Review Article

International Journal of Psychiatry

Mechanisms of Response Prevention and the Use of Exposure as Therapy for Obsessive-Compulsive Disorder

Habibollah Ghassemzadeh[1], Mary K. Rothbart[2] and Michael I.Posner[2*]

[1]*Tehran University of Medical Sciences, Tehran, Iran.*

[2]*Dept of Psychology, University of Oregon, Eugene.*

[*]Corresponding author
Michael I. Posner, University of Oregon, Eugene, OR USA, E-Mail: mposner@uoregon.edu.

Submitted: 14 Nov 2016; **Accepted**: 26 Dec 2017; **Published**: 30 Apr 2017

Abstract

The combination of exposure therapy and response prevention (ERP) is the most widely used and to date the most effective treatment for obsessive-compulsive disorder. We review the two main theoretical mechanisms proposed to account for the effectiveness of ERP: (1) habituation of anxiety due to exposure and (2) extinction due to withholding reinforcement of behaviors undertaken to decrease anxiety. Both of these mechanisms have their origin in behavior theory based upon classical and instrumental conditioning, and relate to the view that OCD is an anxiety-related or anxiety- based disorder. DSM- 5, however, no longer lists OCD as an anxiety disorder, instead positing an obsessive - compulsive disorder spectrum (OCDS), and emphasizing the diversity of OCD symptoms. More recent cognitive and neuroscience approaches have also stressed mechanisms involved in the control of emotional and behavioral responses. In this paper we review habituation and extinction accounts and attempt to integrate the newer neuroscience perspectives, moving toward a more complete framework for understanding OCD treatment.

Keywords: ERP, Habituation, Extinction, OCDS, Neuroscience perspectives

Introduction

Obsessive-Compulsive Disorder (OCD) is a common, chronic disorder in which a person has uncontrollable, reoccurring thoughts or images (obsessions) and/or behaviors (compulsions) that he or she feels the urge to repeat over and over– mostly in a ritualistic manner. OCD has many subtypes or clusters of symptoms. Rasmussen and Eisen studied 560 OCD patients in the USA meeting DSM-III or DSM-III-R criteria [1]. The most prevalent obsession theme in that study was contamination (50%), and the least prevalent was sexual impulse (24%). The other themes included pathologic doubt, somatic concerns, need for symmetry, and aggressive impulses. The most prevalent compulsion was checking (61%) and the least prevalent was hoarding (18%). Other compulsive behavior included cleaning/washing, counting, seeking exactness and expressing a need to confess.

Obsessive- compulsive disorder has been indicated as the fourth most common psychiatric disorder and the tenth leading cause of disability in the world (World Health Organization [2]. The lifetime prevalence of OCD worldwide is approximately 2-3 % and the prevalence in five US communities ranged from 1.9 to 3.3 % [3, 4]. According to the National Institute of Mental Health (NIMH) more than 2.2 million Americans suffer from obsessive-compulsive disorder. It strikes men and women in roughly equal numbers and usually appears in childhood, adolescence, or early adulthood. One-third of adults with OCD developed symptoms as children, and research indicates that OCD may run in families. Although the prevalence of various symptoms tends to vary widely across different cultures and studies, the overall pattern of symptoms is more or less similar [5, 6].

In this paper we examine exposure therapy combined with response prevention (ERP), one of the most widely applied psychological treatments in anxiety-related disorders in general and obsessive-compulsive disorder (OCD) in particular.It is important to note, however, that in the 5th edition of the Diagnostic and Statistical Manual of the American Psychiatric Association the disorder was removed from the set of anxiety disorders and given its own spectrum [7]. Because of the new diagnostic category and recent imaging findings we focus on relating issues of exposure to those of response prevention to develop a common framework for therapy.

In a recent meta-analysis, different pharmacological and psychotherapeutic interventions for OCD in adults were systematically reviewed and analyzed [8, 9]. The three main categories of psychotherapeutic interventions were examined: behavioral therapy (BT), cognitive therapy (CT), cognitive behavioral therapy (CBT) and CBT with ERP. The pharmacological agents included clomipramine, fluvoxamine, and SSRIs. The investigators also considered the combinations of psychological and pharmacological treatments. The criterion for efficacy was based on Yale-Brown Obsessive Compulsive Scale and the waiting list was taken as a control group in most of these studies.

Results showed that all three psychotherapeutic interventions were more effective than drug placebo. Comparing these 3 interventions, cognitive behavioral therapy (CBT) was less effective than BT

and CT and was not different from the psychological placebo (general stress management). But excluding waiting list controls led to a larger effect of CBT. The general conclusion was that all 3 psychotherapies "were more likely to lead to a larger effect than were medications" (p.7). The combined treatment of both medication and psychological treatment was more effective than the latter alone. This finding differs from the Foa et al. study, which showed CBT combined with pharmacological treatment (clomipramine) was not more effective than CBT alone [10].

Although some practitioners using cognitive models of OCD have found cognitive methods to be the best choice for reducing obsessions and compulsions, cognitive therapy and cognitive behavior therapy in this review "are no more effective than ERP"(p.145) [11]. Also as Abramowitz has indicated, "the prognosis for individuals for OCD has changed from poor to very good as a result of the development of ERP" (p.407) [12]. We now consider some of the most popular theoretical models of ERP, and results of brain imaging studies suggesting alternative views of the effectiveness of ERP and the possibility of new treatment approaches.

