein 3
- e) The Hoxb 8 mRNA expression

A synthesis of this research follows:

a. Levels of Dopamine Transporter (o Carrier) (DAT)

Berridge and colleagues [25] have observed that transgenic mice, who show a reduced expression of the carrier enzyme of dopamine (DAT KD), produce some patterns of grooming behavior which can be associated to the sequential super-stereotypy (actions, words, thought), that is noticed in patients affected by Tourette's syndrome and OCD [26]. Given the particular efficacy of the SSRI drugs, which are selective serotonin reuptake inhibitors, for the treatment of OCD, much neurochemical research is

now concentrated on the functionality of the serotonin system.

b. Functionality of the 5-HT_{2C} Receptors

Regarding the role of serotonin, there is a variety of data which suggests that the 5-HT_{2C} receptors have an important task in the etiology of the OCD syndrome [19]. Many human pharmacological challenge studies have shown that the 5-HT_{2b/c} agonist 1-(3-chlorophenyl) piperazine (m-CPP) exacerbates symptoms in OCD patients. However, m-CPP is not highly selective for 5-HT_{2C} agonist and shows IC₅₀ values (inhibitory concentration, used to evaluate the effectiveness of an antagonist) similar to 5-HT₂, 5-HT_{1A}, 5-HT_{1B}, and α ₂-adrenergic receptors. Nevertheless, if the stimulation of 5-HT_{2C} receptors in effect highlights the symptoms DOC, at least in some patients, the transgenic model of 5-HT_{2C} KO mice could provide a model of resistance of the DOC. In addition, it has been shown that in mice the increase of the compulsive pressing of a lever after orbital lesions is blocked by paroxetine (SSRI) administration and is followed by an increase of density of striatal serotonin carrier.

c. NR2B (Glutamate) Receptor Antagonist

Alterations of the glutamatergic systems are implied in various fields of psychiatric disorder like depression, schizophrenia and anxiety disease. Recent researches have shown that a glutamatergic modulator, Riluzole, seems to have important anti-obsessive properties [27]. These researches have clarified that the agents that control the glutamatergic system, inhibiting the marble burying behavior, are a valid model to test the clinic potential of the AMPA receptors in mice. In addition, this evidence allows the clarification that both an agonist of the AMPA receptor and an antagonist of the NR2B receptor could be useful for the OCD treatments.

d. the SAP90/PSD95 Associated Protein 3

The SAP90/PSD95 associated protein 3 is a protein postsynaptic complex that mediates excitatory synapses, highly expressed in the striatum. Welch [28] has shown that Sapap 3 KO mice are characterized by: (1) behavioural overgrooming already during the age of 4-6 months; (2) the presence of lesions (head, neck, muzzle) due to an increase of self-grooming; (3) no peripheral deficit, as, for example, an alteration in the sensorial innervation; (4) an increase of anxiety observed in the open field test, in the elevated plus maze test and in the light/darkness test; and (5) no alterations in the locomotor activity.

e. The Hoxb 8 mRNA Expression

The Hoxb8 gene is a member of the mammalian Hox complex which is a group of 39 transcription factors well known for their role in providing positional information along the anteroposterior axis during early development [29] and is also expressed in the CNS during adulthood. Hundred percent of Hox8 KO mice showed excessive grooming leading to hair removal and deep skin lesions during induced grooming assays and also spontaneously in the home cage. No skin or peripheral nervous system abnormalities were observed [30]. The overgrooming phenotype in these mice was suggested to be similar to the excessive grooming seen in trichotillomania and in some types of OCD.

Nevertheless the pathophysiology of the OCD is still not very clear, although research has noticed underlying neural mechanisms which include the orbitofrontal cortex, anterior cingulate cortex, thalamus, striatum and some neurotransmitter systems, include dopaminergic, serotonergic and glutamatergic [31]. Regarding the dopaminergic system, several behavioral similarities have been found among mice DAT KD and patients affected by both OCD and Tourette syndrome. Evidence [25] has been provided that:

- a) both show superstereotypia symptoms, like rigid sequential components composed of actions, language and thoughts;
- b) the washing rituals, protective behavior or contamination sensation could be correlated to self-grooming activity;
- c) basal ganglia could be implicated in OCD and in Tourette syndrome as well as in the sequential grooming behavior.

