CHAPTER 1

General introduction

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General introduction

Diagnostic criteria

Obsessive-compulsive disorder (OCD) is a complex neuropsychiatric disorder characterized by the presence of obsessions (repetitive intrusive thoughts) and/or compulsions (repetitive ritualistic behaviors; American Psychiatric Association 2013). The obsessions and compulsions are debilitating for patients since they cause significant distress and interfere with daily life due to their time-consuming nature and due to patients avoiding many feared situations. The Diagnostic and Statistical Manual of Mental Disorders (DSM; American Psychiatric Association 2013), is the guidebook that many clinicians use to formally diagnose OCD. According to the recently revised edition (DSM-5) a clinical diagnosis of OCD can be made when an individual has obsessional and/or compulsive symptoms which comply with criteria A-D as described in Box 1.1. Previous versions of DSM traditionally categorized OCD as an anxiety disorder, but in DSM-5 (2013), OCD has its own chapter grouped together with the OCD-related disorders: trichotillomania (hair-pulling disorder), body dysmorphic, hoarding, and excoriation (skin-picking) disorder. This reclassification, although still subject to debate (Mataix-Cols, Pertusa, and Leckman 2007), reflects the common features of these disorders in terms of obsessive preoccupations and repetitive behaviors.

Epidemiology

OCD has an estimated lifetime prevalence worldwide of around 1-3% (Ruscio et al. 2010; Bijl, Ravelli, and van Zessen 1998). Women are more frequently affected than men, with 50-70% of adults patients being female depending on the exact population studied (Angst et al. 2004; Denys, Tenney, et al. 2004; Denys and de Geus 2007). Most patients develop OCD before their mid twenties, with the age-of-onset showing a bimodal distribution with one peak in childhood and another in early adulthood (Ruscio et al. 2010; Pinto et al. 2006).

Although many patients with OCD do not have a positive family history for the disorder, OCD tends to run in families. Studies showed that first-degree relatives of patients with adult-onset OCD have a five-fold increased risk of developing the disorder compared to the general population, this odds ratio ranges from 12-30 for relatives of patients with childhood-onset OCD (Pauls et al. 2014). This familiality is probably due to a combination of genetic and epigenetic risk factors: a meta-analysis of twin studies found that the additive genetic etiological factors accounted for 40% and non-shared environmental factors accounted for 51% of the variance in obsessive-compulsive behaviours observed in the twins (Taylor 2011).

Co-morbidity rates are high in OCD. Studies in the general population and clinical samples suggest that about 90% of individuals with a lifetime diagnosis of OCD also
have an additional Axis-I lifetime diagnosis. These include various anxiety and mood disorders, OCD-related disorders, attention-deficit hyperactivity disorder, eating disorders and substance-abuse disorders (Lochner et al. 2014; Ruscio et al. 2010; Pinto et al. 2006).

**Course and treatment of OCD**

The course and prognosis of the disease for treatment seeking adults with OCD often is waxing and waning or chronic. A follow-up study performed in Sweden showed that although most patients’ symptoms improved over time, only 20% of 122 in-patients treated for OCD were fully remitted 40 years later (Skoog and Skoog 1999). For treatment-seeking youths with OCD the course is more promising than for adults (Geller 2006). Nonetheless treatment strategies for OCD still need improvement. Modern first-line treatments for OCD include psychotherapy and antidepressant medication with or without addition of a dopamine-antagonist. Since the development of the tricyclic antidepressant clomipramine in the 1960s (see Insel and Murphy 1981) it became clear that OCD symptoms can be relieved with antidepressant medication. Nowadays, selective serotonin reuptake inhibitors (SSRIs: e.g. fluoxetine, fluvoxamine, citalopram, sertraline, paroxetine) are the first choice medication for OCD given their improved side effects profile compared with clomipramine (Soomro et al. 2008). When there is only a partial response to anti-depressants, a neuroleptic agent (e.g. aripiprazol, risperidon) can be added as an augmentation strategy (Veale et al. 2014). Additionally, the benefits of drugs targeting the glutamatergic neurotransmission (e.g. memantine) are currently investigated in OCD (e.g. Aboujaoude, Barry, and Gamel 2009).

Cognitive-behavioral therapy (CBT) is the first-line treatment of choice for OCD (Franklin and Foa 2011). CBT protocols involve exposure with response prevention (ERP) and/or cognitive therapy. During ERP, patients (under guidance of the therapist) deliberately seek out those situations that trigger their OCD symptoms (exposure), and are encouraged not to perform their usual compulsions (response prevention). The idea is that during ERP patients can experience and learn that 1) the anxiety will, albeit not immediately, pass with time (habituation will take place), 2) it is possible for them to withstand performing the compulsions, and 3) that the adverse outcome they feared so much (e.g. something bad happening to themselves or loved ones, going mad because the overwhelming anxiety or urge is just too much) does not happen. In cognitive therapy dysfunctional appraisals of intrusions and dysfunctional beliefs are identified and altered. Meta-analyses of randomized controlled trials in pediatric and adult OCD patient samples have shown that CBT is as effective if not more effective than pharmacotherapy with respect to the reduction of symptom severity and the remission rates (Ost et al. 2015; Sanchez-Meca et al. 2014). CBT and/or pharmacotherapy results in 40-60% of patients in a clinical response (i.e. reduction of 30-35% of disease severity score; Romanelli et al. 2014). Adding antidepressant medication to CBT does not
improve outcome compared with CBT only, whereas adding CBT to antidepressant medication does improve outcome compared with antidepressants monotherapy (Ost et al. 2015; Romanelli et al. 2014). Thus in many patients symptoms persist to some level. (Luigjes et al. 2013)

For the approximately 10% of treatment-refractory cases in which severe symptoms remain invasive psychosurgery is a treatment option. Stereotactic ablation procedures (anterior capsulotomy, cingulotomy, and subcaudate tractotomy) in which fronto-striatal connections are irreversibly damaged, have been used since the 1950s for OCD. The last decades there has been growing interest in deep brain stimulation as an - in theory - reversible technique to influence the circuits connecting the orbitofrontal cortex, medial prefrontal cortex, basal ganglia and the thalamus. Promising target locations in OCD include the anterior limb of the internal capsule, the nucleus accumbens (NAcc), the ventral capsule/ventral striatum, the subthalamic nucleus and the inferior thalamic peduncle. About 40-50% of OCD patients treated with psychosurgery show a treatment response with a significant reduction of symptoms (Luigjes et al. 2013; Cleary et al. 2015).

