Journal of Neurodevelopmental Cognition

Journal of Neurodevelopmental Cognition 2 (2022) 110-116
ISSN: 2645-565X
http://jncog.sbu.ac.ir/

10.29252/JNCOG.2022.103445

Animal models of Obsessive-Compulsive Disorder (OCD)

Mohammad Nabizadeh[a,*], Fariba Ahmadi[b]

[a] *Faculty of Psychology, Isfahan University, Isfahan, Iran*
[b] *Faculty of Psychology, University of Science and Research in Tehran, Tehran, Iran*

Abstract

Treatment developments, brain imaging studies and results of pharmacological researches elicit revision of related pathological theories to Obsessive-compulsive disorder (OCD) and new research patterns. One of the important and alluring new research patterns under neurobiological approach corresponding to pathology and treatment of obsessive-compulsive disorder (OCD) are animal models which are used in this disorder. Insomuch, many endeavors have been applied in order to expand animal models of OCD during recent 30 years. In the hope of, increase our understanding and knowledge about pathology as well as treatment of this disorder. By considering the methodology of developing obsessive behaviors in animals, OCD animal models are divided into three classifications of behavioral, pharmacological and genetic. Researches and studies by using different animal models indicate the role of serotonin neurotransmitter particularly 5-HT2c receptor, Dopamine neurotransmitter particularly D1 and D2 receptors and at the less level the role of NMDA receptor of Glutamate neurotransmitter in pathology of OCD disorder.

Keywords: Obsessive-compulsive disorder, Animal models, Behavioral models, Pharmacological models, Genetic models.

1. Introduction

More than 300 years, the syndrome of Obsessive-compulsive disorder (OCD) is known [12]. Early explanations in regard of this disorder focused on different aspects of syndrome while reflected dominated culture of researchers whereas the explanations of English researchers emphasized on religious

* Corresponding author
Email addresses: Mo.Nabizadeh26@gmail.com (Mohammad Nabizadeh), m.ahmadi3366@yahoo.com (Fariba Ahmadi)

CC BY OPEN ACCESS

Received: Novemver 2022 *Revised:* December 2022

aspects and relations to melancholy [25]. Corresponding to this disorder, the French phenomenologists emphasized on the importance of doubt and losing own will [32, 14] and German scope was concentrated on non-logical nature of thoughts and regarded this disorder as psychosis [47]. But generally, main features of Obsessive-compulsive disorder (OCD) are symptoms of obsession and compulsion which their intensities are enough to create significant discomfort for a person. Obsession and compulsion are time consuming and intervene obviously in daily and job related functions, conventional social activities or relationships. A person with OCD may bear obsession, compulsion or a composite form of both. Obsession is a bothering and repeatable thought, feeling, idea or sensation.

Compulsion is a self-conscious, adjusted, repeatable similar to counting or avoidance. Obsession causes increase of anxiety in people whereas compulsion leads to decrease in anxiety. Nevertheless, when a person resists against compulsion also increases person's anxiety. A person with obsessive-compulsive disorder usually understands his/her own non-logical obsessive thoughts. Both obsession and compulsion are known to be ego-dystonic for ill person [36].

If obsessive-compulsive disorder (OCD) is left without treatment, it will become chronic. Obsessive thoughts are very disconsolate and compulsive behaviors are very time consuming and non-adaptive. Thus, people with this disorder are psychologically very distracted [21, 34].

It seems that obsessive-compulsive disorder is diagnosed and treated among all age groups [11]. Research indicates that this disorder afflicts two to three percent of the society [9, 53] and often is accompanied by other psychological disorders such as depression, phobia, panic attacks and generalized anxiety disorder which make its treatment complicated [22] while some disorders including mood disorders, attention deficit hyperactivity disorder (ADHD), conduct disorder, oppositional defiant disorder in children with obsessive-compulsive disorder are also observed [11, 48, 39, 43].