These symptom expressions agree with experiments in which it has been observed that in rats the dorsolateral striatum neurons increase discharge rates by 116% during grooming behavior, suggesting that the caudate nucleus has a specific role in the planning of movement sequences. In addition, studies on cerebral lesions in rats have clarified the role of the neostriatum in sequential patterns of grooming activities, but not in the single motor acts that constitute the grooming behavior. Despite the scientific relevance of this study, research still needs to establish the predictive validity of DAT KD model for aspects of OCD [19].

A neuroimaging study [32] showed an increase of glutamate in the caudate nucleus in OCD patients (children) who had been treated with SSRI drugs. These data suggested that the OCD patients are also subjected to alterations in the serotonin and glutamatergic neurotransmitter suggesting the influence of the glutamate high levels in OCD. In particular, it has been hypothesized that orbitofrontal hyperactivity is caused by high levels of glutamate in the striatum [27,33,34]. It has been highlighted that in the OCD there is an alteration of orbital frontal cortex functionality, mediated by the serotonin system, responsible for the compulsive behavior.

It has been noticed that the drugs that inhibit the serotonin reuptake reduce the symptoms and contribute the increase of the orbitofrontal cortex metabolism in the striatum of OCD patients. Although the interpretation of animal model results cannot be directly related to the clinical human condition, these discoveries increase the likelihood that in some OCD patients an orbitofrontal dysfunction is related to serotonin levels alterations in the striatum and this may promote the expression of OCD symptoms. This condition can be treated by means of specific drugs. Actually, the selective serotonin reuptake inhibitor (SSRI) is the major pharmacological treatment used in OCD, with about 40%-60% of non-responders to SSRI drug treat. So, it is of primary importance to develop a new approach for the treatment of OCD.

Several biological factors have been identified which have effects on the OCD phenotype. The neurosteroid effects of allopregnanolone on compulsive behavior in mice like marble-burying have been demonstrated [20]. These authors showed a significant reduction of marble burying behavior correlated with high levels of allopregnanolone.

The majority of the research using animal models has concentrated on investigating the role of one, or more, gene believed responsible for the OCD pathophysiology. Thus, for a particular candidate gene, a mouse preparation would be created with the gene absent or down regulated. The experiment would then establish the level of the OCD phenotype (DSM-IV) in these mice. To take one example, it is broadly accepted that dopamine plays an important role in OCD pathophysiology. Thus, it has been observed that in OCD patients, dopamine levels are high compared to healthy subjects. The hypothesis is that there is a causal relationship between these two factors. Some researchers [25] have used the dopamine transporter

knockdown mice (DAT-KD) to investigate this proposal in more detail. The DAT KD mouse shows only the 10% of the normal level of the enzyme carrier of dopamine and exhibits the 70% of the increment in the extracellular levels of dopamine [35]. These mice have presented a behavior characterized by long pattern of over grooming and compulsive actions such as the marble burying test. Because rigid sequences of actions, language and thoughts are characteristic symptoms of the DOC, DAT-KD mice may be considered a useful model to reproduce these conditions.

Another important line of research has focused on the effects of serotonin modulation on compulsive behaviors similar to those found in OCD. The experiments [36] were conducted using mice that were genetically manipulated and deprived of the 5-HT_{2C} receptors, a subtype of serotonin receptor family. Since their initial generation, the 5-HT_{2C} KO mice have been extensively characterized [37]. In addition to exhibiting hyperphagia, 5-HT_{2C} knockout mice also show increased chewing of non-nutritive objects. Chou-Green *et al.* [36] characterized object chewing in 5-HT_{2C} knockout mice and suggested that the increased 'neat' and highly organized patterns of chewing observed could provide a promising model of compulsive behavior in OCD. Finally, as suggested by the authors, some more detailed pharmacological studies are needed to determine the relevance of the behavioral abnormalities of 5-HT_{2C} knockout mice compared with compulsive behaviors in patients with OCD. One line of research has identified the Sapap3 protein complex the possibility to play a role in the behavioral symptoms of OCD. The complex SAP90/PSD95 and protein 3 (Sapap3) is a postsynaptic protein, which mediates excitatory synapses, highly expressed in the striatum. Welch and colleagues [28] have shown that the Sapap3 knockout mice show a overgrooming behavior within the first 4-6 months of age and that these animals skin lesions (head, neck, snout), due to a dramatic increase in grooming behaviors. Finally, they found increased levels of anxiety, observed in the "Open Field" test, in the "elevated zero maze" test and in the "light / dark" test. Finally, a model was proposed in the study where the authors have investigated the function of the Hoxb8 gene. Hoxb8 KO mice showed excessive grooming leading to hair removal and deep skin lesions. The overgrooming phenotype in these mice is considered similar to the behavior of excessive washing found in trichotillomania and in some types of OCD disorders [30]. The authors also demonstrated that the Hoxb8