There is also a growing body of evidence for the efficacy of non-invasive brain stimulation over various frontal brain regions (such as transcranial magnetic stimulation, see Box 1.3, or transcranial direct current stimulation) in the treatment of OCD. Randomized controlled trials showed that the effect size of real vs. placebo repetitive TMS is similar to that of pharmacotherapeutical augmentation strategies (see Berlim, Neufeld, and Van den Eynde 2013 for a recent meta-analysis). TMS has shown promise as an augmentation strategy to antidepressant monotherapy in unipolar depression (Berlim, Van den Eynde, and Daskalakis 2013), but it is unknown if it improves outcome when added to CBT or antidepressant use in OCD. These non-invasive brain stimulation techniques, however, have not yet been incorporated into standard clinical practice and are often not available to patients as a treatment option.

**OCD-subtypes**

OCD is a multidimensional disorder with a heterogeneous phenotype. The content matter of obsessions and compulsions can vary widely between individuals such that two individuals with OCD may be completely non-overlapping in their symptoms. This heterogeneity has led researchers to attempts to identify OCD subdimensions, that although also often co-occurring within individuals, are associated with distinct patterns of co-morbidity, response to treatment and neuropsychological deficits (Mataix-Cols and van den Heuvel 2006; Mataix-Cols 2006; McKay et al. 2004; Miguel et al. 2005) and are associated with overlapping but also distinct structural and functional neural correlates (Mataix-Cols et al. 2004; van den Heuvel et al. 2009; Phillips et al. 2000; Phillips and Mataix-Cols 2004). A meta-analysis of factor analytic studies shows a preference for at least a four factor model: 1) symmetry obsessions and repeating, ordering and counting.
Box 1.1. Diagnostic criteria for Obsessive-Compulsive Disorder (DSM-5)

Criteria A. Presence of obsessions, compulsions, or both:

Obsessions are defined by (1) and (2):
1. Recurrent and persistent thoughts, urges or impulses that are experienced, at some time during the disturbance, as intrusive and unwanted, and that in most individuals cause marked anxiety or distress:
2. The individual attempts to ignore or suppress such thoughts, urges or images, or to neutralize them with some other thought or action (i.e. by performing a compulsion).

Compulsions are defined by (1) and (2):
1. Repetitive behaviors (e.g., hand-washing, ordering, checking) or mental acts (e.g. praying, counting, repeating words silently) that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly.
2. The behaviors or mental acts are aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situation; however, these behaviors or mental acts are not connected in a realistic way with what they are designed to neutralize or prevent, or are clearly excessive.

Note: Young children may not be able to articulate the aims of these behaviors or mental acts.

Criteria B. The obsessions or compulsions are time-consuming (e.g. take more than 1 hour per day) or cause significant distress or impairment in social, occupational or other important areas of functioning.

Criteria C. The obsessive-compulsive symptoms are not attributable to the physiological effects of a substance (e.g. a drug of abuse, a medication) or another medical condition.

Criteria D. The disturbance is not better explained by the symptoms of another mental disorder

Specify if:
- **With good or fair insight:** The individual recognizes that obsessive-compulsive disorder beliefs are definitely or probably not true, or that they may or may not be true.
- **With poor insight:** The individual thinks obsessive-compulsive disorder beliefs are probably true
- **With absent insight / delusional beliefs:** The individual is completely convinced that obsessive-compulsive beliefs are true.

Specify if: **Tic-related:** The individual has a current or past history of a tic disorder.

compulsions; 2) forbidden thoughts such as aggressive, sexual, religious and somatic obsessions and checking compulsions; 3) contamination obsessions and cleaning compulsions; and 4) hoarding (Bloch et al. 2008; Mataix-Cols, Rosario-Campos, and Leckman 2005). Indicative of the moving field, recently hoarding disorder has been categorized as a entity on its own, as an OCD-related disorder in DSM-5.

Childhood-onset OCD may be a particular subtype of OCD, given that in patients with childhood-onset versus adult-onset OCD the gender distribution is reversed (more
males). Also, these patients have a different co-morbidity profile with often co-morbid diagnoses of tic disorders, attention-deficit hyperactivity disorder or oppositional defiant disorder (see Pauls et al. 2014). Some authors also suggest that patients with poor insight constitute an separate OCD subtype (Karadag et al. 2011).

**Etiopathophysiology of OCD**

Etiopathophysiological models of OCD try to explain the occurrence of OCD symptoms (presence of intrusions, compulsions, concomitant anxiety), the heterogeneity of the disorder, and the associated neurocognitive deficits observed in neuropsychological, electrophysiological and neuroimaging studies done in OCD. OCD is considered a neurodevelopmental brain disorder in which during development probably several environmental and epigenetic factors interact with multiple genes to give rise to the heterogeneous phenotype. Genome-wide linkage studies in OCD suggest susceptibility loci on several chromosomes, which is in line with the supposed involvement of multiple genetic polymorphisms related to dopaminergic, serotonergic, GABAergic and glutamatergic neurotransmission, neuronal outgrowth and myelination (Pauls 2008; Shugart et al. 2006; Katerberg et al. 2010; Katerberg et al. 2009; Stewart et al. 2013; Monteiro and Feng 2016). Studies using SPECT- and PET-ligand imaging (single-photon emission computed and positron emission tomography) have provided evidence for alterations in serotonergic (Hesse et al. 2005; Perani et al. 2008) and dopaminergic (Kim, Koo, et al. 2003; Denys, van der Wee, et al. 2004; van der Wee et al. 2004) neurotransmission. These findings are in line with the therapeutic actions of SSRIs and dopamine-antagonists in OCD.