Treatment developments, brain imaging studies and results of pharmacological researches elicit revision of related pathological theories to obsessive-compulsive disorder (OCD) and new research patterns. Insomuch that particularly during two recent decades pathological theory of OCD from being a psychodynamics conflict throughout twentieth century tends to consider OCD as a psychiatric nervous illness along with basic biological nerve disorder [5]. Relevant biological reports to OCD were seeking total deficits in specified areas of brain or seeking pathology of OCD under the differences among neurotransmitters. Those studies were particularly concentrated on Serotonin neurotransmitter which contributes in regulation of disposition, emotion, sleep and appetite as well as regulating additional physiological and behavioral functions. Findings that Serotonin reuptake inhibitors medicines (SSRIs) are effective in decreasing these symptoms lead to a primary theory in relation to OCD pathology based on probability of disorder in Serotonin neurotransmitter [49]. Relevant to this theory, researches such as Insel et al study (1985) and Zohar et al study (1988) reported different levels of Serotonin in OCD [29, 54]. A new, important and interesting research pattern included a neurobiological approach in regard of OCD pathology and treatment is animal models which are used in this disorder. Insomuch, many endeavors have been applied in order to expand animal models of OCD during recent 30 years. In the hope of, increase our understanding and knowledge about pathology as well as treatment of this disorder [20]. Hence, by considering mentioned issues in this article, it is tried that animal models to be assessed and studied.

2. OCD animal models

Considering the methodology of developing obsessive behavior in animals, OCD animal models can be divided into three groups of behavioral, pharmacological and genetic models. Most of these models have been studied broadly [15, 13, 23, 50].

2.1. Behavioral models

Most of the animal models are included in this group. This class is divided into repetitive and stereotype behaviors such as chasing own tail, chewing and weaving [13, 50, 37], inhered dynamic behaviors which are arisen for animal during conflict, deprivation and stress. Shift behaviors such as care, clean and peck [13, 50, 33, 31] or following some skill oriented behaviors (Auxiliary behaviors) such as planned persistent thirst and hyperactivity arisen of foodstuff limitation [51, 1] and learned behaviors which are adulterated to become compulsory behaviors such as pushing lever that caused by signal attenuation rat model of OCD [16] (Under this model, pushing lever by animal at primary stages is with prize and food but at the next stages, the same will be without any prize and food).

2.2. Pharmacological models

OCD pharmacological models are based on behavioral changes that are caused by medicines which are similar to some of the especial behavioral features of people who have OCD such as insistence, uncertainty and compulsory rechecking [52, 6, 40]. In addition to behavioral similarity, the arisen function due to adulteration of neurotransmitters' systems implies semi-obsessive behaviors. As in developed model by Yadin et al (1991), after adulterating serotonergic neurotransmitter system; insistence behavior was developed [52]. Furthermore, compulsory rechecking behavior in Szechtman et al model (2001) was developed by adulterating dopaminergic transmitter system [6, 40]. A SSRI medicine was assessed in both of above mentioned models. In Yadin et al model (1991), impacts of Fluoxetine and clomipramine medicines were assessed while in Szechtman et al model (1998), impacts of Clomipramine medicine [52, 8, 41].