Exposure and exposure therapy

Exposure therapy and response prevention (ERP) involves a set of psychological treatment approaches and/or techniques for improving anxiety-related disorders, including OCD. The common core of these approaches and techniques is asking patients to confront their anxiety provoking situations or fearful thoughts while controlling their usual response to the situation.

Two main theoretical mechanisms have been proposed to account for the effectiveness of ERP: habituation due to response exposure, and extinction due to withholding reinforcement of the behaviors undertaken to decrease anxiety [13]. Both of these mechanisms have their origin in behavior theory based on classical and instrumental conditioning, and are for the most part based on the view that OCD is an anxiety disorder. There are problems, however, regarding the theoretical basis of this set of treatments and the mechanism of their efficacy. As argued by Abramowitz, it is crucial to have an up to date theoretical framework in order to design and execute effective treatment [13].

In this paper we review the historical basis for defining the role of habituation and extinction in ERP. In addition, we consider new studies using imaging to identify mechanisms of control of responses in OCD. In particular, brain systems of executive attention have been found to exercise control over both emotional and behavioral responses [14]. We hope this review might aid clinicians to clarify the theory underlying existing therapies and aid in the development of possible new therapies that could improve treatment of OCD. Historically the application of exposure/response prevention goes back to Meyer's innovative work on the treatment of two patients: one with compulsive washing and another with sexual obsessions [15]. The main rationale for this approach was that if OCD patients are asked and persuaded in a fear situation to withhold carrying out the compulsive rituals, they will eventually realize that (1) the feared consequences of not performing the ritual do not occur and (2) their expectations of "disastrous consequences" are not fulfilled [15]. Meyer reported some success in his first study and in a later study, used the same technique with 15 OCD patients. In the second study ten patients were either "much improved" or totally improved [16]. Meyer's main conceptualization was that "a completely successful modification of expectations would lead to a complete elimination of ritualistic behavior" [15].

Although Meyer's treatment was based on modification of expectations, a likely cognitive interpretation, many researchers and clinicians shifted their attention from a cognitive strategy to a behavioral mechanism, attempting to explain the possible treatment effects of ERP within the framework of conditioning terminology [16].

At this time behavior was associated with physical reflexes, for example, Isaac Marks published an article entitled "the current status of behavioral psychotherapy: theory and practice", suggesting exposure as a common principle of most behavioral approaches to the treatment of phobic disorders and compulsive rituals [17]. He refers to Wolpe's desensitization in fantasy as an early form of exposure treatment (imaginal exposure) [18]. He also explains exposure in vivo, which gives quicker results by bringing the patient into contact with the anxiety-provoking situation without relaxation [19].

Emotional processing theory

Probably the most influential recent theoretical approach to OCD has been emotional processing theory. Lang's bio- informational theory described anxiety as an emotional memory stored within a semantic brain network [20, 21]. The emotional memories were hypothesized to contain three categories of information, (1) information about the stimulus or situation that evokes the emotional memory structure; (2) information regarding an individual's responses (physiological, motor and cognitive); and (3) elaboration that defines the meaning of the stimulus and response. Emotions are defined as stored action dispositions, released when a fear structure is activated. Any response pattern depends on arousal level, valence of the stimuli, and degree of control.

Foa extended the ideas of Lang and Rachman and proposed a processing theory, hypothesizing that anxiety occurs as the result of a pathological "fear structure" held in memory [20-23]. A fear structure is a propositional network of information related to a program to escape or avoid danger.

From this perspective, in any systematic exposure therapy session, three important events occur. The first is activation of the fear structure in memory. The second is introduction of corrective information through repeated and prolonged exposure to the feared stimulus, leading to a modification of the fear structure, allowing habituation within the session. The third involves changes in the meaning of the activated fear structure. This change occurs between sessions and is more reliably associated with long-term therapeutic change.

Foa and McNally further revised the emotional processing approach in a more cognitive direction by suggesting that any successful exposure therapy goes beyond the mere modification of existing fear structures [23]. New structures are created, which override the previous associations.

In a more recent revision, Foa, Ruppert & Cahill proposed that symptom reduction is though modification of erroneous associations, not through habituation per se [24]. Accordingly we next examine habituation and extinction as the mechanisms used

to account for effectiveness of therapy.

Habituation

Habituation may be defined as the waning of a response to a stimulus that occurs when the stimulus is repeatedly presented [25]. In contrast to extinction, which is explained as associative learning, habituation is seen as non-associative learning. Habituation as used in stress neurobiology is conceptualized as reduction in physiological responses to a repeated stressor in comparison with initial response to the stressor [26]. In exposure therapy, habituation refers to reductions in fear over time as a person encounter fear-inducing stimuli [27, 28]. Habituation is often measured through physiological variables such as heart rate and skin conductance or through self-report measures such as the Subjective Unit of Distress (SUDS) [29].

Thompson indicated that the notion of habituation is as old as humankind but that experimental studies about habituation began at the end of nineteenth century and early twentieth century [30]. After reviewing the basic properties of habituation as described in classic works, Thompson refers to Thompson and Spencer's review in which nine basic parameters or common characteristics of habituation were identified [30, 31]. These parameters are mostly related to short-term or within - session habituation, emphasizing the importance of repetition, spontaneous recovery, frequency of stimulation, and generalization. Rankin et al. reviewed and revised some of the nine parameters of Thompson and Spencer and added an item that is mostly related to long-term habituation [31, 32]. They proposed that some stimulus repetition protocols might result in response decrement lasting hours, days or weeks, suggesting between session effects that are discussed in the next section.