**Psychological models**

- A brief historical overview

Ideas about the nature of obsessions and compulsions change under the influence of the current Zeitgeist. There are accounts of individuals suffering from unwanted mental states resembling obsessions about aggression and blasphemy from the 16th century, which were interpreted as attacks of the devil (Osborn 1998; Denys and de Geus 2007). In the 19th century the concept of OCD as a neuropathological disorder involving dysfunction of the mind and brain developed. Influential French and German psychiatrists developed modern ways of classifying psychiatric symptoms and debated whether OCD was a disorder of the intellect, will or emotions. The French psychiatrist Esquirol (1772-1840) described OCD as a ‘*monomania*’ (a partial insanity due to disordered will), and Morel (1809-1873) called it a ‘*delire emotif*’ (a disease of the emotions). The German psychiatrist Westphal (1877) saw disordered intellectual function as the source of obsessions, which he called ‘*Zwangsvorstellung*’ (meaning compelled image or idea). At the end of the 19th century ‘neurasthenia’ (impaired tonus of the nervous system) was
developed as a diagnostic category that also included OCD. In 1896 Sigmund Freud (1856-1939) developed the concept of ‘Zwangneurosis’ imbedded in his ideas about psychic architecture and defense mechanisms. Both Freud and Pierre Janet (1859-1947) viewed OCD as the result of disordered development of personality (Denys and de Geus 2007). In the 1960s and 1970s, under the influence of behaviorism, theorists developed cognitive-behavioral models for OCD.

- **Cognitive-behavioral models**

Behavioral and cognitive-behavioral models all predict and explain some but not all aspects of OCD (see for a review Taylor, Abramovitch, and McKay 2007). Under the influence of Mowrer’s (1960) two-factor model of avoidance learning, conditioning models of OCD were developed that proposed that obsessional fears were acquired through classical conditioning and subsequently maintained through operant conditioning mechanisms. In this view, someone with obsessional contamination-related fears, first has a traumatic experience that links the conditioned stimulus (e.g. a public toilet) with an unconditioned stimulus (e.g. a serious illness). Then these fears are maintained through negative reinforcement learning: avoiding the public toilet or excessive hand-washing after contact with one reduces the discomfort and the perceived probability of the feared consequence of getting ill. Although conditioning models did lead to one of the most successful treatments for OCD (exposure and response prevention, see below), there is insufficient evidence for it proposed mechanisms. For example in many patients no such conditioning traumatic experience can be identified. This led scientists to consider other cognitive models of OCD.

Current cognitive-behavioral models of OCD postulate OCD is caused by a dysfunction in cognitive processing (general deficit models), specific dysfunctional beliefs and appraisals (belief and appraisal models) or dysfunctional reasoning processes. General deficit models pose that specific dysfunctions in information processing and control processes (see sections on neuropsychology and neurobiology in OCD below) cause the obsessions and compulsions. Belief and appraisal models (e.g. Steketee, Frost, and Cohen 1998; Salkovskis 1989) build on Beck’s cognitive specificity hypothesis that poses that different types of dysfunctional beliefs cause different types of psychopathology (Beck 1976). In these models the idea is put forward that intrusions are a normal human phenomenon, but that dysfunctional beliefs alter the personal significance and frequency of intrusions, leading to OCD. Examples are: excessive responsibility (‘the intrusion poses threat which I can prevent’), the overimportance of thoughts (‘having the thought increases the likelihood of the corresponding behavior or event’), the overestimation of threat (‘negative events are very likely’), intolerance of uncertainty (‘it is necessary and possible to be completely certain’), and the need to control thoughts (‘the control over one’s thoughts is necessary and possible’). An example of a proposed OCD-specific reasoning process is inferential confusion, in which people do not start with the senses to
reach a conclusion. For example the thought: “Even though my senses tell me otherwise, my intelligence tells me that people may have walked with dirty shoes on this floor” (Aardema, O’Connor, and Emmelkamp 2006).

**Neuropsychology**

- *Increased emotional reactivity during symptom provocation*

When patients with OCD come into contact with the objects or situations that play a role in their obsessions or compulsive behaviors, these disease-relevant stimuli can trigger feelings of distress (e.g. anxiety, disgust, guilt, or a ‘just-not-right feeling’ (JNRF)) and OC-symptoms (Smith et al. 2012). For instance, seeing a wet tissue, may trigger disgust and anxiety in patients with contamination concerns and an urge to check if they came into contact with it or to wash their hands. When confronted with clutter patients with symmetry behavior may feel tense or a JNRF and an urge to order items until ‘it feels right’. When confronted with a kitchen knife lying on the table, patients with harm obsessions may have intrusions about the possibility of using it in an aggressive act on a loved one and start performing mental rituals or compulsions to ‘neutralize’ the concomitant anxiety. For individuals without OCD these same situations are often not salient and mostly emotionally neutral. During exposure to disease-relevant stimuli in the laboratory patients with OCD, compared with healthy individuals, report higher levels of obsessionality and anxiety (Schienle et al. 2005; van den Heuvel et al. 2004), and have greater attentional bias towards these stimuli (Moritz et al. 2009; van den Heuvel, Veltman, Groenewegen, Witter, et al. 2005). Neuroimaging studies using PET and functional magnetic resonance imaging (fMRI) have shown this is accompanied by activation brain regions associated with saliency and emotional processing such as the anterior cingulate cortex (ACC), insula and the amygdala (Rotge et al. 2008).

- *Impaired cognitive control*

Compared with control subjects, OCD patients show impaired performance on various executive functioning tasks tapping into the neuropsychological domains associated with cognitive control (Lenartowicz et al. 2010). These tasks include planning (van den Heuvel, Veltman, Groenewegen, Cath, et al. 2005), response inhibition and cognitive flexibility (Chamberlain et al. 2007; Menzies et al. 2007), and working memory tasks (van der Wee et al. 2003; see Abramovitch, Abramowitz, and Mittelman 2013; Abramovitch et al. 2015 for recent meta-analyses of neuropsychological task performance in adult and pediatric OCD samples). Cognitive control can be defined as the set of processes that underlie the ability to initiate and flexibly change thoughts and action in accord with internal goals (Sabb et al. 2008; Duncan and Owen 2000; Miller and Cohen 2001). Whereas many human behaviors are automatic and seem ‘hardwired’ (such as orienting towards an unexpected sound or movement), cognitive control processes are important
for situations where the relationship between a given sensory input and subsequent thoughts and actions is uncertain (e.g. when there are multiple competing mappings, or their relationship is rapidly changing). How exactly cognitive control is exerted is unknown. Biased competition theories propose that cognitive control is implemented through the maintenance of patterns of activity in (pre)frontal cortex (e.g. Miller and Cohen 2001) and associated structures (e.g. fronto-striatal and frontal-parietal networks (see Shenhav, Botvinick, and Cohen 2013; Hon et al. 2006; Dosenbach et al. 2008). These patterns then represent goals and the means to achieve them (i.e. are representation of ‘the rules of the game’). They provide top-down bias signals to other brain structures, guiding the activity of the neural pathways between sensory input, internal states and the behavioral output necessary for performance of a given task.