2.3. Genetic models

At the moment, five OCD mouse models are included in this category as: the D1CT-7 transgenic mouse model of comorbid OCD and TS (Tourette's syndrome), the mutant mouse Hoxb8 model of trichotillomania, the SAP90/PSD95-associated protein 3 (SAPAP3), the 5-HT2C receptor knockout mouse model of OCD and the DAT knockdown mouse model of OCD and TS [2, 4, 46, 10, 28, 26]. It is important to consider that 5 above mention genetic models are not fulfilled the concept which is pointed by Matthysse (1986) meaning that to be based on known human mutant in relation to OCD [24], but these models are based on behavioral similarities of genetically modified mice with specified aspects of OCD ill ones. The same OCD behavioral similarity is the main foundation of these animal models in dealing with disorder. Unfortunately, there are a few reports regarding impacts of different pharmacological treatments which can indicate relevant of these models with OCD disorder (Except SAPAP3 model which is an exception in this case). Another problem in regard of at least some of these models is that the mutant mice usually show those neurological and behavioral disorders which are not related to OCD. For example, the mice which their 5HT2c receptor is become ineffective are fat and big while eating satisfaction mechanisms are upset in these mice. Those mice show neurological and behavioral disorders which may be related to their addiction to cocaine and Alzheimer's disease [45, 30, 42, 35]. In the same way, some of these models include self-harms which usually are not seen in human OCD disorder. Hence, it seems unlikely that these genetic models can be OCD ones. Although, it is obvious that such a OCD genetic models may help us in knowledge and understanding of specified genes and proteins roles in obsessive behaviors [20]. In the following of this article, we will assess some studies of OCD animal model which are classified into three classes of behavioral, pharmacological and genetic models.

3. Corresponding studies and researches to OCD animal models

Chou-Green et al (2003) in their study of a mouse that its 5-HT2C receptor (One of the post-synaptic receptors of serotonin neurotransmitter) has been knockout and primarily described as a model for obesity disease concluded that ineffectiveness of 5-HT2C receptor generates a pattern for obsessive behavior in the mouse. This study pointed to the role of 5-HT2C receptor in compulsive behavior pathophysiological, although the credibility of this model's prediction for OCD is not evaluated correctly [4]. Tsaltas et al (2005) by using a behavioral model featuring emphasize on insistence (repetition) in award taking periods of time, concluded that 5-HT2C receptor contributes in the main mechanism of compulsive behavior [44].

Joel and Avisar (2001) developed a mouse model based on the hypothesis that insufficient (deficient) response feedback mechanism is a ground for obsessive and compulsive compulsion [17]. By using this model, Joel et al (2005) found that damages on orbital frontal cortex of mouse lead to compulsive compulsion in pushing the lever. While is parallel to increase in density of 5 – HT (Serotonin) neurotransmitter of striatal [19]. This change indicates that in this model, the compulsive behavior is accompanied with changes in striatal serotonergic system. Based on electrophysiological data, Joel and Doljansky (2003) have reported that corresponding compulsive compulsion to pushing the lever is related to aggressive neurotic stimulation of D1 receptors (One of the subgroups of Dopamine neurotransmitter receptors) [18]. Campbell et al (1999) studied the behavioral subsequences of transgenic stimulation in Dopamine subgroup neurons which is indicator of D1 receptor within cortex and amygdala on intracellular cholera toxin (CT) mice. This study reports that persistent stimulation of these neurons including D1 causes a complicated obsessive behavior that is similar to OCD symptoms in human [26]. Furthermore, Campbell et al (2000) reported that persistent stimulation of those neurons including D1 of cortical and limbic part of brain may cause obsessive and compulsive behaviors [3]. In Einat and Szechtman animal model (1995) for OCD where the mice were examined persistently with Quinpirole (QNP) selective agonist of D2/3 receptor (which are subgroups of receptors of Dopamine neurotransmitter), a set of ritual-like behaviors similar to obsessive-compulsive disorder checking behavior have been observed [40, 7]. Analysis was conducted after death of mouse and indicates increase in levels of Dopamine in Nucleus Accumbens and right prefrontal cortex of brain [38]. Confirmed to results of this study, Zor et al (2009) also observed that ritual behaviors such as increase in irrelevant and unnecessary functions in OCD events are related to increase of Dopamine function within nucleus Accumbens and right prefrontal cortex of brain [55]. Finally, McGrath et al (2000) in their transgenic mouse model comorbid TS (Tourette's syndrome) and OCD indicated that MK-801 that is a non-competitive antagonist of NMDA receptor (One of types of Glutamate neurotransmitter receptors) which indirectly stimulates the production of cortico-limbic glutamate increases abnormal behavior of transgenic repeated jumps and ascending up [27].