mRNA is expressed in brain regions called 'OCD-circuit'. However, the Hoxb8 mRNA was also localized throughout the cortex, the olfactory bulb, hippocampus, cerebellum and brain stem, suggesting that the expression of the Hoxb8 gene is widespread, and not specific to brain regions involved in OCD. Nevertheless preclinical studies that have attempted to mimic the best ethological approximation possible to obsessive compulsive disorder, have mainly concentrated on the identification of possible genes involved in disease to find a safe and effective drug treatment. Recently drugs used to treat this disorder have been previously tested through the use of these models, which are a key factor in enhancing the knowledge of the underlying physiological mechanisms and to understand the role of genetic modulation in OCD.

In general, it is possible to argue that basic research presents an objective limit related to the interpretation of cognitive features. Specifically, this is particularly significant in the context of psychopathology, such as OCDs. In this study, the choice of researchers has been directed to the use of small laboratory animals such as rats and mice, which can be easily genetically manipulated, and to achieve greater reproducibility of the data. So, none of these studies may be associated with what happens in an ecological environment, let alone the social and relational context of the human being. In addition, these studies have methodological limitations, because the animals were tested in isolation condition, which is defined a chronic social stress. However, preclinical studies that attempt to mimic the best approximation possible ethological obsessive compulsive disorder, have mainly concentrated on the identification of possible genes involved in disease to find a safe and effective drug treatment.

2.2. Cognitive Hypothesis

2.2.1. Salkovskis

Cognitive approaches used to treat obsessive problems are based on the notion that negative interpretations of intrusive thoughts, images, impulses and doubts are crucial both for the experience of distress and for the motivation towards neutralizing behaviours, suppression of thoughts, avoidance and searching for reassurance.

Underlying the tendency to interpret intrusions in a negative way, the cognitive theory of obsessions suggests that there are beliefs relative to Inflated Responsibility (BIR). The later is defined as: "The belief that one has power which is pivotal to bring about or

prevent subjectively crucial negative outcomes. These outcomes are perceived as essential to prevent. They may be actual, that is having consequences in the real world, and/or at a moral level" [38]. These outcomes can be real or have moral consequences.

We wonder, then, what is the origin and meaning of BIR and how do they evolve. Salkovskis [39] suggests that childhood and adolescent experiences are crucial in forming attitudes that become dysfunctional in a person's life. In particular, hyper or hypo-responsibility and rigid and extreme codes of conduct lead a child to develop beliefs such as "better safe than sorry" which, in turn, contribute to the development of a inflated sense of responsibility. Moreover, to have experienced systematic criticism and high levels of responsibility related to changes that occur in life can trigger the belief of inflated responsibility.

The BIR not only include general attitudes of responsibility but also interpretations of more specific in terms of responsibility that derive from intrusive thoughts. Salkovskis found a link between these beliefs and obsessive symptoms not associated with anxiety or depressive symptoms.

The cognitive theory proposes, therefore, that in obsessive problems, the appearance and/or content of the intrusions (thoughts, images, impulses, and/or doubts) are interpreted as an indication that the person is responsible for the harm done to him/herself or to others. This causes both negative mood states (anxiety and depression) and motivation towards neutralizing actions which may include compulsive behaviours such as checking and washing [39]. Therefore, negative mood states and neutralizing actions may increase the likelihood of further intrusions and the perception of inflated responsibility, leading to a vicious cycle of negative thoughts and neutralizations. The interpretations in terms of responsibility can trigger other reactions such as selective attention, errors in reasoning and the search for reassurance. They have an additional role in maintaining the BIR and the intrusions.

Salkovskis [1,11] proposes in the genesis of obsession, a vicious circle where the intrusive thought acquires salience as a result of an appraisal of responsibility and, therefore, once an affective reaction (anxiety or depression) is determined, it stimulates the neutralization of intrusive thoughts that ultimately ends up being strengthened.