**Neurobiology**

-*The CSTC-circuitry*

Neurobiological models of OCD for long suggested that abnormalities in the integrated and partially segregated loops of the frontal cortico-striato-thalamo-cortical (CSTC) circuitry are related to OCD symptoms and associated neurocognitive deficits. Functional and structural brain changes in OCD, however, are not confined to these frontal-striatal regions but probably also extend to the limbic circuit (see paragraph below), and posterior brain regions such as the parietal cortex (Menzies, Chamberlain, et al. 2008; Milad and Rauch 2012; Pauls et al. 2014). Within the CSTC circuitry the basal ganglia work in concert with cortex to enable an organism to integrate different modes of sensory information about the external world, compare them with its internal states and current goals, and translate this into decision making and flexible motor output (Haber and Behrens 2014). It has become increasingly clear that the CSTC loops are important for cognitive control, and are not only involved in the expression of goal-direct behaviors through movement as was initially thought, but also in the emotional, motivational and cognitive processes leading up to that movement (Haber and Calzavara 2009; Alexander, DeLong, and Strick 1986). The CSTC circuitry not only comprises of recurrent connections of the basal ganglia with frontal cortex but also with parietal and temporal cortex (Middleton and Strick 2000a; Middleton and Strick 2001). Posterior parietal regions are for instance considered part of the dorsal cognitive fronto-striatal circuit (see below). The focus in OCD models, however, has traditionally been on the connections between frontal cortex and the striatum (Pauls et al. 2014). For this reason, below I have focused on the frontal CSTC circuits only.

In the frontal CSTC circuit different functional regions of frontal cortex project with a ventromedial to dorsolateral topography to specific sub-regions of the striatum (caudate nucleus and putamen) and subsequently to the thalamus which has recurrent projections back to cortex (see Figure 1.1 for description of the frontal CSTC circuits; Haber 2014; van den Heuvel et al. 2016). Given its role in orchestrating and executing
planned motivated behaviors, the CSTC circuit requires closely tied motor, cognitive and limbic circuits (Haber 2003). At different levels in the CSTC circuit there is an overlap of inputs from the different loops, which putatively facilitates the crosstalk and the integration and synchronization of information across functional areas that is necessary for adaptation and learning (Haber and Behrens 2014). Given this overlap in anatomical connectedness, different authors propose slightly different classifications of the frontal CSTC circuits, nonetheless, the following circuits have been identified by most (Milad and Rauch 2012; Haber 2003; Alexander, DeLong, and Strick 1986; Tekin and Cummings 2002; van den Heuvel et al. 2016).

* A **Sensorimotor** loop involving caudal and rostral motor areas including the (pre-) supplementary motor area (SMA), (pre-)motor cortex and (posterior) putamen, important for motor actions, involved in the selection of motor plans and stimulus-response based habitual behavior (some authors subdivide this loop into a caudal and rostral part; see Haber 2003; Alexander, DeLong, and Strick 1986; Middleton and Strick 2001).

* A **Dorsal Cognitive** loop involving the dLPFC, dorsomedial PFC (including dorsal ACC) and dorsal caudate (some authors also include the pre-SMA; see van den Heuvel et al. 2016), associated with executive functions such as planning and working memory.

* A **Ventral Cognitive** loop involving the ventral caudate and the ventrolateral PFC / inferior frontal gyrus (also called anterolateral orbitofrontal cortex (OFC)) important for response inhibition and attentional set-shifting.

* An **Affective** loop involving the vmPFC (including medial OFC and rostral and subgenual ACC; Haber and Behrens 2014) and NAcc, associated with stimulus-outcome based motivational behavior.

Within the CSTC loops the balance between excitation and inhibition is mediated by ‘direct’ pathways that serve to increase thalamic excitation of the cortex, and ‘indirect’ and ‘hyperdirect’ pathways that reduce thalamic excitation of cortex (Haber 2003). In the ‘direct’ pathways an excitatory glutamatergic input from cortex arrives in the striatum, which then projects an inhibitory GABA-ergic signal to the internal segment of the globus pallidum (and substantia nigra pars reticulare), resulting in disinhibition of the thalamus and a net excitatory signal to cortex. In the ‘indirect’ pathways an excitatory input from cortex into striatum results in inhibition of the external segment of the globus pallidus, subsequent disinhibition of the subthalamic nucleus and the internal segment of globus pallidus resulting in net inhibition of thalamus and its recurrent cortical projections. In the ‘hyperdirect’ pathways the signal from cortex reaches the thalamus through direct projection to the subthalamic nucleus and then internal segment of the globus pallidus also resulting in cortical inhibition (Nambu, Tokuno, and Takada 2002). The ‘direct’ pathways are self-reinforcing, promoting the intended motor program, and are thus important for the initiation and continuation of behavior. The ‘hyper/indirect’ pathways provide a negative feedback loop enabling the inhibition of specific competing motor plans and the switching between behaviors.
Studies in humans and nonhuman primates have shown that monoaminergic neurotransmitter systems like dopamine, serotonin, norepinephrine, and acetylcholine through their projections to the cortex, basal ganglia and thalamus, modulate executive functions including working memory, set-shifting and response inhibition (see Robbins and Arnsten 2009 for a review). One of the underlying mechanisms by which this is mediated is by alteration of the neuronal network dynamics such that the signal-to-noise ratio is modulated and task-related representations of PFC neurons are altered. Interestingly, the direction of this modulation is dependent on the arousal state of the organism. This stress-sensitivity seems an important notion in psychiatric disorders, such as OCD, in which hyperarousal and anxiety play a role (Simon et al. 2013). Arousal state for instance may influence the amount of presynaptic neurotransmitter release (e.g. phasic versus tonic transmitter release), and different subtypes of receptors (for instance the D1 and D2 receptors that are preferentially expressed by respectively the direct and indirect fronto-striatal pathways) are stimulated optimally at different levels. Further, it has been shown, mainly for dopamine and norepinephrine, that there is an inverted U-shaped Yerkes-Dodson function linking behavioral performance efficiency to activity of these monoamine systems. However, the shape of these inverted U-functions may vary from task to task, such that an optimal level for one task is suboptimal for another (Robbins and Arnsten 2009). This may explain, why different genotypes related to monoaminergic signalling pathways are associated with differential neuropsychological profiles and psychiatric symptomatology.