4. Conclusion

Treatment progresses, brain medical imaging studies and results of pharmacological researches lead to reviewing OCD pathological theories and developing new research patterns. Insomuch that particularly during the recent two decades pathological theory of OCD from being a psychodynamics conflict throughout twentieth century tends to consider OCD as a psychiatric nervous illness along with basic biological nerve disorder [5]. One of the important and alluring new research patterns under neurobiological approach corresponding to pathology and treatment of obsessive-compulsive disorder (OCD) are animal models which are used in this disorder. Insomuch, many endeavors have been applied in order to expand animal models of OCD during recent 30 years. In the hope of, increase our understanding and knowledge about pathology as well as treatment of this disorder [20].

Hence, by considering mentioned issues in this article, it is tried that animal models to be assessed and studied.

Considering the methodology of developing obsessive behavior in animals, OCD animal models can be divided into three groups of behavioral, pharmacological and genetic models [15, 13, 23, 50]. Behavioral OCD models are mostly divided into repetitive and stereotype behaviors such as chasing own tail, chewing and weaving [13, 50, 37], inhered dynamic behaviors which are arisen for animal during conflict, deprivation and stress. Shift behaviors such as care, clean and peck [13, 50, 33, 31] and learned behaviors which are adulterated to become compulsory behaviors. OCD pharmacological models are based on behavioral changes that are caused by medicines which are similar to some of the especial behavioral features of people who have OCD such as insistence, uncertainty and compulsory rechecking [52, 6, 40]. In addition to behavioral similarity, the arisen function due to adulteration of neurotransmitters' systems in pharmacological models implies semi-obsessive behaviors. and at the moment, five OCD mouse models are included in genetic animal models as: the D1CT-7 transgenic mouse model of comorbid OCD and TS (Tourette's syndrome), the mutant mouse Hoxb8 model of trichotillomania, the SAP90/PSD95-associated protein 3 (SAPAP3), the 5-HT2C receptor knockout mouse model of OCD and the DAT knockdown mouse model of OCD and TS (Tourette's syndrome) [2, 4, 46, 10, 28, 26]. Researches and studies by using different animal models generally indicate the role of serotonin neurotransmitter particularly 5-HT2c receptor, Dopamine neurotransmitter particularly D1 and D2 receptors and at the less level the role of NMDA receptor of Glutamate neurotransmitter in pathology of OCD disorder. Some of the relevant researches and studies are: Chou-Green et al (2003), Tsaltas et al (2005), Joel and Avisar (2001), Joel et al (2005), Joel and Doljansky (2003), Campbell et al (1999), Campbell et al (2000), Einat and Szechtman (1995), Szechtman et al (2001), Sullivan et al (1998) , Zor et al (2009), McGrath et al (2000) and Yadin et al (1991).

References

[1] M. Altemus, J. R. Glowa, E. Galliven, Y. M. Leong, and D. L. Murphy. Effects of serotonergic agents on food-restriction-induced hyperactivity. *Pharmacol Biochem Behav*, 53:123–131, 1996.

[2] K. C. Berridge, J. W. Aldridge, K. R. Houchard, and X. Zhuang. Sequential superstereotypy of an instinctive fixed action pattern in hyper-dopaminergic mutant mice: a model of obsessive compulsive disorder and tourette's. *BMC Biology*, 36:1–16, 2004.

[3] K. M. Campbell, M. B. Veldman, M. J. McGrath, and F. H. Burton. TS+OCD-like neuropotentiated mice are supersensitive to seizure induction. *Neuroreport.*, 11:2335–2338, 2000.

[4] J. M. Chou-Green, T. D. Holscher, M. F. Dallman, and S. F. Akana. Compulsive behavior in the 5-HT2C receptor knockout mouse. *Physiol Behav*, 37:641–649, 2003.

[5] V. Eapen. *Obsessive compulsive disorder, current unders tanding and future directions. Genetics of OCD: current understanding and future directions.* National Institute of Mental Health and Neuro Sciences, Bangalore, India, 2007.