The problem of within-and between session habituation

One of the main problems in the formulation and application of emotional processing based exposure therapy is the relation between what has been called within-session habituation to between-session habituation. Foa's initial position was that "The activation of affect, its reduction during exposure sessions, and its decrease across sessions, appear positively related to treatment outcome, denoting evocation and modification of fear memories during therapy" [24]. In most studies, however, a direct relationship between within-session habituation and symptom reduction has not been found [29].

Foa's group discussed this issue in their 2006 update [23]. They conclude that "within-session habituation is not a reliable indicator of emotional processing" and suggest that " some information may take time to be processed, such that disconfirming information that had been presented during exposure is not fully incorporated until some time after the exposure exercise (i.e., between sessions) rather than within the sessions"(p.9).

Foa and McLean further suggest that factors such as distraction and cognitive avoidance may interfere with full incorporation of new information in the structure of memory so that the true change in the structure of memory occurs after the exposure session [33]. Therefore, they propose a "full engagement with an exposure exercise" (without any distraction or cognitive avoidance) to reach a lasting outcome.

Reviewing the research on initial fear activation, within-session habituation, and between-session habituation, Craske et al. conclude that there is not any established relation between these indices and therapeutic outcome [34]. Their suggestion is that we need to move away from immediate fear reduction toward longer term fear tolerance as a primary goal of exposure therapy. As an explanation of exposure therapy they emphasize the inhibitory learning central to extinction as an alternative account of what happens in therapy. We now consider the concept of extinction.

Extinction

Extinction refers to the gradual weakening of an instrumental response that results in the behavior decreasing or disappearing. Extinction can occur if the trained behavior is no longer reinforced or if the type of reinforcement used is no longer rewarding.

As has been shown in extensive empirical work, extinction may be characterized as a form of inhibitory learning rather than an erasure of acquired fear [35]. In other words, it is not simply an unlearning or forgetting but rather a new process that changes the relation between the conditioned stimulus and the unconditioned stimulus. The amygdala has been suggested as the main area that controls such a process [36]. Another area active in extinction learning is the medial prefrontal cortex including the anterior cingulate cortex (ACC), thought to regulate the function of the amygdala [36]. The idea that exposure therapy is an automatic, low-level process, has been challenged and it is believed today that exposure therapy is based on extinction and involves many high-level cognitive elements [37].

In studies of mice, the ability to extinguish fear by extinction has been improved by a reinstatement procedure [38]. Reinstatement involves repeating a fear-inducing stimulus. If after such a reinstatement one introduces a drug that blocks norepinephrine (e.g. propranolol) or carries out extinction trials within a short period of time after reinstatement of the fear, the effectiveness in reducing fear is increased. A recent mouse study has found that stimulation of a circuit from the amygdala to the striatum either optogenetically or by inducing a reward may improve extinction of fear by reducing the tendency for it to spontaneously recover [39].

These findings in mice fit with the importance of the production of anxiety as a predictor of the effectiveness of exposure therapy in patients with OCD [33]. However, subsequent studies of patients with anxiety have shown that extinction may not always occur and we do not know if the reduction of fear by itself will result in improvement of the OCD symptoms [40]. However, the use of reinstatement or simultaneous stimulation of reward pathways may result in improvement of the existing exposure techniques as a treatment for OCD.

Neuroscience approaches to OCD

In the new classification of psychiatric disorders (DSM-5), OCD has been integrated within an obsessive-compulsive disorders spectrum (OCDS). Although some psychologists have criticized this approach, it has led investigators to pay more attention to the different kinds of OCD that may involve different biological mechanisms, including those involved in response prevention [41, 42]. Thus using the term OCD spectrum may be helpful both in research and clinical practice. Imaging studies have led to a better understanding of the regulatory mechanisms by which responses

are prevented and we discuss these mechanisms in relation to different OCD symptoms.

OCDSs in this new system have been characterized by three features:(1) compulsivity, which includes body dysmorphic disorder (BDD), anorexia nervosa (AN), hypochondrias is, and depersonalization disorder; (2) impulsivity, including sexual compulsions, self-injuring behavior, trichotillomania (obsessive hair pulling), kleptomania, compulsive buying, and pathological gambling (PG); and (3) OCDSs with significant neurological symptoms, including Sydenham's chorea, Tourette's syndrome (TS), and autism [43].

Graybiel and Rauch in search of a neurobiological basis for OCD have indicated some key features of OCD which makes their approach very similar to the concept of OCDSs [44]. They have mentioned five features summarized as follows:

- OCD patients are usually aware that their compulsions and obsessions are senseless, but they cannot control them despite effort;
- The symptoms usually are not bizarre;
- There is a considerable degree of consistency in the themes of OCD across cultures, with some degree of heterogeneity in specific symptoms;
- Some patients suffer mainly obsessions or compulsions and others both. In some cases the disorder shows itself as cognitive- affective and in others as executive- behavioral. The two concepts may in fact be related as executive attention serves as a control over affect [14, 45].
- The obsessions as thoughts, images and urges and the compulsions, including washing , cleaning, checking, and doing things right may continue for hours and the only way to stop them is to get enough assurance from others.

These features of OCD suggest that there are neural circuits that trigger repetitive and resistant behaviors and thoughts, and that most often the patient is aware of the existence of these intrusive events [44]. It is important to note that exposure therapy is not applicable for most of the conditions classified under the title of OCDSs. Abramowitz and Jacoby believe this is because "exposure is derived from a specific psychological mechanism involving excessive fear that is maintained by avoidance and ritualistic behavior [41]. This pattern is present in OCD and body dysmorphic disorder, but not in hair pulling, compulsive skin picking, or hoarding" (p.282).