- **The role of the ‘limbic circuit’ in cognitive control**

Emotional processes influence cognition and vice versa cognitive processes can modulate and alter our emotions. Cognition and emotion are integrated in the brain to such an extent that a functional distinction between systems of brain regions involved in purely affective versus purely cognitive processes is difficult, if not impossible (see Gray, Braver, and Raichle 2002; and Pessoa 2008 for reviews). Some authors even postulate that affect is a form of cognition (Duncan and Barrett 2007). Historically, cognition has been functionally located in the PFC (Miller and Cohen 2001) and emotion in the (para)limbic circuit. The limbic circuit is often used interchangeably with the emotional brain, but this has two problems. Firstly, there is no general consensus in the literature about the definition of the limbic circuit, and what brain regions may additionally be called paralimbic. In its oldest definition, the limbic circuit included the thalamus, the hypothalamus, the hippocampus and the cingulate cortex, in addition to other structures such as the amygdala and the septum (Pessoa 2008). Anatomically, limbus refers to the border of the cerebral hemisphere along the cingulate gyrus, and ‘limbic circuit’ in this sense comprises of the anterior cingulate cortex and retrosplenial cortex, the amygdaloid and hippocampal complex and other basal forebrain structures such as the basal nucleus of Meynert. Regions with more complex cytoarchitecture such as the anterior cingulate
cortex are sometimes also referred to as paralimbic. Secondly, there is substantial overlap between brain regions involved in affective processing with those involved in cognition. Subcortical brain regions often associated with affective processing include the amygdala, nucleus accumbens, the hypothalamus, but also the brain stem, the ventral tegmental area and associated mesolimbic dopamine system, the hippocampus, the periaqueductal grey, the septum and the basal forebrain including the nucleus basalis of Meynert. Cortical regions involved in emotion processing include ventromedial prefrontal cortex (vmPFC) comprising of the orbitofrontal cortex and anterior cingulate cortex (ACC; especially the rostral part), but also other regions of the prefrontal cortex have been implicated, as well as the anterior insula, the anterior temporal lobe, the posterior cingulate cortex, superior temporal sulcus, and somatosensory cortex (see (Pessoa 2008; Rotge et al. 2008). In this thesis when assessing functional interactions between cortex and the limbic circuit, we focused on the amygdala and vmPFC, given their proposed role in anxiety and fear extinction in OCD (Milad and Rauch 2012; Phelps and LeDoux 2005; van den Heuvel et al. 2016).

Figure 1.1. Schematic representation of the partially overlapping frontal cortico-striatal-thalamico-cortical (CSTC) and frontal-limbic circuits involved in cognitive and emotional control. Reprinted with permission from (van den Heuvel et al. 2016).
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Studies in animals and humans have shown that the amygdala processes the emotional significance of external stimuli. It is implicated in detecting and attending to emotional information and encoding it into memory, as well as the production of physiological and behavioral arousal in response to salient, emotional stimuli (Phelps and LeDoux 2005). The amygdala consists of a set of nuclei (a.o. the basolateral and centromedial nuclei) that have distinct connections and functionality. Activation patterns in the amygdala can often not be attributed to specific nuclei within the amygdaloid complex due to the relative low resolution of functional MRI scans used in many neuroimaging studies. The amygdala receives multimodal sensory input from sensory and association cortex, the entorhinal cortex/hippocampus, the thalamus, and the brainstem, and subsequently activates or modulates synaptic transmission in target areas such as the midbrain monoamine arousal systems, the striatum and cortex including the PFC (Davis and Whalen 2001). There is increasing evidence that frontal-amygdala as well as fronto-striatal connections are important for cognitive control (see Salzman and Fusi 2010 for a review). Throughout the PFC there are bidirectional connections with the amygdala, with the most dense connections between the amygdala and parts of the vmPFC (including posterior OFC and subgenual ACC) and dorsal anterior cingulate cortex (see Ghashghaei, Hilgetag, and Barbas 2007; Ray and Zald 2012). These bidirectional frontal-amygdala anatomical connections suggest that the amygdala can drive PFC activation and the PFC can drive activation in the amygdala. Indirectly, influence between different regions of PFC and amygdala may be exerted via connections with cortical hubs such as the vmPFC and dorsal ACC (Ray and Zald 2012; Phillips, Ladouceur, and Drevets 2008), or via subcortical structures such as the thalamus or basal nucleus of Meynert (Pessoa 2008). Studies in nonhuman primates have shown that the PFC and amygdala often work in concert during executive functioning (e.g. attention, perception, working memory, planning, the valuation of actions and stimuli), as well as mediating aspects of aversive and appetitive affective processing such as valence and intensity. It is in concert with the amygdala that different neuronal subpopulations in the frontal CSTC circuit encode entangled signals, thus enabling the integration of multimodal stimuli in their temporal and spatial context necessary for cognitive control (Salzman and Fusi 2010).

The mechanisms and intricate circuitries underlying these frontal-amygdala interactions are not yet fully understood. In general, it has been suggested that striking a balance between top-down and bottom-up influences between the frontal cortex and the amygdala in a given situation is crucial for an individual to respond adaptively (Johnstone et al. 2007). Further, it has been proposed that this balance may be disrupted in psychiatric disorders including OCD, leading to dysregulated emotions such as mood disorders and pathological anxiety (e.g Johnstone et al. 2007; Phillips et al. 2003b). However, anatomical and functional models of how information flows between the amygdala and PFC during emotional and cognitive control, only partially overlap (see Ray and Zald 2012 for a review). For instance, the dlPFC often is portrayed as providing
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top-down control (suggesting feedback connectivity), whereas anatomical studies suggest that most dlPFC projections are more likely of a feedforward nature. Nevertheless, top-down control of the dlPFC could be implemented both by feedback signals as well as feedforward bias signals influencing competition between neural representations. Relatively simplistic models on the interaction between cognition and emotion may be useful for identifying new research avenues, but it is important to note that the cortico-cortical and cortico-subcortical interactions during emotional and cognitive control are probably more intricate than current models take into account.