[6] D. Eilam and H. Szechtman. Towards an animal model of obsessive–compulsive disorder (ocd): Sensitization to dopamine agonist quinpirole. *Soc Neurosci Abstr*, 21:192, 1995.

[7] H. Einat and H. Szechtman. Perseveration without hyperlocomotion in a spontaneous alternation task in rats sensitized to the dopamine agonist quinpirole. *Physiol Behav*, 57:55–59, 1995.

[8] A. Fernandez-Guasti, R. E. Ulloa, and H. Nicolini. Age differences in the sensitivity to clomipramine in an animal model of obsessive–compulsive disorder. *Psychopharmacology (Berl)*, 166:195–201, 2003.

[9] K. Gournay. Assessment and management of obsessive compulsive disorder. *Nursing Standard*, 20:59–65, 2006.

[10] J. M. Greer and M. R. Capecchi. Hoxb8 is required for normal grooming behavior in mice. *Neuron*, 33:23–34, 2002.

[11] I. Heyman, E. Fombonne, H. Simmons, T. Ford, H. Meltzer, and R. Goodman. Prevalence of obsessive-compulsive disorder in the British nationwide survey of child mental health. *The British Journal of Psychiatry*, 179:324–329, 2003.

[12] R. Hunter and I. MacAlpine. *Three Hundred Years of Psychiatry*. Oxford University Press, London, 1963.
[13] T. R. Insel, J. Mos, and B. Olivier. *Animal models of obsessive compulsive disorder: A review . In Hollander , E. , Zohar , J. , Marazzitti , D. , and Olivier , B.(eds.) , Current Insights in Obsessive Compulsive Disorder*. John Wiley & Sons , Chichester, 1994.
[14] P. Janet. *Les Obsessions et la Psychasthenie*. BaillieÁre, Paris, 1903.
[15] D. Joel. Current animal models of obsessive compulsive disorder: a critical review. *Prog Neuropsychopharmacol Biol Psychiat*, 30:374–388, 2006.
[16] D. Joel. The signal attenuation rat model of obsessive–compulsive disorder: a review. *Psychopharmacology*, 186:487–503, 2006.
[17] D. Joel and A. Avisar. Excessive lever pressing following post-training signal attenuation in rats: a possible animal model of obsessive compulsive disorder? *Behav Brain Res.*, 123:77–87, 2001.
[18] D. Joel and J. Doljansky. Selective alleviation of compulsive lever-pressing in rats by D1, but not D2, blockade: possible implications for the involvement of D1 receptors in obsessive-compulsive disorder. *Neuropsychopharmacology*, 28:77–85, 2003.
[19] D. Joel, J. Doljansky, and D. Schiller. 'compulsive' lever pressing in rats is enhanced following lesions to the orbital cortex, but not to the basolateral nucleus of the amygdala or to the dorsal medial prefrontal cortex. *Eur J Neurosci.*, 21:2252–2262, 2005.
[20] D. Joel, D. J. Stein, and R. Schreiber. *Animal Models of Obsessive–Compulsive Disorder: From Bench to Bedside via Endophenotypes and Biomarkers ; Animal and Translational Models for CNS Drug Discovery: Psychiatric Disorders*. Elsevier Inc, 2008.
[21] M. Karno and JM. Golding. *obsessive compulsive disorder. In L.R. Robins & D.A.Regier, Psychiatric disorders in America: The epidiologic Catchment area study*. New York: Maxwell Macmillan International, 1991.
[22] M. L. Keeley, E. A. Storch, L. J. Merlo, and G. R. Geffken. Clinical predictors of response to cognitive-behavioral therapy for obsessive–compulsive disorder. *Clinical Psychology Review*, 28:118–130, 2008.
[23] S. Korff and B. H. Harvey. Animal models of obsessive-compulsive disorder: rationale to understanding psychobiology and pharmacology. *Psychiat Clin North Am*, 29:371–390, 2006.