Abramowitz and Jacoby discuss the use and misuse of exposure therapy in OCD and related disorders [41]. The aim of exposure is to facilitate extinction-related reduction in the conditioned anxiety/fear response associated with the feared stimulus. If this is the case, a broadened view of the disorder may help in developing additional treatment approaches to control obsession, impulsivity and compulsivity that are likely to share a common neurobiological basis [44]. Even in these cases, however, preventing response in the presence of relevant stimuli may be important.

Self-Regulation and OCD

One of the main problems in OCD seems to be related to an inhibitory mechanism reflected in the difficulty patients have in stopping the behavior or thoughts. Attention helps the individual to select stimuli that are most relevant and disregard or ignore irrelevant informational sources [46]. In set shifting and flexibility in problem solving, OCD patients show lower performance than controls [47-49]. This deficit is supported by a meta-analysis of 110 previous studies of OCD patients showing a broad impairment in executive functions [50]. The brain system most likely central to these deficits is the executive attention network that includes the anterior cingulate (ACC) and underlying striatum [14].

Compulsivity in OCD has also been associated with addiction. In a review article, Figee et al. demonstrated that compulsivity is not only a central feature of OCD but it is also a key element in addiction [49]. The term addiction in this context includes behavioral addiction along with non-drug - related disorders that have compulsivity as their common feature, such as pathological gambling, and compulsive eating or buying."Receptor-binding studies indicate hyperactivity of the striatal dopaminergic system in OCD, with decreased striatal availability of dopamine D1 receptors and D2-like receptors in [OCD] patients versus controls, which is also found in individuals with substance-use disorders and in some studies with obese patients"[49]. Compulsivity in addictions and OCD may both be related to negative reinforcement. Negative reinforcement in this case may involve avoidance or relief of many kinds of distress based on abnormalities in brain reward and anxiety circuits. The main brain areas responsible for this include bed nucleus stria terminals, amygdala, habenula and medial prefrontal cortex. Moreover, compulsivity in OCD and addictions entails cognitive and behavioral inflexibility, which may be rooted in a shared impairment of ACC and ventro medial prefrontal top-down regulation, along with serotonergic defects and excessive dopamine and glutamate signaling. Finally, habitual responding regardless of its consequences is an aspect of compulsivity that may be related to imbalances between ventral and dorsal frontostriatal activity [49]. As in addictions the OCD patient appears forced to carry out particular behaviors even when resistance is desired. By examining recent efforts to understand the neurobiology of addictive disorders we may gain some perspective on the diagnosis and treatment of OCD.

One view of addictions is to regard them as involving a deficit in self- regulation [51]. The ability to voluntarily regulate behavior including both emotion and memory retrieval has been thought to involve the executive attention network, including the anterior cingulate cortex [14, 51]. There is an anatomical distinction between more dorsal cingulate areas involved in cognitive control and more ventral areas related to emotion regulation [45, 51]. Brain systems of executive attention have been found to exercise control over both emotional and behavioral responses [14]. Abnormalities of these areas are clearly involved in OCD as recognized in meta-analyses of grey and white matter [52, 53].

It is known that craving for drugs often involves the limbic circuit, including the anterior cingulate and ventral striate cortex [54]. One recent study recruited smokers and nonsmokers who were interested in reducing stress. No mention was made of a desire to quit or reduce smoking. Smoking status was one of many variables assessed after recruitment. The study found that tobacco consumption was reduced by 60% in those smokers assigned to two weeks of meditation training, even among those not seeking to reduce smoking [55]. There was no change in smoking among those given relaxation training (the control).The mechanism for this

reduced smoking appears to involve less craving through a change in ventral ACC activity and connectivity to the striatum. Before training, smokers showed reduced activity in the ACC compared to non-smokers. After training, ACC activity and connectivity to the striatum was increased for those smokers assigned to meditation, but not for smokers in the control condition. The smokers' desire to quit smoking was unrelated to the reduction found in smoking behavior.

A meta-analysis of activation studies of OCD patients using functional imaging concludes that there is a consensus that a dysregulation of the frontostriatal circuit is involved in the psychopathology of OCD [8. 9]. A meta-analysis of resting state MRI data confirmed that compared to other anxiety disorders there was a unique abnormality in frontal-striatal pathways in OCD [56].

As with addictions, OCD has been reported to show abnormalities in functional connectivity between midline frontal areas, including connections between the ACC and striatum. However, unlike tobacco and some other addictions [57]. the abnormality sometimes appears as hyper- rather than hypo-connectivity [58]. This dramatic difference in connectivity and the absence of anxiety in early stages of addiction suggests that OCD might not be an addictive disorder despite the possibility of considering compulsive thoughts as being addictions.

The Tian et al. study showed that functional connectivity, that is the correlation among selected brain areas, is increased in patients with OCD compared to controls [58]. This finding suggests stronger connectivity between the ACC and striatum in OCD. However a meta-analysis of studies using Diffusion Tensor Imaging (DTI) to study abnormalities in this circuitry showed hypoconnectivity related to the dorsal more cognitive areas of the cingulate and hyperconnectivity to the more ventral emotional control areas [59]. Moreover altered white matter abnormalities in both hypo and hyper connectivity occurred more widely than just in the ACC striatal connections [59].