-**The CSTC-circuitry and OCD**

There are various hypotheses about how changes in frontal CSTC functioning could contribute to OCD pathogenesis, pathophysiology and associated neurocognitive characteristics. Most authors stress the importance of one or more fronto-striatal loops and hypothesize an imbalance between individual loops or between the direct and indirect pathways within the loops. However, dysfunction of other circuits such as the limbic circuit, or compensatory mechanisms by other neural circuits have also been hypothesized in OCD (see Menzies, Chamberlain, et al. 2008; Milad and Rauch 2012; Pauls et al. 2014; Haber and Behrens 2014; van den Heuvel et al. 2016 for recent reviews). The OFC-striatal circuit (Affective loop) has received much attention in OCD research ever since early neuroimaging studies reported orbitofronto-striatal hyperactivation during symptom provocation (e.g. Cottraux et al. 1996; Rotge et al. 2008) and altered activation in this circuit during tasks probing reward processing and changing stimulus-reinforcement contingencies (Remijnse et al. 2006; Chamberlain et al. 2008). Some authors hypothesize that increased activity of the indirect pathway in the affective loop leads to OFC dysfunction and that this is associated with increased sensitivity to threat and the exaggerated concerns (i.e. intrusions) about danger and harm (Milad and Rauch 2012). Other authors hypothesize that compulsions in OCD arise from the misadaptation to threat signals, and propose that in the OCD brain, engagement in security-related behaviors fails to terminate (i.e. absence of stop signal) the activation of security motivation system mediated by the affective loop, resulting in ongoing compulsive behaviors (Woody and Szechtman 2011). Gillan et al. (Gillan et al. 2011; Gillan and Robbins 2014) postulate that dysfunction in the orbitofronto-strital circuit lead to deficits in goal-directed action and a shift towards overreliance on the habit system (involving the putamen and sensorimotor cortex), which manifests as compulsive behaviors in OCD patients.

The idea that impaired regulatory top-down control over motivational and emotional processes is important for OCD is somewhat similar, but puts more emphasis on dysfunction of the dorsal cognitive loop including dysfunction of the dorsolateral and dorsomedial prefrontal cortex (Mataix-Cols and van den Heuvel 2006). Diminished emotional control in OCD (and other neuropsychiatric disorders; Phillips et al. 2003b)
has been thought to be related to a putative imbalance between the dorsal cognitive and the affective loop, (Mataix-Cols and van den Heuvel 2006; Milad and Rauch 2012; Wood and Ahmari 2015), as well as alterations in the frontal-limbic circuitry including the vmPFC and amygdala important for fear extinction (see Figure 1.1; Milad and Rauch 2012; van den Heuvel et al. 2016). Deficient control over motor action and impaired inhibition are another mechanism by which compulsions could arise, which has been related to a dysfunction of the ventral cognitive loop (Milad and Rauch 2012). Yet, others hypothesize that intrusions are due to a shift in non-conscious information processing (procedural/habit learning mediated by the CSTC circuitry) to conscious information processing mediated by the frontal-hippocampal circuitry (related to explicit learning; Rauch et al. 1997).

How exactly alterations in neuromodulatory systems, such as serotonin and dopamine, interact within the frontal-striatal circuitry and relate to OCD symptoms and neurocognitive functioning is unknown. Also, what role regions outside the fronto-striatal circuit play, such as (para)limbic regions, the parietal and temporal cortices and the cerebellum, in OCD remains to be elucidated.

State versus trait: the endophenotype concept

The difficulty with complex neuropsychiatric disorders such as OCD is that the categorization based on an individuals’ clinical symptoms (such as is done in the DSM) probably does not do justice to the different neurobiological mechanisms leading to the different aspects of the disorder. This is important, because if we understand the basic mechanisms of psychopathology can we may be able to devise new prevention and treatment strategies. From the clinic we know that individuals with different psychiatric DSM diagnoses (e.g. OCD, unipolar depression, anxiety disorders) may respond to the same types of medication (e.g. SSRI) or psychotherapy (e.g. CBT), and in the lab these individuals may also show a varying degree of overlap in their neurocognitive profile (e.g. van den Heuvel, Veltman, Groenewegen, Witter, et al. 2005; Radua et al. 2010; Goodkind et al. 2015). At the same time, different underlying neurobiological mechanisms could have a final common pathway, resulting in similar symptoms and symptoms being lumped together under the same DSM diagnosis despite their diverging origin. Therefore scientists in neuropsychiatry are currently aiming to develop a new way of classifying mental disorders based on dysfunction on subsets of homogenous behavioral dimensions and neurobiological measures that cut across multiple disorders. This approach is in contrast with the current one in which the research starts with the clinical symptoms and works backwards to identify their etiopathophysiological mechanisms. This new aim is reflected in the Research Domain Criteria initiative of the American National Institute of Mental Health, which wants to identify such functional domains and focuses on broad domains such as cognition and motivational and emotional processing (see http://www.nimh.nih.gov/research-priorities/rdoc/index.
Especially the neurodevelopmental trajectories of these domains and their interaction with environment is of interest. In DSM-5, a description of diagnoses using a dimensional approach has not yet been achieved. And in general this dimensional approach will require a paradigm shift in psychiatric science. In the future, however, this approach may be more fruitful for the true understanding of the occurrence of mental disorders.

The identification trait markers in neuropsychiatry is part of this initiative described above (Gottesman and Gould 2003). To elucidate the complex and partly genetic etiology of OCD the field has moved towards identifying endophenotypes (Chamberlain et al. 2005). Whereas state markers are indicators of the clinical disease manifestations in patients, trait markers are measurable aspects of behavioral, neuropsychological or biological processes that play an antecedent and possibly causal role in the pathophysiology of a psychiatric disorder (Chen, Bidwell, and Norton 2006).

An endophenotype is a trait marker that is specifically related only to the genetically influenced phenotypical characteristics, and is a closer lead to the genetic contributions to a disorder than the phenotype itself (Gottesman and Gould 2003; Gould and Gottesman 2006). An endophenotype as such is relatively independent from disease severity and is present more often in unaffected first-degree relatives of patients than in the general population. Comparing brain activation patterns of OCD patients with those of their unaffected first-degree relatives may thus shed some light of the origin of altered brain function in OCD. Differences in brain activity patterns in OCD patients compared with controls may be related to the underlying pathophysiology of OCD, or could alternatively be phenomenon secondary to having the disorder, for instance resulting from the use of psychotropic medication or performing compulsive behaviors. Unaffected family members of OCD patients share some of the genetic susceptibility to OCD, but are not exposed to factors secondary to the disorder. Brain activation patterns in unaffected siblings of OCD patients that are different from healthy controls and similar to OCD patients may thus be related the vulnerability for developing OCD, and are candidate endophenotypes. Alternatively, brain activation patterns that are different in siblings compared to both OCD patients and healthy controls, may be related to the resilience to developing OCD. Identification of these putative fMRI-based endophenotypes could be of use for future genetic studies in OCD. Additionally, identification of neurobiological markers associated with resilience to developing OCD may benefit future studies aiming to understand and improve treatment protocols for the disorder.