[24] S. Matthysse. Animal models in psychiatric research. *Prog Brain Res*, 65:259–270, 1986.
[25] H. Maudsley. *The Pathology of the Mind*. Macmillan, London, 1958.
[26] K. M. MCampbell, L. de Lecea, D. M. Severynse, M. G. Caron, M. J. McGrath, S. B. Sparber, L. Y. Sun, and F. H. Burton. OCD-like behaviors caused by a neuropotentiating transgene targeted to cortical and limbic D1 neurons. *J Neurosci*, 19:5044–5053, 1999.
[27] M. J. McGrath, K. M. Campbell, C. R. Parks, and F. H. Burton. Glutamatergic drugs exacerbate symptomatic behavior in a transgenic model of comorbid tourette's syndrome and obsessive–compulsive disorder. *Brain Research*, 877:23–30, 2000.
[28] M. J. McGrath, K. M. Campbell, M. B. Veldman, and F. H. Burton. Anxiety in a transgenic mouse model of cortical-limbic neuro-potentiated compulsive behavior. *Behav Pharmacol*, 10:435–443, 1999.
[29] T. R. MInsel, E. A. Mueller, I. Alterman, M. Linnoila, and D. L. Murphy. Obsessive-compulsive disorder and serotonin: is there a connection? *Biological Psychiatry*, 20:1174–1188, 1985.
[30] K. Nonogaki, A. M. Strack, M. F. Dallman, and L. H. Tecott. Leptin-independent hyperphagia and type 2 diabetes in mice with a mutated serotonin 5-HT2C receptor gene. *Nat Med*, 4:1152–1156, 1998.
[31] R. K. Pitman. *Historical considerations . In Zohar , J. , Insel , T. , and Rasmussen, S.(eds.) , The Psychobiology of Obsessive–Compulsive Disorder*. Springer Publishing Company , New York, 1991.
[32] T. Ribot. *Les Maladies de la VolonteÁ*. Alcan, Paris, 1904.
[33] J. N. Ricciardi and J. Hurley. *Development of animal models of obsessive–compulsive disorders . In Jenike , M.A., Baer , L., and Minichiello , W.E.(eds.) , Obsessive–Compulsive Disorders: Theory and Management*. Year Book Medical Publishers, Inc, Chicago, 1990.
[34] L. N. Robins, J. E. Helzer, M. M. Weissman, H. Orvaschel, E. Gruenberg, J. D. Burke, and D. A. Reigier. Life time prevalence of specific psychiatric disorders in three sites. *Archives of General psychiatry*, 41:949–958, 1984.
[35] B. A. Rocha, E. H. Goulding, L. E. O'Dell, A. N. Mead, N. G. Coufal, and L. H. Parsons. Tecott, enhanced locomotor, reinforcing, and neurochemical effects of cocaine in serotonin 5-hydroxytryptamine 2C receptor mutant mice. *J Neurosci*, 22:10039– 10045, 2002.
[36] B. Sadock and V. Sadock. Synopsis of psychiatry: behavioral sciences - clinical psychiatry. *Volume II.Tehran: Shahrab, AyandehSazan*, page 221, 2003.
[37] D. J. Stein, N. H. Dodman, P. Borchelt, and E. Hollander. Behavioral disorders in veterinary practice: relevance to psychiatry. *Compr Psychiat*, 35:275–285, 1994.
[38] R. M. Sullivan, H. Talangbayan, H. Einat, and H. Szechtman. Effects of quinpirole on central dopamine systems

in sensitized and non-sensitized rats. *Neuroscience*, 83:781–789, 1998.

[39] SE. Swedo and JL. Rapoport. *Phenomenology and differential diagnosis of obsessive-compulsive disorder. Rapoport JL. Obsessive compulsive disorder in children and adolescents.* Washington, DC: American Psychiatric Press, 1989.

[40] H. Szechtman, M. J. Eckert, W. S. Tse, J. T. Boersma, C. A. Bonura, J. Z. McClelland, K. E. Culver, and D. Eilam. Compulsive checking behavior of quinpirole-sensitized rats as an animal model of obsessive–compulsive disorder(OCD): form and control. *BMC Neurosci*, 33:4, 2001.