A later DTI study of 231 OCD patients compared to controls showed reduced Fractional Anisotropy (FA) thus indicating weaker connectivity of the ACC [60]. This finding was extended in a family based approach which had similar findings for un medicated OCD patients and their siblings compared to normal controls [61]. Another DTI study in children [62]. found reduced fractional anisotropy (FA), suggesting reduced connectivity in some of the same regions in which the Tian et al. study found stronger functional connectivity [58]. Overall, the findings indicate evidence for abnormal white matter in the cingulate to striate connections, but studies differ on whether the connections are stronger or weaker. It is certainly possible that some connections are stronger in OCD than controls while in others they are weaker. We discuss this possibility below.

While there remains uncertainty about the direction of the connectivity abnormalities in OCD, the studies are consistent with abnormal connectivity between the anterior cingulate and striatum in OCD patients. Recent meta-analysis studies of OCD patients have verified abnormalities in white and gray matter in the dorsal and ventral ACC [52, 53]. These findings are supported by another meta-analysis showing that problems in ACC connectivity with the striatum are central to the symptoms found in OCD [63].

The importance of the striatum and its connections has also been supported by the success of some forms of deep brain stimulation in treatments, which have generally targeted areas of the ventral striatum in efforts to relieve the symptoms of OCD [64].

In monkeys the ACC involves multiple connections to other brain areas including the ventrolateral prefrontal cortex which has been involved in the inhibition of motor and posterior areas in the go-no-go task [65].

A recent paper has examined the response of OCD patients to making an error. The study found that while patients showed a normal response to error, they were less likely than controls to slow their responses on the next trial. Thus in this study OCD patients seem to have impaired ability to control response output [66]. One paper has specified a specific cognitive role for the ACC in the etiology of OCD [63]. According to this view dysfunctioning of the ACC generates an inappropriate signal related to the expected value of stimuli, which favors the compulsion in comparison with long term goals. Over-valuation of stimuli related to the compulsion leads to repetitive behaviors by giving priority to stimuli related to the compulsion. This idea is compatible with an important role for the ACC in OCD and provides a possible explanation of that role.

Direction of connectivity

Another approach to ACC function is based on the idea that some pathways to and from the ACC are abnormal in connectivity. For example, pathways carrying information about compulsive events from the striatum (e.g. itching or dirty hands) could be hyper connected, while others such as used for slowing responses following an error could be hypoconnectivity (these pathways could be involved in controlling motor response of scratching or hand washing). We speculate based on the symptoms of OCD that medial frontal pathways involved in self-regulation may be hypoconnected, while those involved in frontal striatal loops are hyperconnected.

Even though more research is clearly needed regarding the direction of connectivity abnormalities in OCD found in various pathways, recent neurobiological studies might point the way toward methods of improving control of compulsive symptoms. Oligodendrocytes are involved in increasing connectivity though increased myelination. Thus activating oligodendrocytes as has been done with motor learning in mice could perhaps be used to increase connectivity and thus provide improved response prevention in OCD treatment [67]. Recent studies in mice and humans have shown improved connectivity following various forms of learning, providing some support for this possibility [68]. Other glial cells including the astrocytes have been implicated in remodeling connections through reduction of myelin [69]. Thus biological findings support the possibility of adjustments to both increase underconnectivity and reduce overconnectivity.

Since medial frontal pathways involved in self-regulation may be hypoconnected, while those involved in frontal striatal loops are hyperconnected, it is possible that methods can be constructed to improve both of these tendencies A preliminary report with OCD patients suggests that transcortical magnetic stimulation with a coil designed for deep stimulation and repeated 20 times per second induced EEG changes in the anterior cingulate and increased responses to error in the Stoop task [70]. If methods

could be found to carryout remodeling of myelin connections in humans, they might prove useful in the treatment of OCD by strengthening the mechanisms of self- regulation while reducing repetitive activation. Approaching OCD through changes in connectivity as suggested in this section, would not necessarily be incompatible with the view that the disorder involves errors in ACC computation of expected value [63].

Since the ACC to hippocampus pathway has been identified as a possible route for control of retrieval from memory, increased activity and connectivity of the ACC could result in improved ability to control obsessive thoughts as well as behaviors [71]. One caution about this approach, however, is that although theoretical models and empirical studies suggest that OCD is caused by functional and structural abnormalities in orbitofrontal and ACC to striatal circuits, there is also evidence that other brain areas may be involved [59,72].

Future directions for understanding the theoretical basis of psychological treatment of OCD

As stated earlier, exposure therapy and response prevention (ERP) involves a set of psychological treatment approaches and/or techniques for improving anxiety-related disorders, including OCD. The common core of these approaches and techniques is asking patients to confront their obsessive or fearful thoughts while controlling their response to the situation. Exposure therapy alone or in combination with response prevention has been identified as the first and most effective psychotherapy for some OCD patients and there is no doubt that Foa and her group has had enormous effect on the evaluation, treatment and investigation of OCD in the past 30 years [73]. The main problem with this set of approaches and techniques is its mechanisms of action on the one hand and the theory underlying this treatment approach on the other [13,74, 75]. By incorporating the neurobiological approaches this paper has attempted to both specify mechanisms and move toward an improved theory of treatment.

In all explanations the most characteristic feature of habituation has been identified as repetition of stimulation. But in exposure therapy in general and exposure therapy applied in OCD in particular, something new happens that goes beyond mere repetition or adaptation. It is the patient's deliberate and systematic confrontation with a supposedly threatening situation. That is, the patient is actively involved in the process of exposure therapy. First, the person wishes to be relieved of OCD symptoms and seeks help. Second, the patient trusts the therapist and generates positive expectations about the effects of therapy. Third, in CBT approaches, the patient is presented with a rationale for the ERP treatment and given assurances that the therapy will work.