**Summary**

This study was set up in 2007-2008 when there was increasing interest in the interaction between dorsal and ventral frontostriatal and limbic circuitry in neuropsychiatric disorders such as OCD in which dysregulated emotions were hypothesized to be of
importance (Phillips et al. 2003b, 2003a). Neurobiological models of OCD postulated involvement of the different CSTC circuits, and speculated about alterations in brain regions outside of this circuitry (see Menzies, Chamberlain, et al. 2008 for an overview). Also, it remained unclear to what extent alterations in brain structure and function were causal to developing OCD, constituting vulnerability markers for OCD (i.e. trait characteristics), and which alterations were a phenomenon secondary to having the disorder and related to clinical symptoms (i.e. state markers). Results from structural and functional neuroimaging studies collected during task-performance and rest only partly converged, which may be, at least partially be explained by studies being underpowered, differing medication-status of included samples, control groups being not well matched to the patient samples, and inclusion of pediatric versus adult samples. This divergence called for well-powered studies testing specific hypotheses about the role of the different CSTC circuits in OCD, but also looking at brain regions outside this circuit, as well as studies trying to disentangle trait- from state-characteristics, for instance using family-study or follow-up study designs.

Aim and outline of this thesis

This thesis focuses on cognitive control processes in OCD. We had the general aim to get a better understanding of the structure and function of the fronto-striatal circuits in relation to cognitive control impairments in OCD. To this aim we used different approaches of analyzing structural and functional MRI scan images (see Box 1.2). We hypothesized that impaired cognitive control in OCD is related to dysfunctional interactions between the dorsal and ventral fronto-striatal circuits and the limbic circuit, leading to executive dysfunction and emotion dysregulation. Specifically we hypothesized that cognitive control deficits in OCD are related to hypoactivation of the dorsal cognitive circuit with loss of top-down control on the ventral frontal-striatal and limbic circuits, which we hypothesized to be hyperactivated and negatively influence dorsal functioning. To test this hypothesis, we set up a study in which we measured activation of the dorsal and ventral circuits during three tasks probing cognitive control: an emotion regulation (chapter 3), a response inhibition (chapter 4 and 5), and a working memory task (chapter 6). We also used a family study design and measured brain activation in unaffected siblings of a subsample of these OCD patients during the cognitive control tasks (chapter 3-6) to test the hypothesis that deficits of fronto-striatal circuits are putative endophenotypes of OCD. Additionally, in a follow-up scan session, we modulated activity of the dorsal cognitive circuit with rTMS, and tested if this would influence top-down control during an emotion regulation task in OCD patients and controls (chapter 3). Further, to assess morphometric changes throughout the OCD brain we compared structural MRI scans (chapter 2) between a large sample of OCD patients with those of healthy controls.
In Chapter 2 we report on the largest structural neuroimaging study performed in OCD so far. With voxel-based morphometry (VBM) it is possible to assess alterations in regional gray and white matter volume across the whole brain. Meta-analyses that were published before our report included 10-14 partially overlapping adult and pediatric voxel-based morphometry studies and had only partially consistent results (Radua and Mataix-Cols 2009; Radua et al. 2010; Rotge et al. 2010; Peng et al. 2012). These inconsistent results could probably be attributed to differences between studies in the used analysis methods, heterogeneity of the study groups (for instance age-differences), and problems with experimental power due to small sample size. Pooling data is a way to increase statistical power due to the increase in sample size. Also, compared to a meta-analytical approach, an image-based mega-analysis on pooled raw data reduces noise associated with differential image processing, and additionally makes it possible to account for participant-level variability in your data. To overcome the abovementioned limitations of previous VBM studies in OCD, we performed a mega-analysis on pooled structural MRI scans of 412 OCD patients and 368 healthy controls collected at the 6 international research sites collaborating in the OCD brain imaging consortium (OBIC). This approach allowed us to assess consistent changes in regional gray and white matter volume in OCD patients compared to controls, and to see how these are related to aging and clinical factors such as co-morbid diagnosis, medication use and the presence of OCD symptom dimensions.

Chapter 3-6 reports on data from the abovementioned cognitive control study. It entails analyses on functional MRI scans recorded during task performance at the VU University Medical Center in a total sample of 46 medication-free OCD patients, 19 of their unaffected siblings and 41 healthy controls between 2009-2011. Patients were recruited through outpatient clinics within the Netherlands OCD Association (Schuurmans et al., 2012), the Academic Anxiety Center Altrecht (Utrecht, the Netherlands), and online advertisements. If patients gave permission, their siblings (without OCD) were contacted for participation in the study. Controls were recruited by local and online community advertisements.

In chapter 3 we assessed the neural correlates of instructed emotion regulation in OCD patients compared with healthy controls. Additionally, we tested if emotion regulation performance could be influenced by a single session of repetitive transcranial magnetic stimulation, a non-invasive brain stimulation technique (see Box 1.3). It has been hypothesized that an impairment in emotion regulation capabilities underlies the increased emotional reactivity seen in OCD patients when confronted with disease-relevant stimuli (Mataix-Cols and van den Heuvel 2006), yet emotion regulation was not studied before in OCD. CBT for OCD involves, in addition to exposure-in vivo with response prevention, teaching patients emotion regulation strategies to help cognitively reframe, i.e. reappraise, negative symptom-eliciting situations as non-threatening. It has been shown that in healthy individuals the use of reappraisal as an
emotion regulation strategy is important for psychological and interpersonal wellbeing (Gross and John 2003). Emotion regulation has shown to be impaired in depression and anxiety (e.g. Goldin, Manber-Ball, et al. 2009; Kanske et al. 2012). Neuroimaging studies in healthy participants have shown that successful reappraisal-related down-regulation of negative affect is associated with recruitment of frontal control areas such as the dorsomedial but also the dorsolateral prefrontal cortex (Kalisch 2009). Previous studies in our group showed deficient dlPFC recruitment in OCD patients during executive functioning, which was associated with impaired task performance and increased amygdala activity (van den Heuvel, Veltman, Groenewegen, Cath, et al. 2005; van den Heuvel et al. 2011). Based on the above, we hypothesized that impaired emotion regulation in OCD would be related to deficient recruitment of the dlPFC, and furthermore, that boosting dlPFC function with rTMS would improve emotion regulation. Insight into the neural substrate of reappraisal in OCD could be relevant for treatment of the disorder. We compared task performance and brain activity during an OCD-specific emotion regulation task between OCD patients and controls to assess the hypothesized emotion regulation deficit. Additionally, we modulated dorsolateral prefrontal cortex activity with rTMS prior to fMRI scanning to enable visualization of rTMS effects on reappraisal-related brain activity, since this may herald future clinical studies combining rTMS with CBT in OCD.