Furthermore, the author shows a correlation between critical experiences in childhood and/or

adolescence and/or real or alleged critical incidents and specific compulsive conduct. In particular, the author points out that:

- Inflated responsibility during childhood leads to the development of rituals (ordering, arranging, and other behaviours aimed to maintaining order) believed to be able to protect family members or strangers.
- Rigid and extreme codes of conduct linked to the tendency towards rumination and perfectionism.
- Children who have over-protective parents tend to show behaviours of washing or checking in order to protect their loved ones.
- Real or alleged adverse incidents that have caused harm to loved ones leading to checking behaviours aimed to prevent and protect the well being of family members or strangers.

Psychological risk factors are the basis for the development of the belief of inflated responsibility. This belief has to interact with life events, prolonged stress and depressed moods to cause a OCD.

2.2.2. *Rachman*

In the study of Obsessive-Compulsive Disorder (OCD), one of the aspects taken into account by Rachman [40] is the *perceived sense of responsibility*. In this disorder, this sense of responsibility turns out to be exaggerated and brings the subject to experience a sense of guilt not only for their own actions but also for those committed by other people.

When the affected people experience an undesirable obsessive thought feel unduly responsible for thinking and its significance: feel a strong responsibility for their obsessive impulses to harm others and for their unacceptable sexual images or other. These experiences obsessive play for them a penalty, for which morality comes into play, as well as the psychological responsibility. When they blame themselves the responsibility of these obsessive thoughts are experiencing guilt. Given that the obsessions are experienced as one's own mental products, this attribution of blame is difficult to avoid.

Usually a sense of responsibility occurs at home and at work, but it may very well spread in every situation in which the person feels a sense of belonging to the place and there is the possibility of causing harm to others. Typically, those affected will have little or no

experience of responsibility in homes or workplaces of other people: they feel responsible in its psychological territory.

Patients sometimes feel relieved to know that all people experience intrusive thoughts. They are also raised in the knowledge that their intrusive experiences are not a sign of mental illness, nor are experiences that should be hidden or feared. These unwanted intrusive thoughts do not lead to disaster but they are a psychological phenomenon, common experiences and not a way of losing control or get mad.

The obsessions become overly significant only in the degree to which the concerned person gives them a special meaning.

Most people reject or ignore their unwanted intrusive thoughts and regards them as waste. However, when people attach great significance to these unwanted thoughts tend to become anxious and adhesives. The tendency to over interpret the meaning of our intrusive thoughts can be taught by direct instruction, religious or moral, but also result from direct experience or from a process of self-education. Moral education can also promote a high level of personal responsibility. It is assumed that the tendency to over interpret the meaning of unwanted intrusive thoughts is general and not specific to a particular intrusive thought.

Because of the high sense of responsibility requires a kind of oppressive "weight", the threat of increased or additional responsibilities may promote intense anxiety. Therefore, it is extremely common for affected people try to cut and avoid additional responsibilities both at work and at home. Additional responsibilities are therefore avoided or postponed. When these responsibilities are inevitable tension increases. The agent or the person who contributes to increase the liability can become the focus of anger and resentment. The delay may be the only way to put off responsibilities, as well as the tendency to leave the task incomplete.

At different times, patients seem to fuse thoughts and actions. The merger refers to the physiological phenomenon in which the patient appears to have obsessive activity and forbidden action is as if it becomes morally equivalent, giving rise to guilt and self-denigration. The obsessive patients have difficulty expressing their angers. One cause of this difficulty could be based on an exaggerated sense of responsibility and therefore the tendency to attribute

internally blame rather than externally. Analyzing the behavioral sphere, Rachman shows how anger is inversely proportional to the exaggerated sense of responsibility, as if the personal liability will be diminished the likelihood of anger increases, and when the personal liability increases the anger decreases and the sense of guilt increases.

An increased sense of responsibility is a common characteristic of people with compulsive control disorders but is less intense and less common than in patients with order and cleanliness disorders. It follows that individuals with control disorders should experience more intense and frequent guilt feelings than those with order and cleanliness disorders.

It is interesting to note that in obsessive patients there is a curious asymmetry between their high sense of responsibility for negative events and their normal, even lower than normal, acceptance of responsibility for positive events. When possible, share or transfer the liability can be effective for therapeutic purposes: in this way you are allowing the patient and the therapist to gain better control of abnormal behavior and a better understanding of the knowledge that cause related behavior. When you reach a reduction of the increased responsibility abnormal behavior is weakened or removed.