These cognitive features and their emotional consequences have in part been addressed by an improved understanding of the mechanisms of attentional control of emotions, thoughts and behavior. Improved self-regulation may thus be a key to response prevention during exposure as well as between therapeutic sessions. The use of meditation training has proven effective in the control of some addictions and may be one of several mechanisms to foster improved response prevention.

We are still in need of a fully satisfactory theoretical and explanatory basis of exposure therapy. Although the new classification of an OCD spectrum may cause some practical problems for clinicians, it can also foster research on neurobiological and cognitive commonalities of different impulsive and compulsive disorders, providing us with new ways of looking at the nature and psychopathology of OCD. In this review we have found clear evidence of abnormal pathways involved in the disorder. These include the ACC and its connections to the striatum. Moreover, at least some results allow speculation concerning methods of improving self-regulation by altering connectivity. This work may help clinicians find new insights about treatment. Most importantly, moving in this direction of connecting cognition and neuroscience with exposure therapy may throw light on the whole area of psychopathology and phenomenology of disorders that involve difficulties in self-regulation [76].

*This work was begun by HG and evolved into the current paper while he served as a visitor at the University of Oregon Institute for Cognitive and Decision Sciences. We express our thanks to Prof. Dennis Galvan, Vice Provost for International affairs, and to Peter DeFazio, and Ron Wyden for their help in arranging this visit.

References

1. Rasmussen SA, Eisen JL (1992) The epidemiology and clinical features of obsessive-compulsive disorder. Psychiatric Clinics of North America 15: 743-758.
2. World Health Organization (1996) The global burden of disease. Geneva, WHO.
3. Weissman MM, Bland RC, Canino GJ, Greenwald S, Hwu HG, et al. (1994) The cross national epidemiology of obsessive-compulsive disorder. The cross National Collaborative Group. Journal of Clinical Psychiatry 55: 5-10.
4. Karno M, Golding JM, Sorenson SB, Burnam A (1988). The epidemiology of obsessive-compulsive disorder in five US communities. Arch Gen Psychiatry 45: 1094-1099.
5. Rasmussen SA, Eisen JL (1989) Clinical features and phenomenology of obsessive-compulsive disorder. Psychiatric Annals 19: 67-73.
6. Rasmussen SA, Eisen JL (1998) The epidemiology and clinical features of Obsessive-compulsive disorder. 15: 743-758. In MA Jenike, L Baer, and WE Minicheillo, (eds), Obsessive-compulsive disorders- Practical management. St. Louis, Mosby. 12-43.
7. American Psychiatric Association (2013) Diagnostic and Statistical Manual of Mental Disorders. 5 ed., Washington, DC: American Psychiatric Publishing.
8. Skapinakis P, Caldwell D, Hollingworth W, Bryden P, Fineberg N, et al. (2016) Pharmacological and interventions for management of obsessive-compulsive disorders: A systematic review and network meta-analysis. Lancet Psychiatry15: 1-10.
9. Skapinakis P, Caldwell D, Hollingworth W, Bryden P, Fineberg N, et al. (2016) A systematic review of the clinical effectiveness and cost-effectiveness of pharmacological and psychological interventions for the management of obsessive-compulsive disorder in children/adolescents and adults. Health Techno l Assess 20: 1-392.
10. Foa EB, Liebowitz MR, Kozak MJ, Davies S, Campeas R, et al. (2005) Treatment of obsessive-compulsive disorder by exposure and ritual prevention, clomipramine, and their combination: A randomized placebo controlled trial. American Journal of Psychiatry 162: 151-161.
11. Abramowitz JS, Taylor S, McKay D (2005). Potentials and limitations of cognitive treatment for obsessive-compulsive