In chapter 4-6 we wanted to know if altered brain activity patterns seen in OCD could be eligible endophenotypes. In chapter 4 and 5 we looked at the functional neural correlates of response inhibition as an endophenotype for OCD. Previous studies showed that patients with OCD and their unaffected first-degree relatives compared with healthy controls behaviorally had increased latencies of the inhibition process (Chamberlain et al. 2007). This inhibition inefficiency in patients and relatives was associated with alterations in frontoparietal gray matter density (Menzies et al. 2007) and white matter integrity (Menzies, Williams, et al. 2008). Until our report it remained unclear, however, to what extent these morphological changes were functionally relevant. In chapter 4 we describe our main results comparing brain activity during a response inhibition task between OCD patients, siblings and controls. In chapter 5 we used psychophysiological interaction analysis and dynamic causal modeling (see Box 1.2) to further explore these findings and see if during task performance there was altered functional connectivity within the response inhibition network or with the amygdala. In chapter 6 we assessed if the neural correlates of visuo-spatial working memory are a candidate endophenotype for OCD. Previous studies showed subtle load-dependent working memory performance impairments in OCD patients versus controls, which was associated with fronto-parietal dysfunction (van der Wee et al. 2003). Whether these changes were also present in unaffected family-members, however, was never studied. Moreover, this task was known to reliably activate the dlPFC, and we included it in our study-design to ascertain the identification of a dlPFC functional hot-spot for rTMS
(see chapter 3). In Chapter 7 the results of the studies in this thesis are summarized and related to the wider OCD literature.
Box 1.2. Brain imaging techniques used in this thesis

Structural Magnetic Resonance Imaging
The anatomy of the brain can be visualized using T1-weighted MRI scan images. Brain tissue can be divided into gray and white matter. Gray matter (the cortex and subcortical nuclei) is mainly composed of neuronal cell bodies, as well as neuropil, glial cells and capillaries. White matter contains the myelinated axons providing the long-range connections between neurons. We performed statistical analyses on voxel-wise gray and white matter concentrations using voxel-based morphometry (Ashburner 2009) as a technique implemented in Statistical Parametric Mapping software suit (SPM8; http://www.fil.ion.ucl.ac.uk/spm/).

Functional Magnetic Resonance Imaging (fMRI)
Brain activation over time can be visualized using a series of T2*-weighted MRI scan images. Communication between neurons (i.e. action potentials and synaptic transmission) costs energy, which is dependent on oxygen. In fMRI it is assumed that a regional infl ow of oxygenated blood through the vasculature is an indication of local neuronal activity. Through the method of Blood Oxygen Level Dependent (BOLD) contrast imaging this hemodynamic response to neuronal activity can be indirectly detected. Oxygen is carried in the blood by hemoglobin. Hemoglobin has different magnetic susceptibility when it is carrying oxygen (oxyhemoglobin) compared to when it does not (deoxyhemoglobin). BOLD contrast imaging relies on this differential magnetic property, and enables visualisation of the relative ratio of oxy- versus deoxyhemoglobin, which is then an indirect measure of brain activation. When applying task-related fMRI, the BOLD response during an activity of interest (e.g. a working memory task) is compared with that during a baseline condition (e.g. responding to stimulus without having to access working memory). The difference in BOLD responses between the condition of interest and the baseline is then interpreted as task-related brain activation that can be compared between study groups.

Functional and effective connectivity
Synchronized activation of brain regions is important for cognition. In health and disease variation in cognitive function has been related to alterations in brain network connectivity (e.g. Goodkind et al. 2015). We used different techniques in this thesis to assess connectivity in fMRI data. With Psycho-Physiological Interaction Analysis (PPI) and Dynamic Causal Modeling (DCM) it is possible to characterize connectivity between brain regions during task performance. With PPI one assesses functional connectivity: it tests the degree to which a seed brain regions’ connection with other regions across the brain (i.e. the extent of their temporal co-activation) is modulated by psychological variables such as different task conditions (Friston et al. 1997). With DCM (Friston, Harrison, and Penny 2003) effective connectivity is assessed. In DCM one estimates the causal architecture of coupled brain regions in a model-driven fashion, testing the hypothesis that one neuronal system exerts influence over another, and assessing if task conditions influence this causal relationship.
Transcranial Magnetic Stimulation (TMS)

Transcranial Magnetic Stimulation is a non-invasive brain stimulation technique in which a patch of neural tissue (and its distant interconnected regions) is electrically stimulated using a TMS coil placed on the scalp (see the figure below). With the TMS coil a single pulse or multiple pulses can be applied. The type of pulse frequency and intensity of stimulation is important for its effect. With a single session of repetitive TMS (rTMS) one can change neural functioning, not only directly during the stimulation period, but also minutes to hours after stimulation. It is currently unclear how this change is mediated. Probably, multiple mutually interacting mechanisms on different neuronal cell types result in net changes in spiking frequency and synaptic transmission. High-frequency rTMS (pulse frequency of 5Hz or higher) is thought to result in temporary excitation of a brain area, whereas low-frequency rTMS (pulse frequency of 1Hz or lower) is thought to result in inhibition (Reithler, Peters, and Sack 2011). In clinical psychiatry, multi-session rTMS is used to reduce psychiatric symptoms, such as depressed mood or OCD symptoms. In these clinical TMS protocols, TMS sessions are repeated daily, for instance five times per week for a number of weeks. The mechanism by which multi-session TMS results in symptom reduction also remains to be elucidated.

Reprinted with permission from Ridding & Rothwell, 2007, Nature Reviews Neuroscience. A current runs through the figure-of-eight TMS coil placed on the scalp of a subject, evoking an electric current in the underlying neural tissue through the mechanism of electromagnetic induction.