2.2.3. Mancini

In the theoretical model of Mancini, the internal profile of the obsessive activity consists of five phases: Critical Event, First Evaluation, Attempts of Solution of First order, Second-Rated level and Attempts of Solution of a Second level. Generally a critical event, a fact like touching an object, a thought, a certain feeling or emotion, generates an attribution of meaning and First Evaluation of imminent threat, grave, unacceptable, but coping. The person feels his moral purpose threatened, which is closely connected with the guilt of irresponsibility, not to have protected himself or delayed sufficiently the occurrence of the event, trying to avoid the guilt of feeling responsible. Some typical phrases are: "Sure it is unlikely that saying or thinking a word could cause a real effect, so it's unlikely, but can I exclude it with certainty? Until now I did so and everything was ok. What costs me avoiding to say or to think a word?". The person is afraid of being accused of not having done what he was supposed to, of superficiality and carelessness, consequently he does not feel up to his responsibilities and focuses on what he can and must do to prevent undue damage he considers himself responsible for.

This fear will lead him to experience a strong sense of anxiety, both before and during the obsessive activity and will also invest his obsessive behaviors towards a single task repeated several times to be sure he did it correctly. He will worry, above all, about the correctness of his performance rather than the result, not accepting the possibility of being guilty of not doing his duty [6]. Often the link between the event and damage is implausible or unlikely, but the patient will seriously consider it, investing time and energy in order to protect himself because he is afraid of having to repent for his underestimation. Facing the criticisms and the convincing reassurances the subject tends to maintain his original belief. The patient seems to be more attentive to prevent any irresponsible act or omission rather than to achieve outcomes he could be proud of. In fact, he feels anxiety facing the possibility of misusing his power and his inadequacy in front of his responsibilities (failure of moral purpose). To cope, prevent or neutralize the threat, the subjects make several attempts of Solution of First Order, like avoidances, attempts to neutralization (ritual washing, formulas), ruminations, mental controls, suppression of thought, requests for reassurance. The obsessed subject is more concerned about the correctness of his performance than of the result; he concerns about preventing the possibility of feeling guilty of not having done his duty. For this reason he focuses on the obsessive repetition of a particular activity [6]. The person who feels guilty cares nothing for the damage itself; his purpose is not to avoid the damage, but to behave in order not to be accused of anything. The focus is his performance which has to be morally blameless. We note some cognitive biases typical of obsessive patients such as the overestimation of the threat and of the assignment of severity of a failure, the very cautious control mode, the focusing on worst-case scenario, the emotional reasoning and the lack of trust in memory. Prevention is a purposeful activity aimed at achieving a goal, but at the same time it is the result of a constraint that the subject suffers paying the consequences of Evaluation of Second Level. In this case the subject tends to evaluate his behaviour exaggerated and maybe unnecessary, sometimes harmful to the quality of his life and the lives of those around him and will tend to remedy implementing Attempts of Second Order Solution. At that point, the measures will be aimed at changing the state of mind, trying to ward off thoughts and images, for example, through the replacement of mental obsessive contents with other not obsessive contents. Otherwise the people try to suppress these thoughts completely obtaining paradoxical results of reinforcement.

Generally, the attempts of Solution of Second Level do not allow the subject an effective resolution and they are often counterproductive because they do not allow a useful re-reading of benefits and costs of performed obsessive activity.

2.2.4. Van den Hout

In several experimental studies, van den Hout and his research group demonstrated that dissociative experiences and increased uncertain about the trustworthiness of visual perceptions are induced by prolonged staring at one object, even in non clinical population [41]. This finding holds true even if staring duration is limited to 30 seconds, evaluated by pre and post-test rating scales [42]. The prolonged visual fixation in OC patients have been considered as an extra problematic safety strategy. Similar findings were also reported about memory: Checking 20 times [43,44] or even just 2-5 times induces memory distrust. Moreover, evidence of uncertainty about attention and perception in OC patients were also reported.