disorder. Cognitive Behavior Therapy 34: 140-147.
12. Abramowitz JS (2006) The psychological treatment of obsessive-compulsive disorder. Can J Psychiatry 51: 407-416.
13. Abramowitz JS (2013) The practice of exposure therapy: relevance of cognitive- behavioral theory and extinction theory. Behavior Therapy 44: 548-558.
14. Petersen SE, Posner MI (2012). The Attention system of the human brain: 20 years after. Annual Review of Neuroscience 35: 73-89.
15. Meyer V (1966) Modification of expectations in cases with obsessional rituals. Behavior Research and Therapy 4: 273-80.
16. Meyer V, Levy R, Schnurer A (1974) A behavioral treatment of obsessive-compulsive disorders. In H. R. Beech (ed.), Obsessional states. London: Methuen.
17. Marks IM (1976) The current status of behavioral psychotherapy: Theory and practice. The American Journal of Psychiatry 133: 253-261.
18. Wolpe J (1973) The practice of behavior therapy. New York: Pergamon Press.
19. Rachman S, Hodgson R, Marks IM (1971) The treatment of chronic obsessive compulsive neurosis. Behavior Research and Therapy 9: 237-247.
20. Lang PJ (1977) Imagery in therapy: An information processing analysis of fear. Behavior Therapy 8: 862-886.
21. Lang PJ (1985) The cognitive psychophysiology of emotion: Fear and anxiety. In A H Turner, and J Maser (Eds.), Anxiety and the anxiety disorders. Hillsdale, NJ. : Lawrence Erlbaum 131-170.
22. Rachman S (1980) Emotional processing. Behavior Research and Therapy 18: 51-60.
23. Foa EB, McNally RJ (1996) Mechanisms of change in exposure therapy. In R.M. Rapee(Ed.), Current controversies in the anxiety disorders. New York: Guilford 329-343.
24. Foa EB, Huppert JD, Cahill SP (2006) Emotional processing theory-An update. In B.O. Rothbaum (Ed), Pathological anxiety: Emotional processing in etiology and treatment. New York: Guilford Press 3-24.
25. Watts FN (1979) Habituation model of systematic desensitization. P. Psychologica Bulletin 86: 627-637.
26. Grissom N, Bhatnagar S (2009) Habituation to repeated stress: get used to it. Neurobiol. Learn. Mem 92: 215-224.
27. Foa EB, Kozak MJ (1986) Emotional processing of fear: Exposure to corrective information. Psychological Bulletin 99: 20-35.
28. Marks IM, Dar E (2000) Fear reduction by psychotherapies-Recent findings and future directions. The British Journal of Psychiatry 176: 507-511.
29. Baker A, Mystkowski J, Culver N, Yi R, Mortazavi A, et al. (2010) Does habituation matter? Emotional processing theory and exposure therapy for acrophobia. Behavior Research and Therapy 48: 1139-1143.
30. Thompson RF (2009) Habituation: a history. Neurobiol. Learn. Mem 92: 127-134.
31. Thompson RF, Spencer WA (1966) Habituation: a model phenomenon for study of neuronal substrat of behavior. Psychol Rev 73: 16-43.
32. Rankin CH, Abrams T, Barry RJ, Bhatnagar S, Clayton DF, et al. (2009) Habituation revisited: an updated and revised description of the behavioral characteristics of habituation. Neurobiology. Learn. Mem 92: 135-138.
33. Foa EB, McLean CP (2016) The efficacy of exposure therapy for anxiety- related disorders and its underlying mechanisms: The case of OCD and PTSD. Ann Rev of Clinical Psychology 12: 1-28.
34. Craske OG, KIrcanski K, Zelikowsky M, Mystkowski J, Chowdhury N, et al. (2008) Optimizing inhibitory learning during exposure therapy. Behavior Research and Therapy 46: 5-27.
35. Myers KM, Davis M (2007) Mechanisms of fear extinction. Mol. Psychiatry 12: 120-150.
36. Phelps EA, Mauricio R. Delgado MR, Nearing KI, Ledoux JE, (2004) Extinction Learning in Humans: Role of the Amygdala and vm PFC. Neuron 43: 897-906.
37. Hoffman SG (2008) Cognitive processes during fear acquisition and extinction in animals and humans-Implications for exposure therapy of anxiety disorders. Clinical Psychology Review 28: 199-210.
38. Schiller D, Kanen JW, LeDoux JE, Monfils MH, Phelps EA (2013) Extinction during reconsolidation of threat memory diminishes prefrontal cortex involvement Proceedings of the US National Academy of Science 110: 20040-20045.
39. Correia SS, McGrath AG, Lee A, Graybiel AM, Gossens KA (2016) Amygdala- ventral striatum circuit activation decreases long-term fear. E Life 5: 12669.
40. Klkucken T, Kruse O, Schweckendiek J, Kuepper Y, Mueller EM et al. (2016) No evidence for blocking the return of fear by disuprting reconsiolidation prior to extinction learning. Cortex 79: 112-122.
41. Abramowitz JS, Jacoby RJ (2014) The use and misuse of exposure therapy for obsessive-compulsive and related disorders. Current Psychiatry Review 10: 277-283.
42. Storch EA, Abramowitz JS, Goodman WK (2008) Where does obsessive-compulsive disorder belong in DSM-V? Depression and Anxiety 4: 336-347.
43. Hollander E, Evers M (2004) Review of obsessive-compulsive spectrum disorders: What do we know ? Where are we go? Clinical Neuropsychiatry 1: 32-51.
44. Graybiel AM, Rauch SL (2000) Toward a neurobiology review of obsessive- compulsive disorder. Neuron 28: 343-347.
45. Bush G, Luu P, Posner MI (2000) Cognitive and emotional influences in the anterior cingulate cortex. Trends in Cognitive Sciences 4: 215-222.
46. Muller J, Roberts J (2005) Memory and attention in obsessive–compulsive disorder: A review. Anxiety Disorders 19: 1-28.
47. Evans D, Lewis MD, Iobst E (2004) The Role of the orbito-frontal cortex in normally developing compulsive-like behaviors and obsessive- compulsive disorder. Brain and Cognition 55: 220-234.
48. Ghassemzadeh H, Mojtabai R, Karamghadiri N, Noroozian M, Sharifi V, et al. (2012) Neuropsychological and neurological deficits in obsessive-compulsive disorder: The role of comorbid depression,International Journal of Clinical Medicine 3: 200-210.
49. Figee M, Pattij T, Willuhn I, Luigjes J, van den Brink W, et al. (2016) Compulsivity in obsessive- compulsive disorder and addictions. European Neuro psycho pharmacology 26: 856-868.
50. Snyder H, Kaiser R, Warren S. Heller W. (2015) Obsessive-Compulsive Disorder Is Associated With Broad Impairments in Executive Function: A Meta-Analysis. Clinical Psychological Science. Clinical Psychological Science; 3: 301–330.
51. Tang YY, Posner MI, Rothbart MK, Volkkow ND (2015) Circuitry of self control and its role in reducing addiction. Trends in Cognitive Sciences 19: 439-445.
52. Eng GK, Sim K, Chen A (2015) Meta-analytic investigations of structural grey matter, executive domain-related functional