[41] H. Szechtman, W. Sulis, and D. Eilam. Quinpirole induces compulsive checking behavior in rats: a potential animal model of obsessive–compulsive disorder (OCD). *Behav Neurosci*, 112:1475–1485, 1998.

[42] L. H. Tecott, S. F. Logue, J. M. Wehner, and J. A. Kauer. Perturbed dentate gyrus function in serotonin 5-HT2C receptor mutant mice. *Proc Natl Acad Sci*, 95:15026–15031, 1998.

[43] PH. Thomsen. *From thoughts to obsessions: obsessive compulsive disorders in children and adolescents.* Jessica Kingsley Publishers, 1999.

[44] E. Tsaltas, D. Kontis, S. Chrysikakou, H. Giannoua, A. Bibac, S. Pallidiet, and et al. Reinforced spatial alternation as an animal model of obsessive-compulsive disorder (OCD): investigation of 5-HT2C and 5-HT1D receptor involvement in OCD pathophysiology. *Biol Psychiatry*, 57:1176–1185, 2005.

[45] S. P. Vickers, P. G. Clifton, C. T. Dourish, and L. H. Tecott. Reduced satiating effect of d-fenfl uramine in serotonin 5-HT(2C) receptor mutant mice. *Psychopharmacology (Berl)*, 143:309–314, 1999.

[46] J. M. Welch, J. Lu, R. M. Rodriguiz, N. C. Trotta, J. Peca, J. D. Ding, C. Feliciano, M. Chen, J. P. Adams, J. Luo, S. M. Dudek, R. J. Weinberg, N. Calakos, W. C. Wetsel, and G. Feng. Cortico-striatal synaptic defects and OCD-like behaviours in Sapap3-mutant mice. *Nature*, 38:894–900, 2007.

[47] K. Westphal. Uber zwangsvorstellungen. *Arch. Psychiatr. Nervenkrank.*, 8:734–750, 1878.

[48] T. Williams and P. Waite. *Obsessive compulsive disorder, cognitive behaviour therapy with children and young people.* Taylor & Francis Group, London and New York, 2009.

[49] T. Williams and P. Waite. *Obsessive compulsive disorder, cognitive behaviour therapy with children and young people.* Taylor & Francis Group, London and New York, 2009.

[50] J. T. Winslow and T. R. Insel. *Neuroethological models of obsessive–compulsive disorder . In Zohar , J. , Insel , T. , and Rasmussen, S.(eds.) , The Psychobiology of Obsessive-Compulsive Disorder.* Springer Publishing Company , New York, 1991.

[51] A. Woods, C. Smith, M. Szewczak, R. W. Dunn, M. Cornfeldt, and R. Corbett. Selective serotonin re-uptake inhibitors decrease schedule-induced polydipsia in rats: a potential model for obsessive compulsive disorder. *Psychopharmacology*, 112:195–198, 1993.

[52] E. Yadin, E. Friedman, W. H., and Bridger. Spontaneous alternation behavior: an animal model for obsessive–compulsive disorder? *Pharmacol Biochem Behav*, 40:311–315, 1991.

[53] B. Zepf. Management strategies for obsessive-compulsive disorder. *American Family Physician*, 70:1379–1380, 2004.

[54] J. Zohar, T. R. Insel, R. C. Zohar-Kadouch, J. L. Hill, and D. L. Murphy. Serotonergic responsivity in obsessive-compulsive disorder: effects of chronic clomipramine treatment. *Archives of General Psychiatry*, 45:167–172, 1988.

[55] R. Zor, H. Keren, H. Hermesh, H. Szechtman, J. Mort, and D. Eilam. Obsessive-compulsive disorder: a disorder of pessimal (non-functional) motor behavior. *Acta Psychiatr Scand*, 120:288–298, 2009.