Intriguingly, reasoning style manipulation may increase the credibility of a feared outcome. The OC patients' typical step-by-step perseverative reasoning linking a current situation to a dreaded and highly improbable catastrophe has been simulated in healthy participants by requiring to generate one or five series of intermediate steps between a neutral situation and a harmful outcome. The results showed that this perseverative-like induced reasoning enhanced the credibility of a negative improbable outcome. An important factor in development and maintenance of the OCD pathology is the patients' tendency to assume their own behavior (e.g avoidance, checking) or their momentary internal state (e.g. state guilt) as very informative on the probability that a dangerous adverse event will occur. By presenting scripts containing objective safety vs. objective danger and safety behavior vs. no-safety behaviour, OCD patients rated the danger perceived as significantly higher in case of pre-activation of danger information and safety behavior information, confirming that such patients tend to activate a danger representation from an occurring safety behaviour. This "behaviour as information effect" was not found in the non-clinical control group. Induced feel of guilt was used as information by high-trait guilt participants when estimating the likelihood and severity of a negative outcome, and the dissatisfaction with preventive performances in two OCD relevant scenarios. High-trait guilt participants, but not low-trait guilt participants, significantly rated the negative scenario as more probable and severe and the

preventive behaviour as less efficient, proving that the concurrent mental state actively interferes with threat perception and evaluation.

3. RESULTS

By doing this review has been expressed both similarities and differences of these various variables and potential triggers in a potential joint model, which could capable to illustrate interactions of cognitive, biological and environmental factors, that to date have been accounted for solely in distinct models of an OCD.

What is clear from the review are the strong influences made by a series of environmental factors which could affect different level of functioning (rigid and extreme codes of conduct and over protecting parent affect directly the behavior maintaining the symptomatology of OCD) and different environmental factor might affect the same cognitive aspect like it happens with sense of belonging, sense of freedom, lack of sharing responsibility, perceived responsibility and high moral standards which affect the belief of inflated responsibility). Another statement which emerges is that there many cognitive factors included that they are typically involved in other pathology (cognitive bias in many pathologies, fears in different fobias, intrusive thoughts in psychotic disorders, TEF-TOF-TAF in PTSD) which gives us an overview of the complexity of the OCD's and how a treatment should be focused on different strategies oriented to the complexity of the functioning of this disease. The biological factors have studied in different researches and what is emerging is that many of anatomical areas and neurochemical aspects are strongly connected with the functioning of this disease which should led a clinicians to consider as one of the first option a combining a psychotherapeutic treatment with a pharmacological one. At the same time we should note that most of the cortical and subcortical areas and the neurotransmitters involved in this analysis are commonly involved in other psychopathologies such Panic Disorder, PTSD, Social Fobia, so that we need to carry on researches which give us a better and more defined outcome on the peculiarity of one brain area and/or neurotransmitter linked with the OCD functioning.

4. CONCLUSIONS AND CLINICAL IMPLICATION

A clear scheme of principle components and their functional connections in OCD from the main biological, cognitive and environmental theories might deliver a common framework and language in multi-disciplinary

teams working with patients with OCDs. Thus, in the clinical approaching it is encouraged to apply a systematic assessment of causing and maintaining factors in order to obtain a global profile of the patients problematic useful for the development of a comprehensive treatment plan, followed by systematic monitoring of the identified factors throughout the joint causal model controlling for treatment efficiency and accounting for necessary adoptions in treatment strategies.

In particular, the possibility to incorporate a variety of variables (neuro-biological, genetic, cognitive, socio-cultural) in a multi-factorial model enables to identify probable indicators of treatment efficiency, that provide major clarification regarding the functional interactions of the variables involved in the maintenance of the OCD in distinction from variables that are associated with a comorbid or differential diagnose. Alongside the clinical advantages of applying a comprehensive causal modeling framework as working grid in assessment and treatment monitoring, there are limitations of a global joint model in terms of reduced specificity and sensitivity. One related issue might represent the poor differentiation between subtypes of compulsive behaviors, leading to a more comprehensive representation of "Checkers" in the joint model than that of subtypes such as "Hording".

However, the principal aim of the present paper was to provide a detailed analysis of existing models of OCD that receive empirical support, following both, quantitative and qualitative approaching. That is, presenting limitations and short-cuts of each identified model and highlighting the emerging consideration of biological, cognitive, behavioral and environmental factors in that model (quantitative approaching), followed by mapping the associations and inter-relations between each model variables that demonstrated an empirical supported in explaining the etiology and treatment of OCD (qualitative approaching).

Although this type of analysis could seem reductionist, however gives a general overview of the theories present in the literature on a disease in order either to let the clinician generating new hypothesis of functioning with regard to a patient or to a group of patient with the same disease or to let researchers to focalize new applied researches on some which has been proposed by other researchers with different background and complementary professional expertise.

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