activations, and white matter diffusivity in obsessive compulsive disorder: An integrative review. Neuroscience and Biobehavioral Reviews 52: 233-257.
53. Magioncalda P, Martino M, Ely BA, Inglese M, Stern ER (2016) Micro structural white-matter abnormalities and their relationship with cognitive dysfunction in obsessive-compulsive disorder. Brain and Behavior 6: e00442.
54. Jasinska AJ, Stein EA, Kaiser J, Naumer MJ, Yalachkov Y (2014) Factors modulating neural reactivity to drug cues in addiction: a survey of human neuroimaging studies. NeurosciBiobehavior 38: 1-16.
55. Tang YY, Tang R, Posner MI (2013) Brief meditation training induces smoking reduction. Proceedings of the US National Academy 110: 13971-13975.
56. Petereson A, Thome J, Frewen P, Lanius RA (2014) Resting-state neuroimaging studies: a new way of identifying differences and similarities among the anxiety disorders. Canadian Journal of Psychiatry 59: 294-300.
57. Hong LE, Gu H, YangY, Ross TJ, Salmeron BJ, et al. (2009) Association of nicotine addiction and nicotine's actions with separate cingulate cortex functional circuits. Arch Gen Psychiatry 66: 431- 441.
58. Tian L, Meng C, Jiang Y, Tang Q, Wang S, et al. (2016) Abnormal functional connectivity of brain network hubs associated with symptom severity in treatment-naive patients with obsessive–compulsive disorder: A resting-state functional MRI study. Progress in Neuro- Psychopharmacology & Biological Psychiatry 66: 104-111.
59. Piras F, Piras F, Caltagirone C, Spalletta G (2013) Brain circuitries of obsessive compulsive disorder: A systematic review and meta-analysis of diffusion tensor imaging studies. Neuroscience and Biobehavioral Reviews 37: 2856-2877.
60. Radua J, Grau M, van den Heuvel OA, Thiebuatmde Schotten M, Stein DJ, et al. (2014) Multimodal voxel-based meta-analysis of white matter abnormalities in obsessive-compulsive disorder. Neuropsychopharmacology 39: 1547-1557.
61. Fan S, van den Heuvel OA, Cath DC, van deer Werf Y, de Wit S, et al. (2015) Mild white matter changes in un-medicated obsessive-compulsive disorder patients and their unaffected siblings. Human Fronties 9: 495.
62. Rosso IM, Olson EA, Britton JC, Stewart SE, Papadimitriou G, et al. (2014) Brain white matter integrity and association with age at onset in pediatric obsessive-compulsive disorder. Biology of Mood and Anxiety Disorders 4: 1-10.
63. McGovern RAk, Sheth SA (2016) Role of the dorsal anterior cingulate cortex in obsessive-compulsive disorder: converging evidence from cognitive neuroscience and psychiatric neurosurgery Journal of Neurosurgery, Ahead of Print : 1-16.
64. Alonso P, Cuadras D, Gabriëls L, Denys D, Goodman W, et al (2015) Deep Brain Stimulation for Obsessive- Compulsive Disorder: A Meta-Analysis of Treatment Outcome and Predictors of response 10: e0133591.
65. Medalla M, Barbas H (2010) Anterior cingulate synapses in prefrontal areas 10 and 46suggest differential influence in cognitive control. Journal of Neuroscience 30: 16068-16081.
66. Agram Y, Greenberg JL, Isom M, Falkenstein MJ, Jenike E, et al. (2014) Aberrant error processing in relation to symptom severity in obsessive – compulsive disorder: A multimodal neuroimaging study. 17: 141-151.
67. McKenzie IA, Ohayon D, Li H, De Faria, JP Emery B, et al. (2014) Motor skill learning requires active central myelination. Science 346: 318-322.
68. Wang S, Young KM (2014) White matter plasticity in adulthood. Neuroscience 276: 148-160.
69. Fields RD (2016) Oligodendrocyte and myelin plasticity in information processing and learning. Paper presented at the Virtual Neuroscience Conference on White Matter.
70. Harrison P (2016) High-frequency, deep TMS offers novel approach to OCD Medscape.
71. Anderson MC, Bunce JG, Barbas H (2016) Prefrontal–hippocampal pathways underlying inhibitory control overmemory. Neurobiology of Learning and Memory 134: 145-161
72. Menzies L, Chamberlain SR, Laird AR, Thelen SM, Sahakian BJ, et al. (2008) Integrating evidence from neuro imaging and neuropsychological studies of obsessive-compulsive disorder: The orbitofronto-striatal model revisited. Neuroscience and Bio behavioral Reviews 32: 525-549.
73. Kozak MJ, Coles ME (2005) Treatment for OCD: Unleashing the power of exposure. In JS. Abramowitz and AC.Houts, Concepts and controversies in obsessive-compulsive disorder.293-304.
74. McNally RJ (2007) Mechanisms of exposure therapy: How neuroscience can improve psychological treatments for anxiety disorders. Clinical Psychology Review 27: 750-759.
75. MacLeod C, Mathews A (2012) Cognitive bias modification approaches to anxiety. Annual Review of Clinical Psychology 8: 189-217.
76. Wolpe J (1973) The practice of behavior therapy. New York: Pergamon Press.